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HPA Axis Activity under Psychosocial Stress in Patients with Acute and Remitted Panic Disorder

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Abstract

Background: Panic disorder (PD) has been linked to an altered activity of Hypothalamic-pituitary-adrenal (HPA) axis. To understand the elevated risk for future psychiatric episodes in PD it is of interest how remitted patients might differ from healthy controls in the activity of the HPA axis.
Methods: Fourteen patients with PD and 14 healthy controls were exposed to the Trier Social Stress Test (TSST) on consecutive days twice before and twice after psychotherapeutic intervention. Salivary cortisol and heart rate variability (HRV) were measured repeatedly.
Results: The healthy controls showed normal increase of salivary cortisol. By contrast, in patients with PD cortisol responses were absent on all testing days. In respect to RMSSD, the TSST exposure led to a decrease in both groups.
Conclusion: The findings suggest that in patients with remitted PD, a hypo-response pattern of the HPA axis after significant symptom reduction might be a risk for future psychiatric episodes (German J Psychiatry 2011; 14(2): 72-79).

Keywords: panic disorder, hypothalamic-pituitary-adrenal (HPA) axis, heart rate variability, psychological stress

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Introduction

Panic disorder (PD) is a common disorder with a severe burden for the individual (Greenberg et al., 1999; Yates, 2009) and has been linked to an increased probability of cardiovascular disease and mortality (Albert et al., 2005; Scherrer et al., 2010; Smoller et al., 2007). The patients describe symptoms that healthy controls show under high stress and during an activated Hypothalamic-pituitary-adrenal (HPA) axis, such as high heart rate, sweating, dizziness and trembling.

Anxiety disorder patients in remission are, by definition, free of psychopathology. However, relapse is a frequent condition in PD (Yonkers et al., 2003). To understand the elevated risk for future psychiatric episodes (Fava et al., 1995) it is of interest how remitted patients might differ from healthy controls and particularly how these differences might be related to the development of future psychopathology. Based on the patients' symptomatology and stressful life events the literature indicates that remitted patients have a disturbed psychophysiological stress response (Barlow, 1988; Finlay-Jones & Brown, 1981; Leyton et al., 1996; Siegmund et al., 2011). This dysfunctional psychophysiological response might increase the probability for developing severe anxiety in the future. A prominent vulnerability factor for low therapeutic outcome and for relapse might be an altered HPA axis response (Appelhof et al., 2006; Siegmund et al., 2011).

Concerning the activation patterns of the HPA axis in patients with PD the findings are inconsistent. In most of the studies PD patients show higher plasma level of cortisol compared to healthy controls (Abelson et al., 2007; Erhardt et al., 2006; Heuser et al., 1994; Leyton et al. 1996; Schreiber et al., 1996), however, a few studies observed normal levels (Brambilla et al., 1992; Garcia-Leal et al., 2005; Hoehn et al., 1997; Targum, 1992) or even reduced levels of cortisol (Petrowski et al., 2010b; Stones et al., 1999). These differ-

ences might be due to differences in the kind of stressors, the stressor intensity and severity of PD.

Until now, only two studies have been published on the HPA axis reactivity in remitted PD patients. Garcia-Leal et al. investigated once remitted PD patients after treatment with antidepressants (Garcia-Leal et al., 2005). Leyton et al. observed a single time remitted, medication-free PD patients (Leyton et al., 1996). Both studies implemented different social stressors, but only Leyton et al. could observe a stress induction followed by a hypercortisolism in remitted PD patients compared to healthy controls (Leyton et al., 1996). In both studies, hypotheses concerning changes of HPA axis under symptom reduction cannot be answered since the HPA axis of the same sample was not investigated in the acute state. In addition, the stressors did not consistently activate the HPA axis in healthy individuals. Therefore, future studies should apply a social stressor with sufficient intensity to activate the HPA axis in most participants. The Trier Social Stress Test (TSST) (Kirschbaum et al., 1993) can be regarded as such a potent psychosocial stress test that reliably activates the HPA axis in most participants under standardized conditions (Kirschbaum et al., 1993; Kirschbaum et al., 1995; Kudielka et al., 2007; Schommer et al., 2003). The TSST consists of a free speech as well as an arithmetic task and induces stress by way of the personal relevance of the speech and the extent of social-evaluative threat (Dickerson & Kemeny, 2004; Dickerson et al., 2008).

