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The Effects of Psychosocial Stress on Heart Rate Variability in Panic Disorder

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Abstract

Background: Since panic is characterized by stress-induced autonomic cardiac sensations, such as increased heart rate and palpitations, effects of experimental psycho-social stress on heart rate variability are of interest.
Methods: 25 patients with a current panic disorder and 25 healthy controls matched by age and sex underwent the Trier Social Stress Test on two consecutive days. Heart rate and heart rate variability (HRV) were assessed before and during test performance as well as under recovery conditions.
Results: An increase of heart rate was observed in both patients suffering from panic disorder and in healthy controls under conditions of experimental psycho-social stress. Root mean square successive differences (RMSSD), a time domain parameter of HRV, was decreased in both groups of participants during the stress conditions. Low frequency/high frequency ratio (LF/HF), a frequency domain parameter of HRV, was found increased in patients with panic disorder when performing the Trier Social Stress Test whereas no such change was found in healthy controls.
Conclusions: Induction of psychosocial stress increases heart rate and impairs heart rate variability. The latter effect reflects activation of the sympathetic and/or inhibition of the parasympathetic autonomous nervous system (ANS) that is more pronounced in patients suffering from panic disorder than in healthy controls (German J Psychiatry 2010; 13 (2): 66-73).

Keywords: heart rate, psychological stress, sympathetic nervous system, parasympathetic nervous system, panic disorder

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Introduction

Panic disorder (PD) is characterized by suddenly occurring panic attacks. Palpitations and tachycardia are the most common symptoms of such attacks (Birkhofer et al., 2005). PD has been recognized as being associated with an enhanced risk of coronary artery disease for which the reason is not known (Gomez-Caminero et al., 2005). Alvarenga and colleagues indicate the range of cardiac complications during panic attacks in patients with PD: triggered cardiac arrhythmias, recurrent emergency room attendencies with angina and electrographic changes of ischemia, and coronary artery spasms, in some cases complicated by coronary thrombosis and myocardial infarction (Alvarenga et al. 2006). Autonomic dysbalance and impaired physical fitness have been suggested to be closely associated with PD (Asmundson, 1994; Ito et al., 1999). Since panic attacks are perceived as a severe psycho-social stressor (Larson et al., 1991; Sive, 1991), the functioning of autonomous neurocardiac control under conditions of psychosocial stress may

give insight in the pathophysiological link between PD and an increased cardiac risk.

Loss of normal autonomic nervous system control of heart rate and cardiac rhythm is an important risk factor for adverse cardiovascular events. For example, after myocardial infarction, reduction in heart rate variability, a measure of cardiac autonomic innervation by the brain, is a strong predictor of sudden death and cardiac arrhythmias (Bigger et al., 1992).

Heart rate normally varies on a beat-to-beat basis principally because of parasympathetic innervation to the heart, transmitted from the brain by the vagus nerve. With the loss of vagal innervation, as occurs in patients with severe neuropathy and heart transplant recipients, there is a marked attenuation of the heart rate variability. It is speculated that such reductions in parasympathetic innervation leave the heart exposed to unopposed stimulation by the sympathetic nervous system. This makes the heart vulnerable to arrhythmia and sudden death and also accelerates the development of atherosclerotic coronary artery disease (Bigger et al., 1992; Van Ravenswaaij-Arts et al., 1993).

It has been demonstrated that patients suffering from PD have impaired heart rate variability (Middleton, 1995; Yeragani et al., 1993). Enhanced sympathetic outflow to the heart can trigger ventricular arrhythmias and sudden death most likely in patients with heart failure (Kaye et al., 1995; Meredith et al., 1991). Natural catastrophes such as earthquakes may increase the risk of fatal myocardial ischemia and cardiac arrhythmias due to the influence of an increased cardiac sympathetic outflow to the heart occurring with acute mental challenges (Esler et al., 1989; Lucini et al., 2005). Sympathetic nervous activation has been demonstrated during panic attacks by means of direct sympathetic nerve recording (Alvarenga et al., 2006; Wilkinson et al., 1998). Circulatory monitoring methods such as the measurement of low-frequency (LF) heart rate spectral power may be used to indirectly measure cardiac sympathetic activity (Axselrod et al., 1985).

