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Heart rate and heart rate variability in panic, social anxiety, obsessive–compulsive, and generalized anxiety disorders at baseline and in response to relaxation and hyperventilation

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ABSTRACT

It remains unclear if diminished high frequency heart rate variability (HF-HRV) can be found across anxiety disorders. HF-HRV and heart rate (HR) were examined in panic (PD), generalized anxiety (GAD), social anxiety (SAD), and obsessive–compulsive disorder (OCD) relative to healthy controls at baseline and during anxiety stressors. All disorders evidenced diminished baseline HF-HRV relative to controls. Baseline HRV differences were maintained throughout relaxation. For hyperventilation, PD and GAD demonstrated greater HR than controls. Psychotropic medication did not account for HF-HRV differences except in OCD. Age and sex evidenced multiple main effects. Findings suggest that low baseline HF-HRV represents a common index for inhibitory deficits across PD, GAD, and SAD, which is consistent with the notion of autonomic inflexibility in anxiety disorders. Elevated HR responses to hyperventilation, however, are specific to PD and GAD.

1. Introduction

A robust literature examined cardiac psychophysiology at rest and in response to provocation among individuals with anxiety disorders. Most studies focused on panic disorder (PD), and to a lesser extent, on generalized anxiety disorder (GAD) and social anxiety disorder (SAD; see Friedman, 2007). Within these studies, heart rate variability (HRV) and heart rate (HR) were the most common measures of cardiovascular activity. HRV in the high frequency spectrum (HF-HRV) represents an index of respiratory sinus arrhythmia (RSA), which involves regular patterns of HR fluctuations that are linked to the breathing cycle and modulated by the parasympathetic nervous system (Thayer and Lane, 2000). Extensive research demonstrated associations between HRV and various physical diseases, psychopathology, and emotion regulation (e.g.,Camm et al., 1996; Beauchaine, 2001; Friedman, 2007). Most important, theories have proposed close links between low RSA and psychopathology, especially anxiety disorders.

The Polyvagal theory (e.g., Porges, 2007) links autonomic regulation and RSA to a variety of (psycho-) pathological states and behaviors. Adaptive behavior and autonomic responses emerge from the hierarchical organization of different phylogenetic subsystems of the autonomic nervous system with phylogenetically newer systems inhibiting older ones. These inhibition processes are essential for adaptive behavior with (autonomic) variability being associated with healthy responses. Deficits in these inhibitory processes are seen as a risk for emotion dysregulation and psychopathology more generally (Beauchaine, 2001). The related neurovisceral model of cardiac and emotion regulation proposes specific links between cardiovascular variability and anxiety disorders (Thayer and Lane, 2000; Friedman, 2007). It outlines a central and peripheral network that integrates autonomic, attentional, and affective systems involved in emotion self-regulation. Within this homeodynamic view, healthy physiological variability involves the ability to adaptively react to environmental demands to maintain the stability of an organism. Anxiety disorders (and other affective disorders) are characterized by a rigid emotional response style with responses not reflecting environmental demands. More specifically, this rigid response style expresses as an inability to inhibit inappropriate anxious responses in non-threatening situations. HF-HRV predominantly represents the parasympathetic nervous system output of this integrated network and, thus, serves as an important index of the adaptability and regulatory ability of an organism, with decreased HF-HRV associated with less flexible responding to the environment. Thus, this model predicts that the rigid responding in anxiety disorders is associated with lower HRV.

In support, numerous studies demonstrated that relative to non-anxious controls, individuals with anxiety disorders evidence lower HF-HRV at rest or in response to anxiety stressors (Klein et al., 1995; Friedman and Thayer, 1998a, 1998b). This lower parasympathetic

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cardiac control has been especially found in PD (see Friedman, 2007). The smaller number of GAD and SAD studies demonstrate more mixed results, with some showing lower HF-HRV at rest or in response to anxiety-related provocation relative to non-anxious controls (Thayer et al., 1996, 2000; Grossman et al., 2001) and others showing no differences, particularly for SAD (Kollai and Kollai, 1992; Mauss et al., 2003). The sole published study examining HRV in obsessive–compulsive disorder (OCD) (Slaap et al., 2004) found no HRV differences between OCD and control patients. This study, however, also reported null findings on HRV differences between PD and control patients, contradicting much of the literature and suggesting that sample or other study-specific variables may account for the findings. Overall, findings regarding lower HRV at rest across anxiety disorders remained mixed.

Recent studies also demonstrated stronger HRV reactivity to certain stimuli or tasks in anxiety disorders. PD patients, for example, showed a larger decrease in HRV in response to panicogenic substances like sodium lactate or yohimbine (Yeragani et al., 1992, 1994), or a stronger increase in sympathetic-parasympathetic ratios after isoproterenol (Pohl and Yeragani, 2001). These elevated task-specific effects on HRV are also evident in other anxiety disorders. For example, similar effects were found for individuals with dental phobia when confronted with phobia-relevant stimuli (Johnsen et al., 2003), for PTSD patients during speech or mental arithmetics (Keary et al., 2009), or for general measures of anxiety (Shinba et al., 2008). Particularly within homeostatic approaches, differences between individuals with and without anxiety disorders in tonic and phasic HR have been investigated. Despite mixed findings, many studies demonstrate higher HR at baseline and in response to anxiety-related stressors among individuals with anxiety disorders controls (see Aikins and Craske, 2010). Thus, the rigid response style with little variability in anxiety disorders is not only observable as low tonic HRV (e.g., at rest or during relaxation), but also as an inadequate over-reactivity in HR and HRV to certain tasks and stimuli.

So far, most studies have focused on HF-HRV or HR differences among individuals with one anxiety disorder (versus controls) or have compared two anxiety disorder groups (Asmundson and Stein, 1994; Friedman and Thayer, 1998b). A notable exception investigated more than two anxiety disorders within a single sample, but did not investigate HF-HRV in response to anxiety-related provocation (Licht et al., 2009). While yielding important information, this narrow focus limits the capacity to examine HF-HRV and HR differences across the full spectrum of the anxiety disorders. Including a broader range of anxiety disorders would enable investigation of disorder-specific versus shared features of cardiac psychophysiology. A finding of similar features of cardiac psychophysiology across different nosological categories would favor a functional perspective of anxiety disorders (van Praag et al., 1990).