In the present study a sample of PD patients was investigated twice using the TSST: with symptoms and after remission of the symptoms. It is hypothesized that stress reactivity in patients with remitted symptoms is altered compared to healthy individuals since PD patients show a disturbed psychophysiological stress response (Barlow, 1988; Finlay-Jones & Brown, 1981; Leyton et al., 1996) and an increased probability of developing severe anxiety in the future.

Materials and Methods

Participants and study design

A sample of 14 patients with a current diagnosis of PD with agoraphobia (6 males, 8 females, mean age = 35.7, SD = 11.9) was tested twice before (t1, t2) and twice after (t3, t4) psychotherapeutic intervention (Margraf & Schneider, 1990) which on average lasted for ten weeks. Three patients were smokers and five patients took oral contraceptives. The mean age at the onset of PD was 27.5 years (SD = 11.3) of age and the mean duration of the PD was 8.2 (SD = 11.8) years. According to the Panic and Agoraphobia-Scale (PAS) (Bandelow, 1979) the severity of PD was rated as moderate (M = 23.5, SD = 11.5).

Patients were recruited from the Clinic for Psychosomatic Medicine and Psychotherapy of the Technical University Dresden, Germany. The Structured Clinical Interview (SCID) (Spitzer et al., 1990; Wittchen et al., 1990) was used to ascertain the diagnosis of PD with agoraphobia (American Psychiatric Association, 2004). As a comorbidity, a current diagnosis of dysthymia or of current mild to moderate depression were included, excluding any other mental disorder according to the SCID as well as any acute and/ or chronic medical illness as assessed by medical history and physical examination. Hereby, 8 patients (3 males, 5 females) with a comorbid diagnosis of depression were included [dysthymia: n = 1; mild depression (F32.0, F33.0): n = 2; moderate depression: F32.1, n = 2; F33.1, n = 3]. Of the 14 patients, 8 were on psychoactive drugs at the time of testing: selective serotonin reuptake inhibitors (SSRIs) (n = 3), serotonin norepinephrine reuptake inhibitors (SNRIs) (n = 1), tetracyclic antidepressant (n = 1), tricyclic antidepressant (n = 1), phytosedative (n = 2), monoamine oxidase inhibitor (n = 1) and phenothiazine (n = 1). The medication was stable over the testing period.

A sub-sample of 14 healthy controls (6 males, 8 females, mean age = 35.7, SD = 12.7) with no life-time mental disorder was tested at the same time points. The healthy controls were matched by age, gender and use of oral contraceptives to the patient sample. Four participants were smokers and n = 5 females took oral contraceptives. Both groups did not differ in age, gender, number of cigarettes smoked and use of oral contraceptives (all $p > .05$).

Before testing, all participants were screened for stressful life-events in the past six months. Only participants without stressful life-events were included. Moreover, only participants were included who slept at least seven hours during the night before the testing sessions. Further inclusion criteria were body mass index <27, habitual smoking of 10 cigarettes a day at maximum and females were only tested during the luteal phase.

The study protocols were approved by the local Ethics Committee of the Medical Faculty of the Technical University Dresden, Germany.

Study procedures

The study included the Trier Social Stress Test (TSST), which had previously been described by Kirschbaum et al. (1993). The participants were asked to refrain from eating, drinking, and smoking for at least two hours before testing as well as during the one-and-a-half-hour testing session. The participants underwent the TSST between 3:00 and 6:00 p.m. in order to minimize the circadian variations in cortisol levels (Smyth et al., 1997). Briefly, it started with a 15-min-rest period to dissipate the influence of any previously experienced stress on the baseline cortisol level. The rest period was followed by a baseline saliva probe. A second saliva probe was taken after the first 5 minutes of preparation time for the mock job interview. After the mock job interview and a task of mental arithmetic were completed, a third saliva probe was taken. Further saliva probes were taken every ten minutes for one hour while the participants were resting (seven probes in all).