In the present study we aimed to assess time and frequency domain parameters of HRV including LF component spectral power in patients with PD and in healthy controls when performing a standardized stress task. The hypothesis was that the patients with PD would show an impaired heart rate variability compared to the healthy individuals. Furthermore, the indirect measurement of the cardiac sympathetic activity (the low-frequency (LF) heart rate spectral power) may also reveal differences in the cardiac sympathetic activity between patients with PD as well as the healthy individuals.

Table 1: Sample description concerning matching criteria

	Panic Disorder Patients	Healthy Controls	
Total, N	25	25	
Female, n (%)	15 (60.0)	15 (60.0)	
Age, M (SD)	32.2 (10.03)	32.4 (10.13)	p = .94*
BMI, M (SD)	23.5 (3.4)	22.3 (3.5)	p = .18*
Smokers, n (%)	5 (20.0)	9 (36.0)	p = .35#
Contraceptives, n (% of females)	7 (46.7)	5 (33.3)	p = .71#
Psychopharmacological drugs, n (%)	11 (55.0)	0 (0)	

* t-test; # Fisher's exact test; n = Sample Size; M = mean; SD = Standard Deviation; BMI = Body Mass Index

Materials and Methods

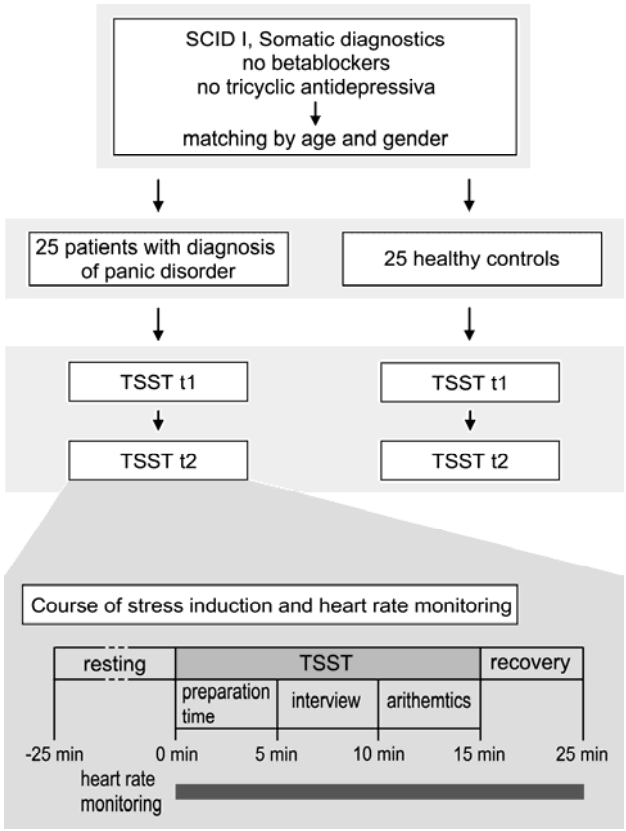
Participants and study design

25 patients with a main diagnosis of PD with or without agoraphobia confirmed by the Structured Clinical Interview (SCID) for DSM-IV (Spitzer et al., 1990; Wittchen, 1990) were included. The SCID was performed by an approved rater. Patients treated with tricyclic antidepressants and/ or beta-blockers and those receiving psychotherapy were excluded. Further, patients suffering from hypertension and/or diabetes were excluded.

Thus, the patient sample consisted of N = 25 patients with a current diagnosis of panic disorder. 18 of them had a diagnosis of PD with agoraphobia and seven of them had a diagnosis of PD without agoraphobia. Hereby, 14 patients exclusively showed a panic disorder and 11 a panic disorder with a comorbid diagnosis of depression. The patient's characteristics are described in Table 1. The 15 female and ten male patients were in average 32.19 years old (SD = 10.03). The mean age at the onset of panic disorder was 25.70 (SD = 8.19) years of age, and the mean duration of the panic disorder was 5.46 (SD = 10.86) years. According to the Panic and Agoraphobia-Scale (PAS) (Bandelow, 1979) the average range of the patient-rated PAS total score was rated as moderate (M = 19.22, SD = 10.34). The scale ranges from 0 to 52. Of the 25 patients, 11 were on psychopharmacological drugs at the time of testing [including one taking multiple medications: selective serotonin reuptake inhibitors (SSRIs) (n = 5), serotonin norepinephrine reuptake inhibitors (SNRIs) (n = 2), tetracyclic antidepressants (n = 2) and phytosedatives (n = 3)].