The present study, therefore, examined HF-HRV and HR differences among individuals with a DMS-IV (American Psychiatric Association, 2000) anxiety disorder at baseline and in response to two distinct anxiety-related experimental tasks, hyperventilation and relaxation. A recent finding might suggest that association between anxiety disorders and low HRV is accounted for by antidepressant medication use (Licht et al., 2009). This finding calls into question the theorized mechanism of HRV and HR abnormalities in anxiety disorders, and at the very least, suggests that analyses should account for different covariates like psychotropic medication use as well as comorbid mood disorders (Rottenberg, 2007). Therefore, we tested and controlled for the effects of psychotropic medication use and comorbid mood disorders, as well as the contributions of age, sex, and respiration, each of which can affect HRV (Grossman et al., 2001; Burriss et al., 2007; Rottenberg, 2007; Licht et al., 2009). In sum, the present study investigated the following questions: (1) Do patients with an anxiety disorder (all anxiety disorder patients combined) show lower HF-HRV or higher HR at resting baseline than a non-anxious control group (CG)?; (2) Are these differences evident across the different subdivided anxiety disorder groups (ADGs; PD, GAD, SAD, OCD)?; (3) Do anxiety disorder patients combined and the subdivided ADGs show lower HF-HRV responses and/or greater HR responses during the two anxiety-related tasks than the CG?; (4) Is lower HF-HRV and/or higher HR associated with higher symptom severity?; and (5) Are potential differences in HF-HRV and HR solely explained by relevant demographic variables (age, sex), differences in respiration (for HF-HRV) or certain clinical variables (comorbid mood disorder or psychotropic medication use)?

2. Materials and methods

2.1. Participants

The current study included 131 participants, including 82 treatment-seeking patients with a primary DSM-IV anxiety disorder and 39 non-anxious controls. The UCLA Internal Review Board approved all study procedures and all participants gave informed consent. Participants were originally recruited for a clinical trial study comparing cognitive behavioral and acceptance and commitment therapy (see Arch et al., 2012). Data presented herein reflect the pretreatment laboratory assessment. Table 1 shows the clinical and demographic characteristics of the CG and the ADGs. Anxiety disorder patients were diagnosed with the Anxiety Disorders Interview Schedule-IV (ADIS-IV; Brown et al., 1994). They were included if they met DSM-IV criteria for PD with or without agoraphobia, SAD, GAD, or OCD with a clinical severity rating (CSR) of four or higher. The CSR is an interviewer rating made on a 0 to 8 scale based on current symptom severity, distress, and disablement (0 = none, 2 = subclinical, 4 = clinically significant, 6 = moderately severe, 8 = most severe). Patients were stabilized on psychotropic medications for a minimum length of time (1 month for benzodiazepines and beta blockers, 3 months for heterocyclics and SSRIs/SNRIs) or medication free. Exclusion criteria for the ADGs included a history of psychiatric hospitalization in the last five years, active suicidal ideation, severe depression (clinical severity rating > 6 on ADIS-IV, see below), or a history of bipolar disorder, psychosis, mental retardation or organic brain damage. In all groups, individuals with substance abuse or dependence within the last 6 months, or with any severe diseases or pregnancy were excluded. CG participants were medication free and were administered the Mini International Neuropsychiatric Interview (MINI) for DSM-IV (Lecrubier et al., 1997; Sheehan et al., 1998) to rule out any mental disorders, including anxiety disorders (for further details see Arch et al., 2012).

If patients met criteria for multiple anxiety disorders, they were assigned to more than one ADG to increase statistical power. The number of patients with primary diagnosis and specific comorbidities in each subdivided ADG are shown in Table 2. Thus, the subdivided ADGs do not represent pure individual disorders, but rather subgroups of patients with shared symptomatology and different comorbidities. Due to the overlapping ADGs, each ADG was compared to the CG, but subdivided ADGs were not compared to one another. There were no significant differences between the CG and anxiety disorders patients combined, as well as any of the subdivided ADGs in age, all $ps > .16$, years of education, all $ps > .09$, sex ratio, all $ps > .29$, or ethnicity, all $ps > .08$.

2.2. Questionnaire battery

The following questionnaires were used to measure disorder-specific symptom severity: (a) the Anxiety Sensitivity Index (ASI; Reiss et al., 1986; Peterson and Reiss, 1992) was used as a panic-specific measure of severity, because it relates most strongly to panic symptoms; (b) the Penn State Worry Questionnaire (PSWQ; Meyer et al., 1990) was used as GAD-specific measure; (c) the revised Padua Inventory (Burns et al., 1996) was used to measure severity of obsessive and compulsive symptoms common in OCD; and (d) the Fear Questionnaire–Social Phobia Subscale (FQ-S; Marks and Mathews, 1979) was used as a SAD-specific measure of severity.

Table 1
Descriptive means and standard deviations for the specific disorder groups and healthy controls.

	Controls	All anxiety disorders	PD	GAD	SAD	OCD
N of females (%)	23 (58.97)	49 (55.1)	23 (58.97)	19 (65.51)	14 (56)	8 (47.06)
Age in years	34.83 (12.75)	36.75 (12.07)	34.93 (10.07)	38.37 (11.53)	35.96 (13.45)	40.17 (13.25)
Education in years	15.38 (1.62)	15.25 (2.28)	15.07 (2.06)	16.13 (2.43)	15.00 (2.28)	15.47 (1.54)
Ethnicity – White/European-American (%)	16 (41.0)	58 (65.2)	24 (61.5)	19 (65.5)	16 (61.5)	13 (76.5)
N with comorbid mood disorder (%)		21 (23.6)	8 (20.5)	9 (31.0)	8 (30.8)	4 (23.5)
N with current medication use (%)		45 (50.6)	24 (61.5)	15 (51.7)	11 (42.3)	11 (64.7)
SUDS after relaxation	6.02 (10.29)	27.06** (27.66)	29.23** (30.86)	33.15** (30.24)	26.76** (22.17)	37.00* (32.23)
SUDS after hyperventilation	18.23 (17.86)	40.69** (27.53)	49.84** (24.33)	35.84* (27.90)	38.92** (23.72)	40.00* (34.19)
Symptom measures						
ASI		30.85 (11.55)	34.08 (9.59)	30.00 (12.35)	30.81 (10.23)	27.50 (13.23)
PSWQ		47.14 (12.17)	45.99 (11.25)	51.53 (10.36)	50.21 (8.98)	53.78 (9.96)
FQ–S		13.56 (9.09)	11.11 (6.53)	14.17 (9.09)	20.76 (9.51)	15.33 (10.78)
PADUA		22.87 (18.22)	19.58 (11.06)	25.96 (20.40)	26.27 (21.77)	35.99 (24.13)

Note. Means (and standard deviations) for descriptive data and task responses for the disorder groups and healthy controls. PD = Panic Disorder; GAD = Generalized Anxiety Disorder; SAD = Social Anxiety Disorder; OCD = Obsessive–Compulsive Disorder; ASI = Anxiety Sensitivity Index; PSWQ = Penn State Worry Questionnaire; FQ–S = Fear Questionnaire–Social Phobia Subscale; PADUA = Padua Inventory; SUDS = Subjective Units of Distress; * = significant difference compared to healthy controls at $P<.05$; ** = significant difference compared to healthy controls at $P<.001$.