The participants were tested in the same setting with identical procedures during every one of the four TSST sessions. To avoid the possibility that participants would present a

pre-learned speech or remember the sequence of correct answers for the mental arithmetic task on the second, third, and fourth visit, the tasks of the stress test were changed minimally. For the speech, the job description the subjects had to apply for was modified each time. For the arithmetic task, the initial number of the serial subtraction was altered. The two-person-panel was replaced after each testing session in order to avoid a stress reduction due to the familiarity with the panel-members.

For a quick and hygienic collection of salivary cortisol, sampling was carried out using Salivette cotton swabs in tubes (Sarstedt, Nümbrecht, Germany); the probes were refrigerated immediately at –20 °C. The HRV was monitored throughout the whole procedure via a polar system (S810, Polar® Electro GmbH Deutschland) for the wireless transmission of HRV with electrocardiogram precision with a sampling frequency of 1,000 Hz. Root mean square successive differences (RMSSD), a time domain parameter of HRV, were calculated over 3 minute-intervals during each part of the testing procedure (preparation, interview, arithmetic and recovery) by means of the Polar® analysis software.

In order to ascertain habituation in patients with PD, the TSST was accomplished on two consecutive days (t1, t2) and another two consecutive days (t3, t4) after psychotherapeutic intervention (Margraf & Schneider, 1990). The cognitive-behavioural exposure therapy was carried out for ten weeks.

Psychopathological assessments

The psychopathological burden was measured by three instruments: (1) the Panic and Agoraphobia-Scale (PAS) (Bandelow, 1979) assessed the severity of PD with a range from 0 to 52 and (2) the Symptom-Check-List (SCL-90-R) (Derogatis 1977; Franke 2002) assessed their own psychological and physical impairment. Depressive symptoms were evaluated by (3) the Beck-Depression-Inventory (BDI) (Beck et al., 1961; Hautzinger et al., 1994).

Cortisol analysis

Before analysis, the saliva probes were centrifuged at 3000 rpm for five minutes to produce a clear supernatant of low viscosity. From each saliva probe, 50 µl was used for a duplicate cortisol analysis. The cortisol in the saliva was measured with a time-resolved immuno-assay and fluorometric end point detection (DELFIA) as described in detail elsewhere (Dressendörfer et al., 1992). The lower detection limit of this assay was approximately 0.43 nmol. Intra- and inter-assay variations were less than ten percent at 3, 11 and 21 nmol.

Statistical analysis

The data were analysed by SPSS 17.00. The course of the cortisol release as well as the HRV were analysed by analyses of variance (ANOVAs) for repeated measures to reveal possible main or interaction effects of time, session and group with group (patients, controls) as the between-subjects factor and time (0, 5, 10, 20, 30, 40, 50 min) and session as the within-subjects factors. The degree of freedom was adjusted with the Greenhouse-Geisser approach, taking sphericity into account. A cortisol response to the TSST was defined as an increase in cortisol levels of 2.5 nmol/l over the baseline (Van Cauter & Refetoff, 1985). Influencing factors such as psycho-pharmaceuticals, comorbidity and smoking status were controlled for by one-way ANOVAs. As subjects were matched by age, gender and use of oral contraceptives these variables were not taken into account as influencing factors. To evaluate the changes in subjective symptoms from t1 to t4, ANOVAs for repeated measures were calculated.