Additionally, 25 healthy subjects matched for age and sex were investigated. For the matching the age was allowed to

Figure 1: Flow-Chart: procedure of the TSST



SCID = Structured Clinical Interview for DSM IV; TSST = Trier Social Stress Test; t1 = day 1; t2 = day 2

vary two standard deviations between the matched pairs. The 15 female and ten male patients were in average 32.42 years old (SD = 10.13). The participants were included after their medical history and physical examination was taken.

Patients were recruited from the Clinic for Psychotherapy and Psychosomatic Medicine of the University Hospital of Dresden, Germany. Subjects were recruited by means of newspaper advertisements.

Participants received the evaluations and experimental treatment at no cost and without other inducements. Written informed consent from the participants and approval from the University Hospital Ethics Committee (Dresden, Germany) were obtained.

All of the participants were scheduled for the standardized Trier Social Stress Test (TSST) and measurements of heart rate (HR) and heart rate variability (HRV) on two consecutive days (t1, t2) between 3:00 and 6:00 p.m. (Figure 1). The procedure was implemented on two subsequent days to replicate the effects and to minimize the probability of errors. On the study days the participants were asked to refrain from eating, drinking and smoking prior to testing.

Experimental psychosocial stress

The TSST is a procedure has been developed at the University of Trier, Germany, for induction of moderate psychosocial stress in humans under laboratory conditions. The test protocol and the effects of the TSST procedure on salivary cortisol have been described previously (Kirschbaum et al., 1993, Petrowski et al. 2009).

In brief, participants were asked to assume the role of a job applicant who was invited to a personal interview with the company's staff managers (selection committee). The participant was told that after a preparation period of 5 minutes duration they should introduce themselves to the managers in a free speech of 5 min duration and convince the managers that they were the perfect applicant for the vacant position. Subsequently, a mental arithmetic task with the participants counting backwards from a large prime number (2083, for example) in increments of 13 was conducted. After the mock job interview and task of mental arithmetics were completed, a five-minute-resting period was added. Subjective stress induction was evidenced by means of visual analogue scales (VAS-TSST). Six factors known to activate the HPA system were assessed: novelty, unpredictability, anticipation, negative consequences, interference and personal relevance (Dickerson, 2004).

Heart rate and heart rate variability

The heart rate (HR) and hear rate variability (HRV) variables were calculated over 3 minute-intervals during each part of the testing procedure (preparation, interview, arithmetic and recovery). The heart rate analysis was performed by means of the Polar ® watch system (S810, Polar, Finland) as previously described in detail (Radespiel-Tröger et al., 2003). Briefly, RR-intervals were recorded automatically by means of a receptor belt and stored using a wrist sensor unit, and transferred by means of an interface to a microcomputer. The S810 recorded with the sampling frequency of 1,000 Hz, giving a temporal solution of 1 ms for each RR period. The Polar S software corrects for artefacts using an error filter and beat protection function. The Polar S analysis software was used for HRV analysis. To evaluate the heart rate variability the following parameter were used: The root mean square successive differences (RMSSD) were calculated for a time domain parameter of HRV. The mean heart rate as well as RMSSD were assessed by means of the Polar ® analysis software. Furthermore, the high frequency power (HF; 0.15-0.40 Hz), the low frequency power (LF; 0.04-0.15 Hz) and the LF/HF ratio were assessed by means of a fast Fourier transformation algorithm to specify the HRV.

Statistical analysis

For the analysis of the global time effects during the TSST, an ANOVA for repeated measures with the preparation-, the stress- (speech and mental arithmetic) and the post-stress-time as the time factor was used separately for each group as

Table 2: Results of ANOVA with repeated measures (factor: TSST) and contrasts between phases of TSST procedure at day 1 and day 2