2.3. Baseline and experimental tasks

2.3.1. Baseline

A 5 min quiet sitting period at the beginning of the assessment was used to collect baseline HR and HF-HRV. These baseline data were used as the first interval (intercept) in the different HLM models to investigate baseline differences and change from baseline in the experimental tasks.[1]

2.3.2. Meditative relaxation task

Previous studies have found that requests to "relax" (perhaps due to the "letting go" of vigilance and control that are necessary to relax) can induce anxiety and panic responses in anxiety disorder patients (Heide and Borkovec, 1983, 1984; Craske et al., 2005). During the relaxation task, participants were told to silently and passively repeat a word ("ah-nam") for an unstated duration of 15 min. Following a brief practice period, participants reclined nearly horizontally in a comfortable chair, the lights were dimmed, and the experimenter left the room. After 15 min the experimenter reentered and participants rated their maximum subjective anxiety using Subjective Units of Distress (SUDS) ratings, in which participants were asked to rate their current anxiety level on a 0–100 scale (0 = no anxiety at all, 100 = most severe anxiety; Wolpe, 1990).

2.3.3. Hyperventilation task

During hyperventilation, participants were sitting and asked to breathe rapidly in pace with a metronome (set to 76 beats per min; for more details see Arch and Craske, 2010). Participants were told that this task was designed to measure their "respiratory efficiency or the efficiency of your breathing", and that they might experience physiological symptoms such as dizziness or shortness of breath. For continuous carbon dioxide (CO_2) output monitoring, participants wore a facemask attached to a Datex Model 200 infrared CO_2 analyzer. Before starting, the experimenter modeled proper hyperventilation breathing and participants practiced hyperventilating for 10 s. Participants then were asked to hyperventilate for an unrevealed duration of 60 s. If CO_2 levels did not drop at least 50% (about 20 mmhg) after the first 30 s, participants were instructed to breathe more rapidly. At the end, participants again rated their maximum subjective anxiety using SUDS ratings.

2.4. Physiological data recording and processing

All physiological data were recorded with a LifeShirt system (VivoMetrics), an ambulatory monitoring vest that is worn against the skin and collects ECG, respiration and posture data. The ECG was continuously recorded at a sampling rate of 250 Hz. Two Ag/AgCl disposable electrodes were attached under the right clavicle and the lowest rib on the left. An additional Ag/AgCl electrode was attached to the left clavicle and served as ground electrode. Respiration was collected by two embedded sensor bands around the participant's chest and abdomen.

For HR and HRV measures, cardiac R-wave detection was performed with VivoMetrics software. All relevant segments were visually inspected and corrected for false or undetected R-waves, movement artifacts, and ectopic beats. Inter-beat-intervals were calculated and transformed into beats per min for HR. HF-HRV was calculated as normative units of the spectral power density of HRV in the high frequency range of 0.15–0.40 Hz (see Camm et al., 1996) with fast Fourier transform (resample rate = 4 Hz, FFT window length = 512). Normative units were calculated as HF-HRV n.u. = 100*(HF absolute power/(total absolute power − very low frequency absolute power)). Here, total power was defined as the total power (area under the curve)

Table 2
Comorbidities in the subdivided anxiety disorder groups.

	PD	GAD	SAD	OCD
Total N	39	26	29	17
Patients with primary diagnosis	35 (89.74%)	18 (55.17%)	16 (69.23%)	14 (82.35%)
Without comorbid anxiety disorder	27 (69.23%)	9 (31.03%)	14 (53.85%)	8 (47.06%)
With comorbid anxiety disorder	8 (20.51%)	7 (24.14%)	4 (15.38%)	6 (35.29%)
Specific comorbidities with other groups[a]				
Comorbid PD		8 (30.77%)	1 (3.45%)	5 (29.41%)
Comorbid GAD	8 (20.51%)		10 (34.48%)	4 (23.53%)
Comorbid SAD	1 (2.56%)	10 (38.46%)		3 (17.65%)
Comorbid OCD	5 (12.82%)	4 (15.38%)	3 (10.34%)	

Note. Absolute (and relative compared to subgroup sample size) frequency of primary diagnosis and comorbidities within the single anxiety disorder subgroups. PD = Panic Disorder; GAD = Generalized Anxiety Disorder; SAD = Social Anxiety Disorder; OCD = Obsessive–Compulsive Disorder.

[a] The number of comorbid diagnosis is higher than the number of patients with comorbidities, because two patients were diagnosed with three anxiety disorders (PD, GAD, OCD and SAD, GAD, OCD).

[1] Further baseline data were collected at the end of the assessment for a subsample of the participants (55 ADG and 36 CG participants; due to missing data). No significant differences in HF-HRV between the different baselines were found for these subsamples (all $ps>.66$) and HLM analysis yielded similar results.

over all frequencies for the specified time range and very low frequency power as power in the frequency range of 0–0.003 Hz (Camm et al., 1996). For respiration, mean respiratory cycle time was extracted from the integrated respiration channel (combining chest and abdomen data) using VivoMetrics software. Scores for all physiological variables (HR, HF-HRV, and mean respiratory cycle time) were calculated for the 5 min baseline period, three 5 min intervals during the relaxation task, for two 30 s intervals during hyperventilation, as well as another 30 s interval immediately following hyperventilation.

2.5. Statistical analysis

Analyses were conducted in HLM 6.0 (Raudenbush et al., 2004) and SPSS 17.0 for Windows. Analyses aimed to investigate the questions outlined in the Introduction. To address Questions 1–3, a series of 2-level hierarchical linear growth curve models (HLMs; Raudenbush and Bryk, 2002) were used for each group comparison (1) all anxiety disorder patients combined versus the CG; (2) each subdivided disorder (PD, GAD, SAD, or OCD) versus the CG, with HR or HF-HRV as the dependent variable, Time as the repeated level-1 predictor, and Group as the level-2 predictor of interest. HLM analyses are particularly well-suited for the analysis of repeated psychophysiological data (e.g., Kristjansson et al., 2007), because they do not require independence of observations for repeated observations, utilize subjects with missing data, and produce lower Type I error rates than standard GLM procedures (Raudenbush and Bryk, 2002). Examination of the original data plots suggested the use of linear and quadratic time components to model HR outcomes, and linear components for HF-HRV outcomes. R^2 values were used as effect sizes and represent the proportion of variance explained by the Group variable; they were calculated by subtracting the variance obtained with the Group predictor from the variance obtained without the group predictor, and dividing by the latter (Raudenbush and Bryk, 2002).[2] For the relaxation task, repeated measures (i.e., Time on level-1) included the 5 min baseline and three 5 min relaxation task intervals to compare both baseline (y-intercept) and task response (slopes) between groups. For HR during hyperventilation, repeated measures included mean HR during baseline, the two 30 s hyperventilation intervals and one 30 s interval immediately after the hyperventilation. For HF-HRV during hyperventilation, we examined the two 30 s hyperventilation intervals and the 30 s interval immediately afterwards.