Results

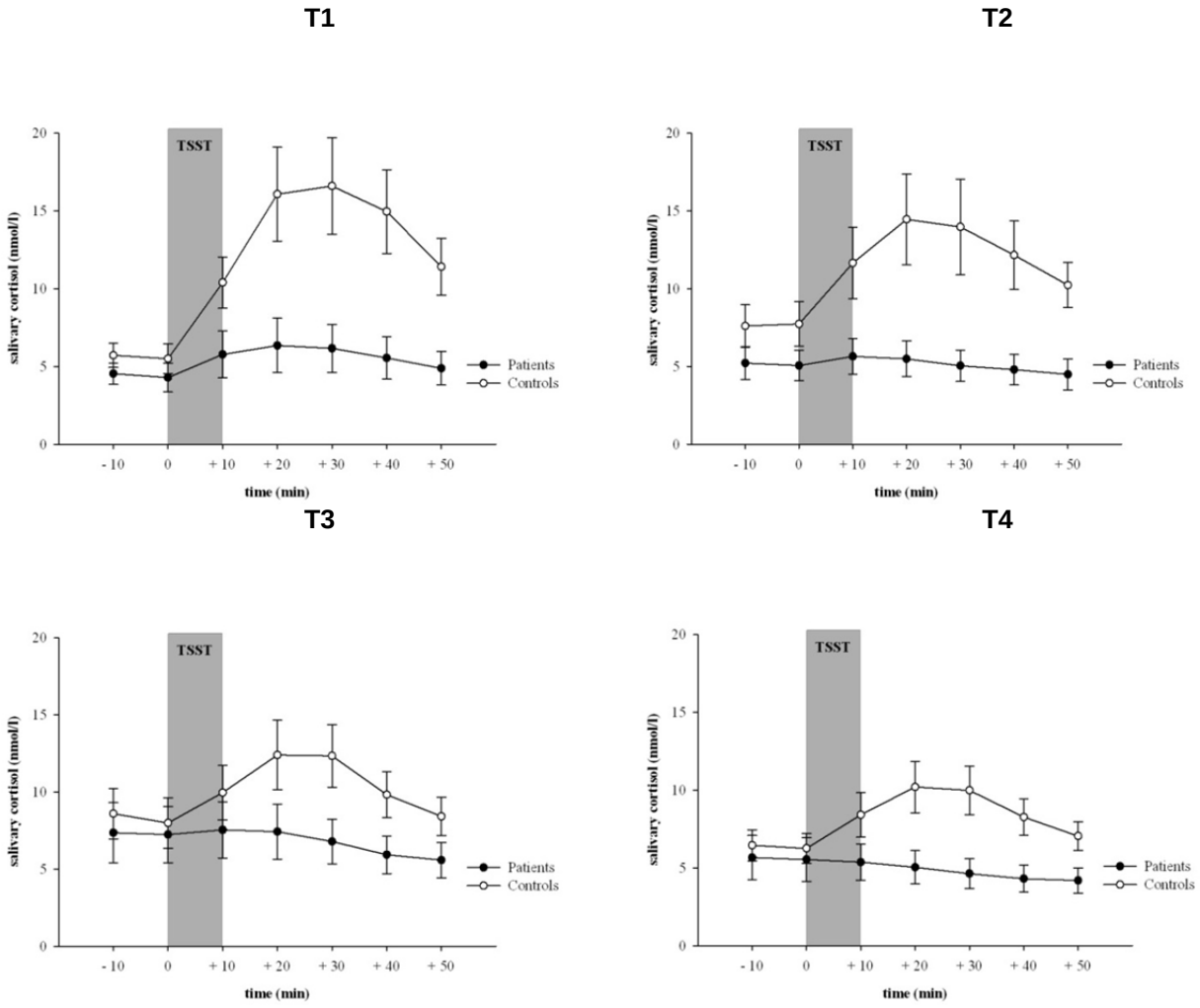
There were no significant differences in age between both samples ($t = .016$, $df = 26$, $p = .988$). Likewise, there were no significant differences in smoking status between healthy controls and patients ($\chi^2 = .190$, $p = 1.000$).

There were no significant differences in the baseline cortisol between healthy controls and patients in any of the TSST sessions ($F (3, 78) = .304$, $p = .737$). A significant impact on baseline cortisol levels could be excluded for psychotropic medication ($F (1, 12) = .011$, $p = .917$) and comorbid depression ($F (1, 12) = .009$, $p = .926$) within the group of PD patients.