	Day 1						Day 2					
	ANOVA Time Effect			Contrasts of TSST Phases			ANOVA Time Effect			Contrasts of TSST Phases		
	F	df	p	0 vs. 1	1 vs. 2	2 vs. r	F	df	p	0 vs. 1	1 vs. 2	2 vs. r
Patients												
Bpm	53.63	2.08	**<.01**	**s**	n.s.	**s**	44.22	1.52	**<.01**	**s**	n.s.	**s**
RMSSD	6.91	1.52	**.01**	**s**	n.s.	**s**	5.27	1.48	**.02**	**s**	n.s.	**s**
LF/HF	8.14	1.93	**<.01**	**s**	n.s.	**s**	4.12	1.30	**.04**	**s**	n.s.	n.s.
Healthy Controls												
Bpm	35.07	1.90	**<.01**	**s**	n.s.	**s**	23.57	1.97	**<.01**	**s**	n.s.	**s**
RMSSD	8.55	1.53	**<.01**	**s**	n.s.	**s**	5.26	1.45	**.02**	**s**	n.s.	**s**
LF/HF	1.72	1.80	**.19**	n.s.	n.s.	n.s.	0.90	1.27	**.38**	n.s.	n.s.	n.s.

bpm = beats per minute; LF = low frequency (0.04 – 0.15 Hz); HF = high frequency (0.15 – 0.40 Hz); 0 = TSST preparation; 1 = TSST-interview; 2 = TSST-arithmetics; r = recovery after TSST; s = significant ($p < 0.05$); n.s. = non significant ($p > 0.05$)

well as for both testing days (t1 vs. t2). The homogeneity of variances was controlled by Mauchly's-test of sphericity. The ANOVA results were corrected by Greenhouse-Geisser whenever necessary.

Results

The successful matching of the age between patients and healthy individuals was tested (Table 1). There were no significant differences in age between the two groups ($t = -.08$, $df = 48$, $p = .94$). There were no significant differences in BMI between the two groups ($t = 1.37$, $df = 48$, $p = .18$). The stress induction was monitored by repeating the procedure twice as well as by evaluations using visual analogue scales (VAS-TSST). On both testing days 100 % of the patients (t1: M = 51.44, SD = 11.17; t2: M = 51.02, SD = 10.78) as well as 100 % of the healthy individuals (M= 54.44, SD= 13.60; t2: M = 52.36, SD = .8.03) experienced stress on the VAS-TSST at values higher than 0. The stress level induced by the stress test did not significantly differ between the healthy individuals and patients with PD (t1: $t = -0.69$, $df = 23$, $p = .50$; t2: $t = -.29$, $df = 23$, $p = .77$).

As it is shown in table 2 and figure 2 the heart rate significantly increased after the onset of experimental psychosocial stress and decreased during the recovery phase in patients with PD as well as in healthy subjects.

RMSSD significantly decreased following induction of psychosocial stress and increased during the recovery phase in patients with PD as well as in healthy volunteers. These changes were noted under conditions of repeated testing. The patients with PD showed a significant increase of the LF/HF ratio during administration of psychosocial stress and a decrease when recovering from it (table 2, figure 2). The increase of the LF/HF ratio during experimental stress was noted on either study days whereas the corresponding decrease during recovery was seen on the first study day only. Psychosocial stress did not influence LF/HF ratio in healthy subjects to a significant extent on both study days.

For the panic disorder patients' group all the analyses were repeated by using the intake of psychopharmacological drugs as a group factor (Table 3). There was no significant difference between patients receiving antidepressant drugs and those not taking CNS active medication. Furthermore there were no significant differences between patients exclusively showing a panic disorder and patients with a comorbid depression at t1 and at t2 (table 3).

Discussion

HRV has previously been suggested to be a measure of mental stress (Hjortskov et al., 2004). The results of the present study indicate that patients with PD as well as healthy individuals experience diminished HRV and increased heart rate during conditions of experimental psychosocial stress. This finding is in line with previous studies in healthy subjects who underwent various psychological stress tasks (Delaney, 2000; Moses et al., 2007; Seong et al., 2004). Several epidemiological studies have implicated psychological stress as a risk factor for cardiovascular disorders (Belkic et al., 2000; Marmot et al., 1997; Stansfeld et al., 2002). However, the mechanisms underlying an association between psychological stress and an increased risk for cardio-

Table 3: Results of ANOVA with repeated measures (factor: TSST) comparing patients and healthy controls as well as the subsamples of patients at day 1 and day 2