To address Question 4 (relationship between lower HF-HRV and/or increased HR and self-report symptoms), a series of linear regressions were conducted across all anxiety disorder patients with each symptom measure serving as the dependent variable. First, models were built to examine baseline HF-HRV. Second, an average across the three 5 min intervals was used for HF-HRV and HR during relaxation, because analyses yielded no significant change across the task. Third, separate analyses for both 30 s intervals of the hyperventilation were conducted, because analyses yielded a significant change across the task. Baseline HR was not tested due to missing differences between ADGs and CG (see below).

Finally, to address Question 5, age and sex were entered and maintained as covariates for intercept and slope within all HLMs. This was done to account for previous findings regarding the association of sex and age and cardiac measures and the small sample sizes in the subdivided ADGs, which might not provide sufficient power to detect significant effects of these variables.[3] We also investigated respiratory cycle time in all HF-HRV models to determine whether potential differences in respiration accounted for differences in HF-HRV between groups. Respiratory cycle time was used as a covariate for HF-HRV scores of the same interval (e.g., baseline respiratory cycle time was covaried in the baseline HF-HRV analysis). Finally, the influence of current psychotropic medication use (yes or no) and the presence of clinically significant mood disorders (yes or no) were tested in within-group ADG analyses only, because they were exclusion criteria for the CG and thus confounded with Group.

3. Results

3.1. Self-reported responses to the experimental tasks

SUDS responses to the experimental tasks, scores on the disorder specific questionnaires, and significant group differences between the ADGs and CG are summarized in Table 1. In comparison to the healthy controls, all ADGs showed significantly higher SUDS ratings following both relaxation and hyperventilation. Further, within the subdivided ADG, paired t-tests demonstrated significantly higher SUDS after hyperventilation than relaxation in the PD, $t\,(38) = 3.82$, $p < .001$, and SAD groups, $t\,(24) = 2.46$, $p = .022$, but not in the GAD or OCD groups, all $ps \geq .8$.

3.2. Differences in cardiovascular activity at baseline

The HLMs involving baseline HR did not show any significant differences between all anxiety disorder patients or the subdivided ADGs and CG, all $ps > .3$ with all $R^2 < .01$. The CG, however, evidenced significantly higher baseline HF-HRV than all anxiety disorders patients combined, $\beta = 7.96$, $t\,(110) = 2.93$, $p = .005$, $R^2 = .09$, as well as compared to the PD, $\beta = 8{:}65$, $t\,(70) = 2.86$, $p = .006$, $R^2 = .14$, SAD, $\beta = 7.32$, $t\,(57) = 2.00$, $p = .05$, $R^2 = .06$, and OCD groups, $\beta = 7.54$, $t\,(49) = 2.01$, $p = .05$, $R^2 = .08$, and marginally higher HF-HRV than the GAD group, $\beta = 6.52$, $t\,(61) = 1.88$, $p = .064$, $R^2 = .06$ (see Fig. 1).[4]

3.3. Responses to the relaxation task

Analysis for HR change during relaxation yielded an overall linear decrease in HR and an overall positive curvilinear change across groups for all comparisons, all $ps < .001$, indicating decreasing HR across groups during relaxation. However, there were no significant differences in HR change during relaxation between all anxiety disorders patients combined or any of the subdivided ADGs and CG, all $ps > .3$ with all $R^2 < .01$. Although baseline differences in HF-HRV were maintained or slightly increased during the relaxation task for some comparisons, as shown in Fig. 1, there were no significant group differences in HF-HRV change between the subdivided ADGs and CG, all $ps > .65$ with all $R^2 < .01$. In addition, analysis did not yield a significant overall change across groups, all $ps > .15$, indicating that relaxation had no main task effect on HF-HRV.

[2] R^2 values were separately calculated for both HLM intercept and linear slope.

[3] Power analyses, conducted in Optimal Design (Raudenbush and Liu, 2000), indicated that our sample size was sufficient to detect large and medium differences between all anxiety disorder patients compared to the CG, but medium power (43%–56%) for smaller comparisons of subdivided diagnostic groups to the CG.

[4] For comparison, non-normalized, mean absolute power of HRV in the high frequency range transformed in natural logarithmic units (Ln[HF-HRV absolute power]) during baseline were: (1) for the control group: $M = 6.03$, $SD = 1.12$; (2) for all anxiety disorders patients combined: $M = 5.22$, $SD = 1.49$; (3) for the PD group: $M = 5.27$, $SD = 1.41$; (4) for the GAD group: $M = 5.26$, $SD = 1.49$; (5) for the SAD group: $M = 5.40$, $SD = 1.53$; 6) for the OCD group: $M = 4.96$, $SD = 1.33$.

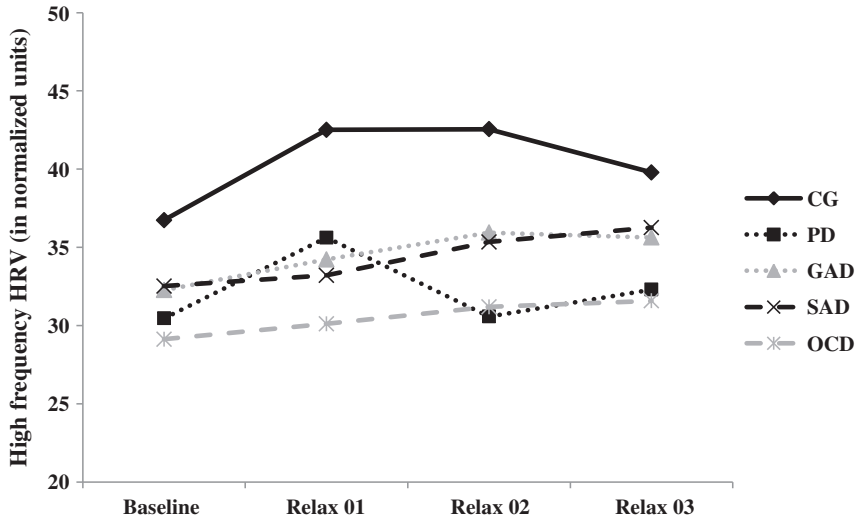

Fig. 1. Normalized high frequency heart rate variability (HRV-HF n.u.) during baseline and relaxation (three 5 min intervals; Relax 01–Relax 03). HF-HRV n.u. = 100*(HF absolute power/(Total absolute power- very low frequency absolute power)). PD = Panic Disorder; GAD = Generalized Anxiety Disorder; SAD = Social Anxiety Disorder; OCD = Obsessive–Compulsive Disorder; CG = Control Group.