While TSST led to the well-documented increase in cortisol levels in healthy controls, patients with PD showed no such cortisol response. ANOVA results show a significant effect of time ($F (6, 156) = 10.853$, $p < .001$) and a significant group by time interaction effect ($F (6, 156) = 9.188$, $p = .001$) for all testing sessions. There was a significant main effect of group ($F (1, 26) = 6.450$, $p = .017$). Furthermore, the differences in responder rates between healthy controls and patients reached statistical significance in testing session t1, t2 and t4 (controls vs. patients, t1: 85.7 % vs. 21.4 %, $\chi^2 = 11.638$, $p = .003$; t2: 71.4 % vs. 7.1 %, $\chi^2 = 13.906$, $p = .001$; t3: 42.9 % vs. 14.3 %, $\chi^2 = 4.384$, $p = .112$; t4: 57.1 % vs. 0 %, $\chi^2 = 12.571$, $p = .002$) (see figure 1).

When repeating the TSST, cortisol response is attenuated from the first to the following testing session due to habituation. While healthy controls showed a habituation effect with lower cortisol responses upon the second, third and fourth stress exposure (testing session x time, $F (18, 234) = 6.908$, $p < .001$), no differences in cortisol response patterns could be elucidated in the patient group (testing session x time: $F (18,234) = 2.286$, $p = .088$). Within the group of PD patients, neither use of psychotropic medication ($F (1, 12) = .130$, $p = .725$) nor a comorbid depression had a significant impact on the cortisol response ($F (1, 12) = .143$, $p = .712$). For both groups, the impact of smoking status on cortisol response could be ruled out ($F (1, 24) = .041$, $p = .841$). Separate analyses with only nonsmokers did not change the results.

Figure 1: Cortisol reactivity at baseline and under repeated psychosocial stress for healthy controls (N = 14) and patients with PD with agoraphobia (N = 14) during testing sessions t1, t2, t3, t4.



There were no significant differences in the baseline HRV between patients and healthy controls in any of the testing sessions ($F(3, 78) = .942$, $p = .390$). There were no significant impact of psychotropic medication ($F(1, 12) = 4.353$ $p = .059$) and comorbid depression ($F(1, 12) = 2.668$, $p = .128$) on baseline HRV within the group of PD patients.