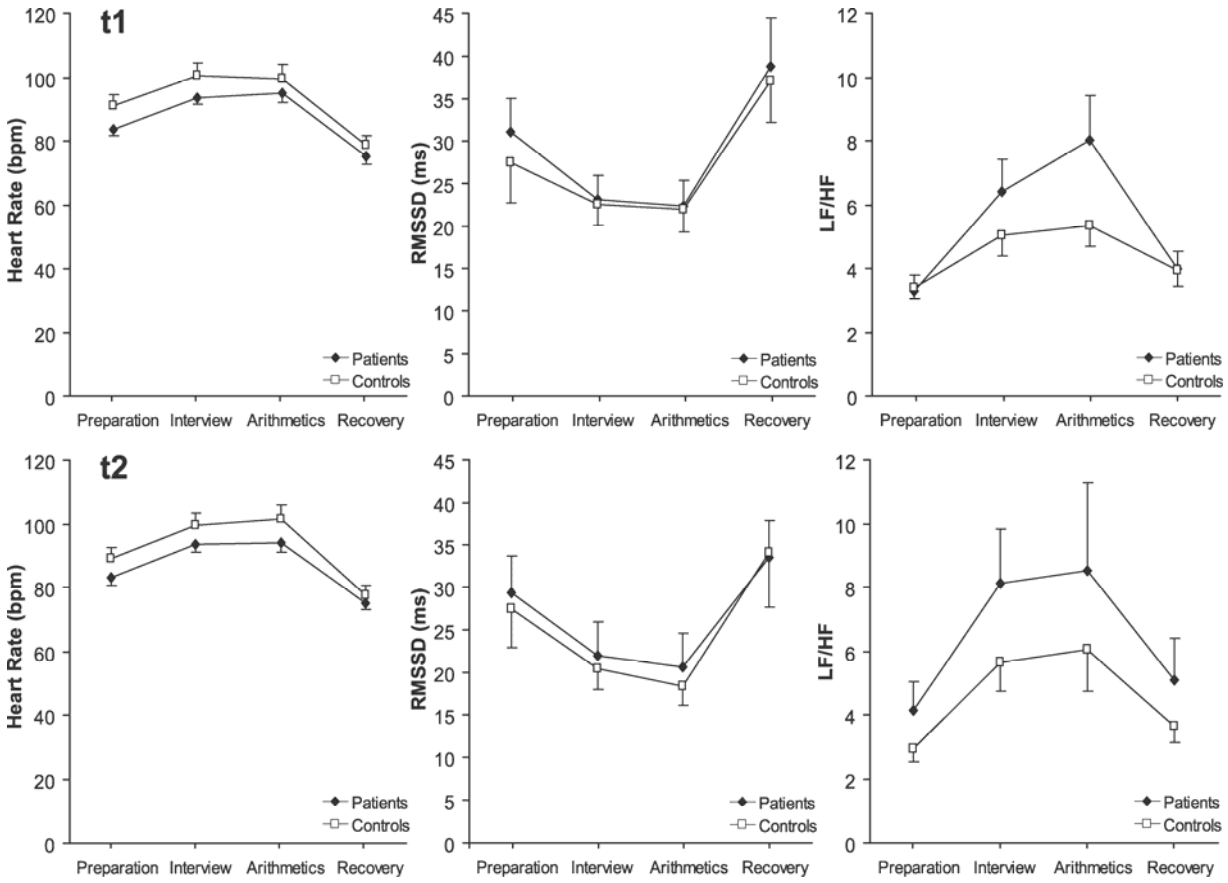
	Patients vs. Healthy Controls			Subsamples of Patients					
				With vs. Without Psychopharma-cological drugs			Exclusively Panic Disorder vs. Comorbid Depression		
	F	df	p	F	df	p	F	df	p
Day 1									
Bpm	0.99	2.14	.38	2.75	2.29	.07	1.89	2.20	.16
RMSSD	0.18	1.75	.81	1.00	1.47	.36	1.83	1.55	.18
LF/HF	2.30	2.04	.11	1.27	1.97	.29	0.62	1.91	.53
Day 2									
Bpm	0.92	1.97	.40	2.60	1.30	.11	2.02	1.64	.16
RMSSD	0.08	1.52	.87	0.87	1.74	.42	0.41	1.53	.62
LF/HF	0.14	1.31	.78	0.60	1.32	.49	0.50	1.26	.55

bpm = beats per minute; LF = low frequency (0.04 – 0.15 Hz); HF = high frequency (0.15 – 0.40 Hz)

vascular disorders remain unclear. Psychosocial stress may increase the risk of cardiovascular disease through direct activation of neuroendocrine responses to stressor, or more indirectly through unhealthy behaviours that increase the risk of cardiovascular disorders, such as smoking, lack of exercise, or excessive alcohol consumption. One of the main axes of neuroendocrine stress responses is the autonomic nervous system (ANS). Repeated activation of the ANS is characterized by lowered HRV. HRV depends on autonomic parasympathetic and on sympathetic balance.