3.4. Responses to the hyperventilation task.

Analyses of CO_2 levels verified proper hyperventilation as indicated by a drop in CO_2 levels of at least 50%.[5] HR during hyperventilation intervals is shown in Fig. 2. Lower linear increase in HR during hyperventilation compared to the CG were found for all anxiety disorders patients combined, as well as PD and GAD patients; all anxiety disorders patients combined, $\beta = -6.41$, $t\ (121) = -2.10$, $p = .037$, $R^2 = .04$; PD, $\beta = -8.93$, $t\ (71) = -2.37$, $p = .021$, $R^2 = .08$; GAD patients, $\beta = -7.62$, $t\ (61) = -2.12$, $p = .038$, $R^2 = .06$. Similarly, these groups yielded an increased curvilinear HR change during hyperventilation; all anxiety disorders patients combined, $\beta = 2.09$, $t\ (121) = 2.23$, $p = .028$, $R^2 = .05$; PD, $\beta = 3.01$, $t\ (71) = 2.56$, $p = .013$, $R^2 = .10$; GAD, $\beta = 2.19$, $t\ (61) = 1.99$, $p = .049$, $R^2 = .05$. Together, these results indicate a steeper HR increase during hyperventilation and correspondingly steeper decrease in recovery for all anxiety disorders patients combined and specifically PD and GAD patients. No significant differences were found for SAD and OCD patients, all $ps > .27$ with all $R^2 < .01$.

HF-HRV during hyperventilation is shown in Fig. 3. Significantly lower HF-HRV during the first 30 s of hyperventilation than the CG was found in all anxiety disorders patients combined, as well as PD and OCD patients; all anxiety disorders patients combined, $\beta = 6.02$, $t\ (113) = 2.01$, $p = .046$, $R^2 = .06$; PD, $\beta = 7.53$, $t\ (67) = 2.18$, $p = .033$, $R^2 = .20$; OCD patients, $\beta = 8.55$, $t\ (47) = 2.66$, $p = .011$, $R^2 = .12$. In GAD, there was no significant lower HF-HRV during this interval although the group factor accounted for 6% of the variance, $\beta = 4.65$, $t\ (60) = 1.27$, $p = .209$, $R^2 = .06$. This might have been caused by the small sample size. No group differences during the first interval were found for SAD, $\beta = 5.18$, $t\ (56) = 1.34$, $p = .186$, $R^2 = .02$. In addition, no group differences for change across hyperventilation were found for any comparison, all $ps > .19$ with all $R^2 < .01$.

3.5. Association between cardiovascular activity and symptom severity

No significant relationships were found between cardiovascular measures and disorder-specific symptom measures across all anxiety disorders patients combined, all $ps \geq .10$ with all $R^2 < .037$. In the GAD group, baseline HF-HRV was predicted by PSWQ scores, $\beta = -.42$, $t\ (23) = -2.18$, $p = .040$, $R^2 = .178$, with lower baseline HF-HRV associated with higher PSWQ scores. No other significant relationships were found within the subdivided ADGs for the disorder specific symptom measures, all $ps \geq .16$ with all $R^2 < .062$.

3.6. Associations of demographic and clinical variables on HF-HRV and HR outcomes

Higher age significantly predicted lower baseline HF-HRV in all models , except in the comparison between SAD and CG; all anxiety disorders patients combined, $\beta = -0.30$, $t\ (110) = -2.69$, $p = .009$; PD, $\beta = -0.44$, $t\ (70) = -3.39$, $p = .001$; GAD, $\beta = -0.43$, $t\ (61) = -3.32$, $p = .002$; SAD, $\beta = -0.15$, $t\ (57) = -0.80$, $p = .425$; OCD, $\beta = -0.45$, $t\ (49) = -3.33$, $p = .002$. In addition, higher age significantly predicted lower linear, but greater curvilinear HR change during hyperventilation in the comparison between the CG and all anxiety disorders patients combined, linear, $\beta = -0.42$, $t\ (121) = -3.78$, $p < .001$; curvilinear, $\beta = 0.13$, $t\ (121) = 3.87$, $p < .001$; as well as for PD, linear, $\beta = -0.33$, $t\ (71) = -2.06$, $p = .043$; curvilinear, $\beta = 0.11$, $t\ (71) = 2.22$, $p = .029$; and SAD, linear, $\beta = -0.35$, $t\ (58) = -2.37$, $p = .021$; curvilinear, $\beta = 0.11$, $t\ (58) = 2.36$, $p = .022$. No other significant effects regarding age were found, all $ps \geq .10$.

Sex was also a significant covariate of baseline HF-HRV in all models, with female participants demonstrating higher HF-HRV, except in the comparison between GAD and CG; all anxiety disorders patients combined, $\beta = 10.202$, $t\ (110) = 3.94$, $p < .001$; PD, $\beta = 9.61$, $t\ (70) = 3.25$, $p = .002$; GAD, $\beta = 6.14$, $t\ (61) = 1.77$, $p = .081$; SAD, $\beta = 12.13$, $t\ (57) = 3.14$, $p = .003$; OCD, $\beta = 8.28$, $t\ (49) = 2.34$, $p = .023$. No other significant effects regarding sex were found, all $ps \geq .09$.

Across all anxiety disorders patients combined, the use of psychotropic medication had no effect on baseline HF-HRV, $\beta = -.046$, $t\ (81) = -1.46$, $p = .147$, $R^2 = .02$, change across the relaxation task,

[5] In the current sample, CO_2 levels at pre-hyperventilation were $M = 34.74$ ($SD = 4.19$) in the PD group, $M = 36.25$ ($SD = 2.85$) in the GAD group, $M = 34.38$ ($SD = 3.76$) in the SAD group, $M = 34.27$ ($SD = 4.74$) in the OCD group, and $M = 36.82$ ($SD = 3.34$) in the CG. CO_2 levels after hyperventilation were $M = 11.00$ ($SD = 6.03$) in the PD group, $M = 8.29$ ($SD = 4.07$) in the GAD group, $M = 9.00$ ($SD = 4.01$) in the SAD group, $M = 10.80$ ($SD = 6.63$) in the OCD group, and $M = 8.53$ ($SD = 4.06$) in the CG. As expected, all groups showed a >50% reduction in CO_2 levels, all $ts > 10.20$, all $ps < .001$. Interestingly, all anxiety disorder patients combined, $t\ (107) = -2.32$, $p = .022$, as well as the PD, $t\ (67) = -2.29$, $p = .025$, the SAD, $t\ (57) = -2.57$, $p = .013$, and the OCD group, $t\ (51) = -2.22$, $p = .031$, but not the GAD group, $t\ (60) = -0.69$, $p = .495$,showed significantly lower CO_2 levels before the hyperventilation trial than the CG. In addition, the PD group showed a significantly higher CO_2 level after hyperventilation than the CG, $t\ (67) = 2.03$, $p = .046$.