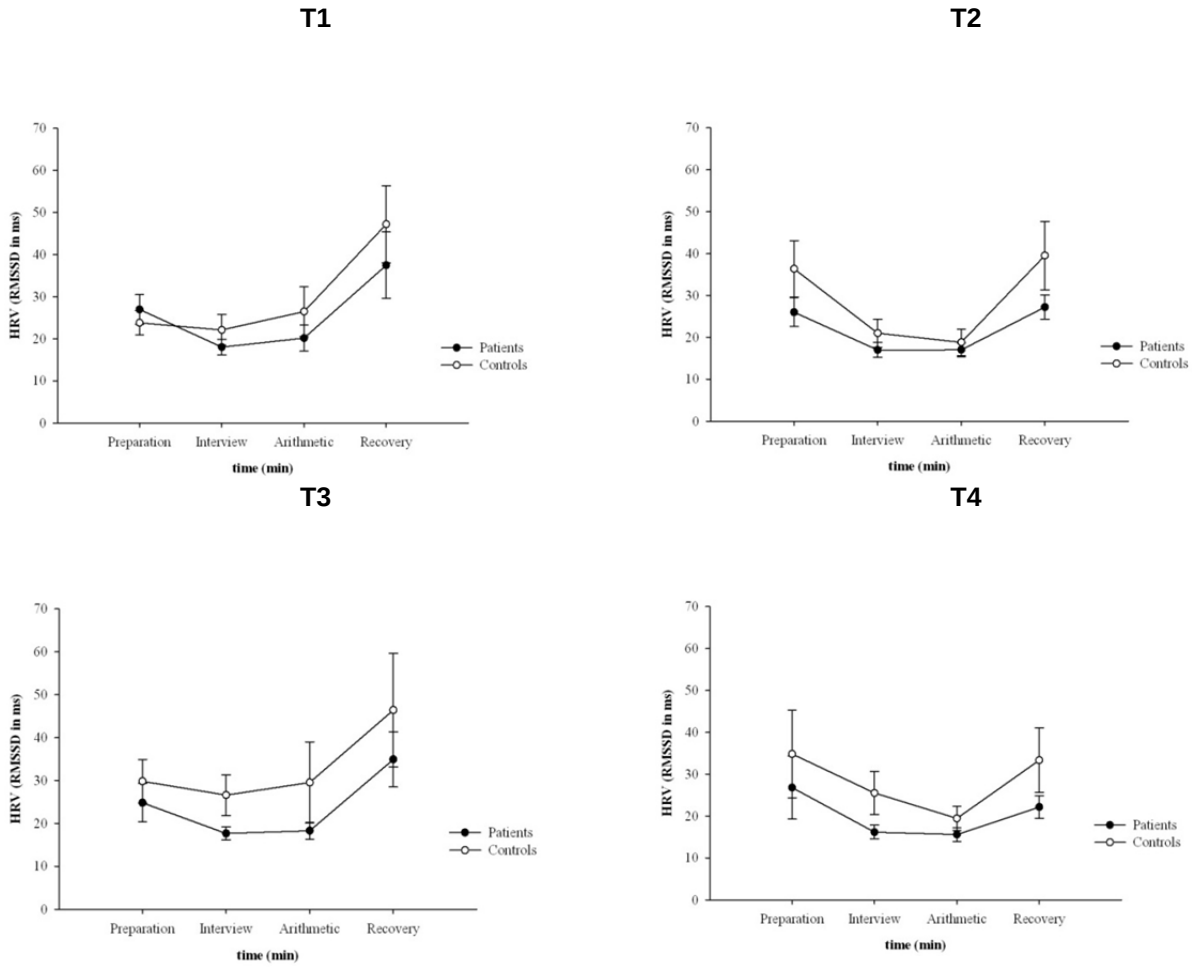
The HRV decreased in all four testing sessions as shown in the significant main effect of time ($F(3, 78) = 17.925$, $p < .001$). Neither a significant main effect of group nor a significant group by time interaction were present. A change of HRV due to repetition could not be shown neither for healthy controls nor for patients (controls: $F(9, 117) = 2.801$, $p = .095$; patients: $F(9, 117) = 1.862$, $p = .172$, see figure 2). Within the group of PD patients, neither use of psychotropic medication ($F(1, 12) = 4.644$, $p = .052$) nor a comorbid depression ($F(1, 12) = 2.900$, $p = .114$) had a significant impact on HRV. For both groups, the impact of smoking status on HRV could be ruled out ($F(1, 24) = .368$, $p = .550$).

Even though the cortisol release did not change over the repeated stress exposures, symptom severity on the psychoticism-scale ($F(1, 9) = 12.694$, $p = .006$), the anxiousness-scale ($F(1, 9) = 5.865$, $p = .039$) and phobic-anxiety-scale ($F(1, 9) = 5.704$, $p = .041$) of the SCL-90 decreased significantly. The BDI-score improved significantly from t1 to t4 ($F(1, 9) = 8.585$, $p = .017$).

Discussion

In the present study, the functioning of the HPA system in patients with PD before and after symptom reduction was investigated. Cortisol levels of acute patients with PD did not increase significantly under psychosocial stress whereas HRV decreased. A significant decrease in HRV under psychosocial stress with no differences to healthy controls in RMSSD confirms former results (Petrowski et al., 2010a). However, the findings of hypo-activity in the HPA system in patients with acute PD contradict the conclusions drawn by Abelson et al. (2007) that PD patients would show an enhanced responsiveness of HPA axis to novel and uncontrollable situations. The present data rather suggest a hypocortisolism in patients with acute PD which Jezova et al. (2010)

Figure 2: Heart rate variability (RMSSD in ms) at baseline and during TSST for healthy controls (N = 14) and patients with PD with agoraphobia (N = 14) during testing sessions t1, t2, t3, t4.



have also found after hypoglycemic stress. The present finding also agrees with former results showing an attenuated plasma cortisol response to an experimental psychosocial stress in healthy controls with high level of trait anxiety (Duncko et al., 2006; Jezova et al., 2004) and is also in line with former results suggesting a striking pattern of cortisol non-responsiveness under psychosocial stress in patients with PD (Petrowski et al., 2010b).