Psychosocial stress may augment sympathetic drive and/ or withdrawal of vagal tone and thus lower HRV (deGeus et al., 1990). It has been hypothesized that a pattern of increased sympathetic and decreased parasympathetic cardiac activity during psychological stress may increase atherosclerotic risk by promoting endothelial dysfunction, which is a precursor to the development of atherosclerosis (Harris, 2004). In support of this speculation is accumulating evidence from studies on animals of different species which suggest that increased sympathetic activation during periods of stress may contribute to endothelial dysfunction by promoting blood flow disruption (shear stress) that injure the endothelium or by facilitating inflammatory processes that form atherosclerotic plaques (Gordon et al., 1981; Kaplan et al., 1991; Manuck et al., 1983). There is also evidence that efferent cholinergic activity of the vagus nerve, the parasympathetic arm of the ANS, may inhibit the cellular activation of macrophages and inflammatory cytokines – processes that are presumptively involved in atherosclerotic plaque formation (Tracey, 2002). Symptoms of perceived chronic psychosocial stress have been linked to enhanced sympathetic vasomotor modulation and vagal withdrawal in healthy individuals (Lucini et al., 2005). Dysphoric emotional states such as anger and anxiety have been demonstrated to lower HRV among healthy adults (Gorman, 2000). To our knowledge, this is the first study demonstrating reduced HRV in patients with PD during conditions of psychosocial stress. Stress induced impairment of HRV was observed more pronounced by us in patients with PD as compared to healthy subjects: LF/HF ratio was noted increased in PD patients but remained unchanged in healthy subjects undergoing the TSST, a standardized psychosocial stress test whereas RMSSD was diminished in both groups of participants under conditions of experimental psychosocial stress. The LF/HF ratio has been proposed to reflect sympathovagal balance, with higher ratios representing greater sympathetic modulation of heart rate and lower ratios representing a lower sympathetic or potentially greater parasympathetic modulation of heart rate (Friedman, 1998). Thus, the present finding of reduced LF/HF ratios among PD patients during conduction of TSST could show lower sympathetic modulation and/or parasympathetic modulation under conditions of experimental psychosocial stress. It is important to note, however, that the interpretation of the LF/HF ration is controversially debated in the literature (Eckberg, 1997). It is considered by some to be a marker of sympathetic modulation (Malliani et al., 1991; Montano et al., 1994; Pagani et al., 1997), and by others to be a variable that includes both sympathetic and parasympathetic influences (Appel et al., 1989; Harris, 2004). Previous studies have demonstrated that acute sympathetic withdrawal during ganglionic blockade and muscle sympathetic nerve activity coincides with reduction in the LF/HF ratio (Diedrich et al., 2003; Pagani et al., 1997). Therefore, the changes in the LF/HF ratio in the present study have been interpreted as reflecting sympathetic modulation. Thus, sympathetic activation induced by acute psycho-social stress deems to be more pronounced in patients with PD as compared to healthy subjects However, parasympathetic inhibition may also be a marker of the disease.

Figure 2: Heart rate and rate variability parameters between phases of TSST procedure at day 1 (t1) and day 2 (t2) in patients with PD (n=25) and in healthy controls (n=25)



The strengths of this study are: 1st the use of a standardised psycho-social stress test that has a well-documented in the literature and 2nd methodological procedures that avoid confounders (e.g., repetition of the effect on two subsequent days). The small sample size of this study is a limitation that makes it difficult to draw conclusions on the majority of patients. Lack of control of respiration and blood pressure is a further limitation as psychological testing may have altered both parameters. For future research the results have to be replicated in a larger sample under conditions of standardized breathing and controlled blood pressure. Furthermore, the influence of chronification could be of interest since psychological symptoms that prevailed for years may impact the autonomic nervous system in the same way as long term stressors do.

Taken as a whole, the present study hints at a significant impairment of HRV by experimental induction of psychosocial stressor in patients with PD and in healthy controls.

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