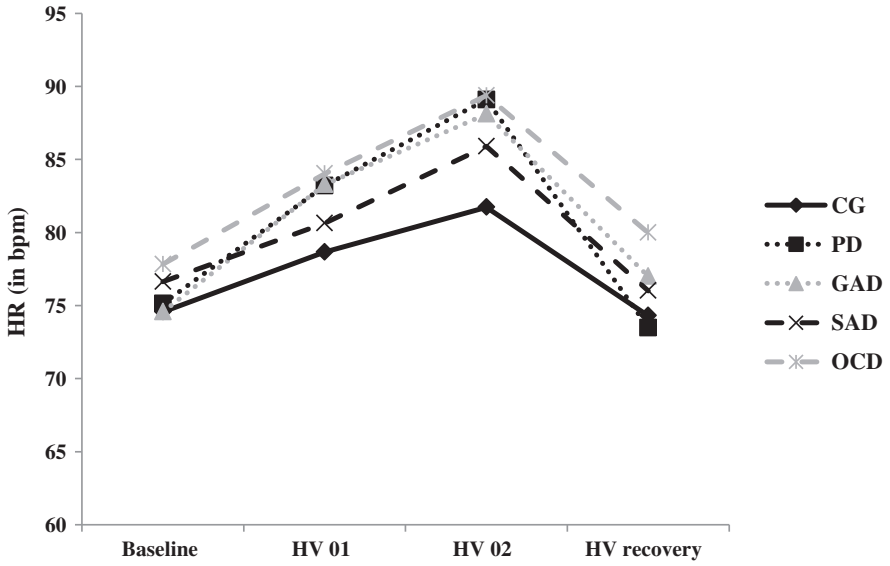

Fig. 2. Heart rate in beats per min (bpm) during baseline and hyperventilation (three 30 s intervals). HV 01/02 = first/second 30 s interval of hyperventilation; HV recovery = 30 s interval immediately after hyperventilation; PD = Panic Disorder; GAD = Generalized Anxiety Disorder; SAD = Social Anxiety Disorder; OCD = Obsessive–Compulsive Disorder; CG = Control Group.

$\beta = -.016$, $t\,(81) = -1.42$, $p = .147$, $R^2 = .03$, or across hyperventilation, $\beta = -.001$, $t\,(79) = -0.21$, $p = .834$, $R^2 < .01$. Within the subdivided ADGs, the influence of current psychotropic medication use on baseline HF-HRV was significant only in the OCD group, with lower HF-HRV for OCD patients currently taking medication, $\beta = -0.18$, $t\,(15) = -3.29$, $p = .005$, $R^2 = .49$. To clarify whether differences between the OCD group and the CG in baseline HF-HRV were fully due to use of psychotropic medication, the corresponding HLM was conducted again with OCD patients not currently using medication only (n = 6). No significant differences between these patients and the CG were found, $\beta = .002$, $t\,(38) = 0.03$, $p = .980$. Medication use had no further significant effects on baseline HRV-HF or change across the relaxation task for any ADG, all $ps \geq .1$ with all $R^2 < .02$.

Furthermore, across all anxiety disorders patients combined, the presence of a comorbid mood disorder had no effect on baseline HF-HRV, $\beta = -.018$, $t\,(81) = -0.44$, $p = .660$, $R^2 < .01$, change across the relaxation task, $\beta = .014$, $t\,(81) = 1.40$, $p = .166$, $R^2 = .01$, but a trend to predict a diminished change across hyperventilation for patients without comorbid mood disorder, $\beta = -.055$, $t\,(76) = -1.97$, $p = .052$, $R^2 = .18$. In the subdivided ADGs, presence of a comorbid mood disorder predicted linear HRV-HF change during relaxation in the PD group, $\beta = 0.03$, $t\,(35) = 2.37$, $p = .023$, $R^2 = .68$, such that PD patients with a comorbid mood disorder showed a diminished linear increase in HF-HRV during the relaxation task relative to PD patients without a comorbid mood disorder, despite a lack of baseline HF-HRV differences for this covariate, $\beta = 0.01$, $t\,(35) = 0.08$, $p = .941$, $R^2 < .01$. Comorbid mood disorder did not significantly affect HRV-HF in the other subdivided ADGs or across all anxiety disorder patients, all $ps \geq .098$ with all $R^2 < 2\%$.

Finally, descriptive data for respiratory cycle time are shown in Table 3. In general, the ADGs tended to yield longer respiratory cycle times (i.e., less breaths per min) than the CG, except for the

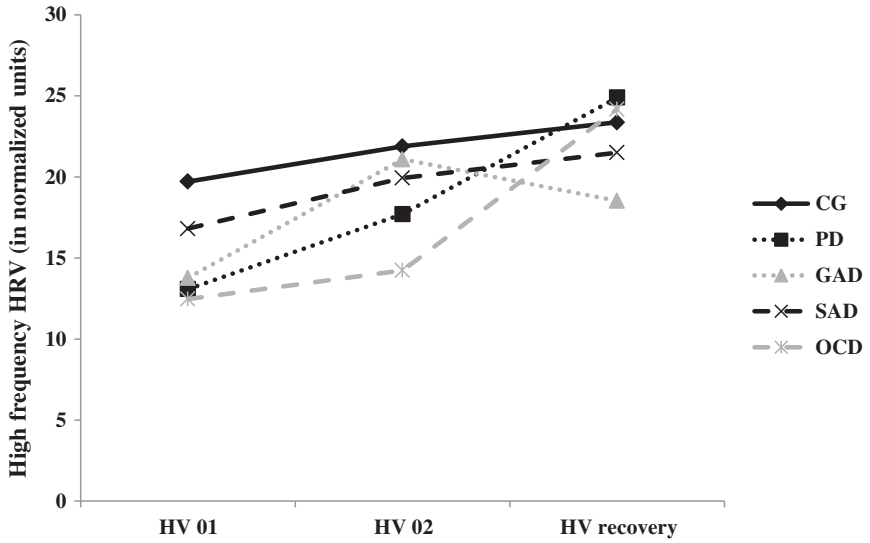

Fig. 3. Normalized high frequency heart rate variability (HRV-HF n.u.) during and immediately after hyperventilation (three 30 s intervals). HF-HRV n.u. = 100*(HF absolute power/(total absolute power − very low frequency absolute power)). HV 01/02 = first/second 30 s interval of hyperventilation; HV recovery = 30 s interval immediately after hyperventilation; PD = Panic Disorder; GAD = Generalized Anxiety Disorder; SAD = Social Anxiety Disorder; OCD = Obsessive–Compulsive Disorder; CG = Control Group.