After ten weeks and a significant symptom remission the cortisol release as well as HRV under psychosocial stress in patients with remitted PD did not change. These results are consistent with the literature in which a reduction in PD symptoms was not connected to changes in the cortisol release (Garcia-Leal et al., 2005). According to the lack of cortisol response the influence of cortisol on extinction learning and the inhibition of central excitatory neurotransmission have to be discussed (Siegmund et al., 2011). The altered HPA axis reactivity even after symptom reduction might be one explanation for the elevated risk of remitted PD patients for future psychiatric episodes (Barlow, 1988). The literature rather suggests the explanation that the altered functioning of the HPA system is a vulnerability factor for PD and not an adaptation of the HPA system to the symptoms. Recent findings by Wahlberg et al. (2009) show that a persistent inability to mount an adequate stress response to psychosocial stress could constitute a pre-existing vulnerability factor resulting in impaired coping and long-term sick leave. This is in line with results promoting that a decreased reactivity of the HPA axis render subjects vulnerable for stress-related bodily disorders (Heim et al., 2000) and atypical depression (Rohleder et al., 2004). However, a representative longitudinal study and studies of unaffected relatives including subjects before the onset of panic disorder are necessary to differentiate whether the altered functioning of the HPA system is a vulnerability factor for PD or is an adaptation of the HPA axis system to the symptoms and changes after symptom reduction.

Due to the lack of cortisol response under acute psychosocial stress in PD an adaptation of the organism to stress cannot be completely assured and prevents successful active coping strategies (Wahlberg et al., 2009). Since glucocorticoids have a function to suppress the production and activity of cytokines, this function cannot be fulfilled in PD patients with a hypocortisolism (Rohleder et al., 2004). An increased immune and inflammatory reaction can take place as in Posttraumatic stress disorder patients (Rohleder et al., 2004). When the hypocortisolism lasts longer, the probability increases for the development of autoimmune illness, inflammation, allergies as well as infection disease (Nijs et al., 2002). Due to the hypocortisolism, there is also a reduced

negative feedback regulation of cortisol on catecholamines which might have an effect on the cardiovascular system. These processes might be responsible for the association found in PD patients to cardiovascular disease (Scherrer et al., 2010).

It is a limitation of this study that an influence of psychopharmacological drugs through the 5-HT system on the HPA axis (Lesch 1991) and HRV (Rechlin et al., 1994) cannot be ruled out. As also patients with PD under treatment with psychopharmacological drugs have a high relapse rate during follow-up independent of antidepressants (Barlow et al., 2000) a large sample with patients under antidepressant drug-treatment should be included in further studies and should be compared to a sample of drug-free patients with regard to HPA axis reactivity and HRV.

Future studies should consider the pre-treatment HPA axis reactivity under standardized psychosocial stress in order to constitute the HPA axis reactivity as possible vulnerability factor for the prediction of symptom remission and relapse under different treatment conditions. Therefore future studies should replicate the present findings on a large sample of patients including random assignment to different treatment conditions (Barlow et al., 2000) considering the single and synergetic short- and long-term impact of cognitive-behavioural therapy and antidepressant drug treatment on HPA axis, HRV and psychopathology. These studies should take into account the pre- and post-treatment HPA axis reactivity as a possible risk factor for relapse as has been already done in studies for depressive disorders (Appelhof et al., 2006). Besides, further studies should include a concurrent sampling of salivary and plasma cortisol as well as plasma ACTH.

Generally, the present findings suggest that a normal response pattern of HPA axis is not restored after cognitive-behavioural therapy although a significant improvement of symptomatology was present. This finding alludes an innate or acquired vulnerability of HPA axis in patients with PD which increases the risk of future psychopathology and cannot be restored by ten weeks of psychotherapy intervention.

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