Table 3
Means and standard deviations for mean total respiratory cycle time.

	Controls	All anxiety disorders	PD	GAD	SAD	OCD
Baseline	3.63 (0.68)	3.89 (0.97)	3.91 (1.10)	4.14* (1.04)	4.03 (0.97)	3.59 (0.71)
Relaxation						
0–5 min	4.70 (1.41)	4.89 (2.01)	5.32 (2.43)	5.26 (2.70)	4.72 (1.32)	4.64 (1.61)
5–10 min	4.23 (1.10)	4.94 (2.59)	5.48 (3.51)	5.39 (3.91)	4.60 (1.08)	4.61 (1.52)
10–15 min	4.21 (0.85)	4.72 (2.04)	4.91 (2.35)	5.10 (2.69)	4.56 (1.33)	4.44 (1.53)
Hyperventilation						
Hyperventilation (60 s)	1.03 (0.33)	1.05 (0.37)	1.11 (0.47)	1.04 (0.24)	1.06 (0.32)	0.88* (0.08)
30 s after Hyperventilation	5.17 (4.06)	4.08 (1.53)	4.05 (1.02)	3.92 (1.17)	3.86 (1.23)	4.08 (1.48)

Note. Means (and standard deviations) for mean total respiratory cycle time, with Breaths per min = 60/total respiratory cycle time. PD = Panic Disorder; GAD = Generalized Anxiety Disorder; SAD = Social Anxiety Disorder; OCD = Obsessive–Compulsive Disorder; * = significant difference compared to healthy controls at P<.05.

hyperventilation intervals.[6] In addition, respiratory cycle time did not account for significant group differences in the different HLM models.[7]

4. Discussion

The present study investigated whether patients with anxiety disorders in general, as well as subdivided disorder groups (PD, GAD, SAD, and OCD) differed significantly in HRV and HR at baseline and in response to hyperventilation and relaxation tasks, relative to a matched healthy control group.

4.1. Heart rate variability during baseline

At baseline, all anxiety disorder patients combined showed significantly lower HRV than the healthy participants, even after accounting for age and sex. This effect was especially pronounced in the PD group, which is consistent with past research (Yeragani et al., 1990; Klein et al., 1995; Friedman and Thayer, 1998b). Smaller effect sizes for GAD, and SAD, supported more modest diminished HRV within these disorders. The finding of lower HRV in the OCD group provided first evidence that OCD might also be associated with diminished HRV. For all groups, respiratory cycle time and comorbid depression did not account for these group differences in HRV. Further analyses, however, suggested that lower HRV in OCD patients might be related to the use of psychotropic medication. Given the small OCD subgroup (total n = 17, and only 6 OCD patients without current medication use), larger OCD samples are clearly needed to reexamine these effects. Psychotropic medication use, however, did not show a significant effect on HRV across all anxiety disorders patients combined or within the other subdivided ADGs. This is consistent with recent studies (e.g., Kemp et al., 2010), but contrasts with a larger study reporting that the use of medication solely accounted for differences in HRV between anxiety disorder patients and healthy individuals (Licht et al., 2009). One possible explanation might be that Licht et al. (2009) analyzed a supine resting baseline which differed in length across participants and included repeated, potentially stressful blood pressure measures. Thus, the baseline was neither recorded at rest nor standardized in time. This is problematic in that HRV measures tend to increase with longer analysis intervals and different interval lengths can bias HRV scores (Berntson et al., 1997). In contrast, the present study used a standardized 5 min sitting baseline, which was identical in length, sitting body position, location, and activity level for all participants. In sum, given the independence from the different control variables, our finding supports the notion that autonomic inflexibility per se (Friedman, 2007) accounts for diminished HRV in anxiety disorders.

Theoretically, the results are consistent with the neurovisceral model of cardiac and emotion (dys-) regulation (Thayer and Lane, 2000; Friedman, 2007). In this model, anxiety disorders are characterized by an impaired ability to flexibly generate emotional responses that are appropriate for current internal and environmental conditions. One proposed similarity across anxiety disorders (and others that might be characterized by low HRV), therefore, are deficits in inhibitory processes emerging from prefrontal cortex areas, which can be seen in different symptoms common across anxiety disorders. For example, attentional biases like hypervigilance to threat can be found in all anxiety disorders (Bar-Haim et al., 2007). These deficits in inhibiting unadaptive attentional responses have been linked to low HRV (Park et al., 2012) and the underlying neurovisceral network (Thayer and Lane, 2000). A similar role of inhibitory processes has recently been proposed for fear conditioning (Davis et al., 2000). Thus, low HRV might serve as an index variable of potential deficits in inhibitory processes that are common to different anxiety disorders and other forms of psychopathology.

These underlying dysfunctions can be interpreted within a functional view of psychopathology (van Praag et al., 1990). Instead of differentiating anxiety disorders into discrete nosological categories which can be separated by their unique symptomatology, a functional approach promotes viewing each disorder as a combination of underlying psychological dysfunctions, such as deficits in inhibitory processes. Shared underlying dysfunctions across anxiety disorders, which are associated with lower HRV, might help explain the mixed results regarding the association between cardiac measures and subjective symptom severity. In GAD, lower baseline HRV was associated with pronounced worrying, indicating a concordance between self-reported symptoms and cardiac measures in GAD. However, HRV was not concordant with symptom severity among the other disorders or any symptom measure within all patients combined. This reflects a decoupling of HRV and self-reported anxiety disorder symptoms, which has previously been reported (e.g., Mauss et al., 2004, 2005). This might suggest that potentially shared underlying dysfunctions, as indexed by low HRV across anxiety disorders, can manifest in different subjective symptoms of anxiety across different individuals.

The functional perspective also connects to the issue of comorbidity in the current sample. Patients were included in multiple ADGs if they met DSM-IV criteria for more than one anxiety disorder. Our findings are, therefore, limited in that no pure single disorders were

[6] During baseline, the GAD group showed a significantly higher mean respiratory cycle time than the CG, t (66) = 2.35, p = .023. During hyperventilation, the OCD group showed significantly slower cycle times than the CG, t (52) = −2.69, p = .010. No other significant differences were found, all $ps \geq .08$.

[7] Across all anxiety disorder patients, respiratory cycle time had no effect on baseline HF-HRV, $\beta = -.001$, t (109) = −0.76, p = .448, or across hyperventilation, $\beta = -.002$, t (113) = −1.19, p = .235. However, mean respiratory cycle time during relaxation showed a significant effect on linear HF-HRV change during relaxation across all anxiety disorder patients, $\beta = 2.06$, t (109) = −4.34, p<.001.Within the subdivided ADGs, mean respiratory cycle time during hyperventilation yielded a significant effect on linear HF-HRV change for the PD group only, $\beta = -0.041$, t (68) = −2.289, p = .025. No other significant effects of respiratory cycle time were found, all $ps \geq .17$.

investigated. The results for the subdivided disorder groups might be biased by the number of overlapping comorbid disorders, rather than indicating disorder-specific results. This might especially be true for our findings in the GAD group as this group included only 55% of patients with primary GAD. Recent research, however, found similar results for GAD samples (e.g., Thayer et al., 1996). Also, in that anxiety disorders are characterized by significant comorbidity with other anxiety disorders (Kessler et al., 2005), our approach is ecologically valid and obtaining single DSM-IV disorder, non-overlapping samples might be quite challenging and unrepresentative of actual patients. Thus, although the present study cannot be completely separated from issues related to comorbidity, a functional view on similarities between different nosological disorders might actually help to understand the high rates of comorbidity in anxiety disorders. Low HRV and related deficits in inhibitory or other neural processes might represent such a shared psychological dysfunction in anxiety disorders.

4.2. Cardiovascular responses during relaxation

In general, the relaxation task only showed minimal cardiac effects across all groups with no main effect on HRV. The differences in baseline HRV were maintained but did not increase during the relaxation task. These results support a recent finding of a significant HRV difference between GAD patients and healthy controls at baseline that carried over but did not increase during relaxation (Thayer et al., 1996). Similarly to HRV, HR during relaxation did not differ between groups. For self-reported anxiety following relaxation, however, the ADGs reported moderate levels of anxiety that were significantly higher than those of healthy participants. Anxiety induction in the relaxation tasks, therefore, appeared too weak to cause a significant shift in cardiac responding, but still caused moderate subjective anxiety. These findings support the notion of a desynchrony of cardiac and self-reported responses, which is assumed be more evident during relatively mild levels of anxiety or fear (Hodgson and Rachman, 1974; Rachman and Hodgson, 1974; Lang, 1979). Thus, results suggest a decoupling of self-reported anxiety and cardiac responses during induced relaxation in anxiety disorder patients.

4.3. Cardiovascular responses during hyperventilation

During hyperventilation, the combined anxiety disorder group showed lower HRV during the first 30 s. Within the subdivided disorder groups, however, only PD and OCD patients showed this initial diminished HRV. These effects were independent of age, sex, and use of medication. Thus, anxiety disorder status and specifically the presence of PD and OCD predicted a brief, 30 s period of diminished HRV during hyperventilation, which, however, did not endure for the remainder of hyperventilation or recovery. Considering the significance of medication use for baseline HRV and the small sample size for OCD, however, the OCD results should be interpreted cautiously.

In addition, all anxiety disorder patients combined yielded elevated HR responses compared to healthy participants. Specifically, the PD and GAD groups showed significantly greater HR responses to hyperventilation. OCD patients showed a similar pattern of HR responding, with lack of significance likely due to its smaller group size. The SAD group did not differ from healthy participants, suggesting that the task did not possess the same anxiety-related significance for this group. These findings are consistent with a disorder-specific relevance of hyperventilation. Hyperventilation is known to evoke sensations similar to panic attacks, and, thus, should be most aversive for PD patients (e.g., Ley, 1985, 2005). Although GAD and OCD patients in part demonstrated similar response patterns to hyperventilation, HR and HRV responses were most pronounced in PD. The subjective anxiety ratings and post-hyperventilation CO_2 levels further supported this view. Thus, our findings are in line with a disorder-specific task relevance of the hyperventilation task.

Previous studies have found similar differences in self-reported anxiety, but a lack of differences in physiological responding during hyperventilation. For example, Asmundson and Stein (1994) did not find any differences in HR or RSA between healthy controls and PD or SAD patients during hyperventilation; Wollburg et al. (2008) replicated this null finding in PD and control patients for respiratory parameters. However, hyperventilation in the present study was significantly more intense, with a mean respiration rate of approximately 60 breaths per min (versus 20 in Asmundson and Stein, 1994) and a mean CO_2 level of approximately 9–10 mmgh (versus 20–25 in Wollburg et al., 2008). Overall, the results suggest that hyperventilation must be sufficiently intense for anxiety disorder-related group differences to emerge.

4.4. Limitations

Further limitations to the study should be noted. First, we did not control for respiration volume in the HRV analyses as recommended (e.g., Grossman and Taylor, 2007), although we did examine respiratory cycle time. Thus, HRV results cannot be interpreted as direct measures of vagal tone. However, the main focus of the present study was to test differences in HRV to distinguish individuals with and without clinically severe anxiety disorders. Second, our ECG sampling rate (250 Hz) was below the current recommended standards for HRV analysis (e.g., 500–1000 Hz; Berntson et al., 1997). However, different authors suggested that a rate of 250 Hz is sufficient for normal ECGs of human adults, like in our sample (see Berntson et al., 1997). Third, additional factors have been found to influence HRV, including physical diseases, physical activity levels, cardiovascular problems, smoking, alcohol use, or body mass index (see Licht et al., 2009; Rottenberg, 2007). Individuals with serious or chronic diseases, including cardiac diseases, as well as substance abuse and dependence were excluded; however, we did not assess body mass index, physical activity, minor alcohol use and smoking. Although these factors have been found to influence RSA, controlling for these factors did not significantly change the relations between anxiety disorder status and RSA (Licht et al., 2009). Nevertheless, future studies should control for these factors. Fourth, although participants were upright during baseline and hyperventilation, participants were reclined nearly horizontally during the relaxation task. This change in body posture might have caused a reduction in HRV during relaxation, which may have resulted in the lack of a significant main task effect for HRV during this task. However, this cannot account for the reported group differences as procedures were identical for all participants.

4.5. Conclusion

The present results suggest that even after accounting for age, sex, respiratory cycle time and psychotropic medication use, diminished baseline HRV was demonstrated strongly in PD, and to a lesser degree in GAD and SAD. Our findings suggest that diminished HRV represents a shared feature of these anxiety disorders with disorder-specific intensity of expression and may serve as an index for deficits in anxiety related inhibitory processes.

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