Abschlussbericht

Projekt 2.13 „ Zytokinverlauf bei Panikstörungen“

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Introduction

Cytokines are important proteins regulating the immune response in injuries, infections, and other stress the organism is exposed to (Hoge et al., 2009). Current research findings seek to explain psychosocial stressors and their influence on the development of psychological disorders (e.g. anxiety disorders, affective disorders) via the investigation of pro-inflammatory cytokines and changes in the immune system (Schiepers, Wichers, & Maes, 2005; Simon et al., 2008). The connection between the cortisol stress reactivity and psychological disorders has already been proven (Petrowski, Herold, Joraschky, Wittchen, & Kirschbaum, 2010; Petrowski, Wintermann, Kirschbaum, & Bornstein, 2012; Petrowski, Wintermann, Schaarschmidt, Bornstein, & Kirschbaum, 2013; Wichmann, Kirschbaum, Böhme, & Petrowski, 2017). Hereby, the secretion of cortisol under stress induction has the function of suppressing the production of pro-inflammatory cytokines and thus of counteracting the development of inflammatory reactions (Padgett & Glaser, 2003; Rohleder, Joksimovic, Wolf, & Kirschbaum, 2004). Therefore, a malfunction of

45 the stress response may be accompanied by an increase in susceptibility for infectious and autoimmune
46 disorders as well as with inflammatory processes (Padgett & Glaser, 2003).

47 The influence of stressors plays an essential role in the development and triggering of anxiety
48 symptoms (Bandelow et al., 2000). In regard to the development of a panic disorder (PD), numerous
49 studies have been able to prove an altered stress reactivity of the hypothalamus –hypophysis-adrenal
50 (HPA) axis and, hence, changed levels of the hormone products adrenocorticotropic hormone (ACTH) and
51 cortisol (Bourgeois, 1993; Erhardt et al., 2006; Heuser, Yassouridis, & Holsboer, 1994; Roy-Byrne et al.,
52 1986; Schreiber, Lauer, Krumrey, Holsboer, & Krieg, 1996). Hereby, more recent findings are indicative of
53 a suppressed reactivity of the HPA-axis under physiological as well as psychosocial stress induction (Jezova,
54 Vigas, Hlavacova, & Kukumberg, 2010; Petrowski et al., 2010; Petrowski et al., 2012; Wichmann,
55 Kirschbaum, Böhme, et al., 2017). A reduction in cortisol secretion has the effect of a raised production of
56 pro-inflammatory cytokines similar to the way this could already been proved successfully in patients with
57 a posttraumatic stress disorder [PTSD; for review: Rohleder, Wolf, and Wolf (2010)]. Hence, alterations in
58 the immune parameters may also be observable in patients with other anxiety disorders.

59 In patients with a PD diagnosis, overall findings so far suggest a broad spectrum of raised baseline
60 peripheral pro-inflammatory cytokine levels (Hoge et al., 2009). Hoge et al. (2009) observed significantly
61 raised values in TNF-α, MIP-1- α, GM-CSF, IL-6, IL-1-α, IL-1-β, IL-4, IL-7, IL-8, IL-10, IL12p70, IL-13, IL-15, and
62 IL-10 in patients with a PD at rest one week after the diagnosis had been made. Furthermore, the increase
63 in anti-inflammatory cytokines (IL-4, IL-10) leads to the assumption that they, too, increase in reaction to
64 the increase in pro-inflammatory cytokines (Opal & DePalo, 2000). In the sample reported by Hoge et al.
65 (2009) 87% of the PD patients showed an increased pro-inflammatory cytokine level in comparison to 25%
66 of the healthy control group. Likewise, increased IL-1-β values were also reported (Brambilla et al., 1994).
67 However, contradictory to this elevated pattern, some investigations suggest lower cytokine
68 concentrations in PD patients [IL-2: Koh and Lee (2004); Van Duinen, Schruers, Griez, and Maes (2004)] or

failed to reveal any differences between PD patients and healthy control groups [IL-2R, IL-6, IL-8, TNF-α: Van Duinen et al. (2008); IL-2, IL-3: Weizman, Laor, Wiener, Wolmer, and Bessler (1999); IL-1-α, IL-1-β: Koh and Lee (2004); Rapaport and Stein (1994)].

Research on stress-induced cytokine secretion produced also mixed results. Meta-analytic evidence exists that cytokines respond to acute psychosocial stress (Steptoe, Hamer, & Chida, 2007) and Weizman et al. (1999) reported a negative correlation of the IL-3 concentration with the severity of the state of the anxiety so that a state-dependent modulation of immune parameters must be assumed. However, after acute stress induction, Van Duinen et al. (2008) were unable to determine any alterations in the cytokine secretion (TNF-α, IL-6, IL-8, IL-10) in patients with PD before as well as after a 35% CO2 inhalation in comparison to healthy individuals. The authors presume that the bidirectional communication between the immune system and the HPA-axis, among others in the etiology of affective disorders, probably plays a role but less so, or not at all, in the etiopathogenesis of PD. As yet, there have been no investigations reported for patients with PD under psychosocial stress induction. In healthy individuals, psychological stress (medicine exam) produced increased pro-inflammatory (TNF-α, IL-6, IL-1RA, IFN-gamma) and anti-inflammatory (IL-10) cytokine concentrations (Maes et al., 1998).

Some causes for the state of the findings in patients with a panic disorder may lie in the differences of the paradigms employed (induced cytokine production vs. measuring of circulating cytokines), differences in the examined cytokines, the assays used, differences in the time in point of measuring the cytokines [circadian rhythm of the cytokines; Vgontzas et al. (2005)] as well as the influence of variables such as depressive comorbidity, age, sex, body mass index (BMI), smoking, and psychopharmaceutic intake (Hoge et al., 2009). Furthermore, due to taking a singular blood sample under baseline conditions, differences, which would be present under stimulation/psychosocial stress, may remain hidden (Van Duinen et al., 2008). Beyond that, it is assumed that the existence of a chronic, low grade pro-inflammatory state, the risk of somatic illnesses such as arteriosclerosis or cardiovascular diseases is elevated and

correlated positively with the extent of the psychopathology (von Känel et al., 2007). Therefore, the present study focuses on the question to which extent patients with PD display increased pro-inflammatory cytokine (IL-6, TNF-α) and decreased values in anti-inflammatory cytokine (IL-10) concentrations in response to psychosocial stress induction. The reduced cortisol availability under mental stress found so far (Jezova et al., 2010; Petrowski et al., 2010; Petrowski et al., 2012; Wichmann, Kirschbaum, Böhme, et al., 2017) might be accompanied by an increased production of pro-inflammatory cytokines, thus explaining the creation of a cardiovascular morbidity in patients with a panic disorder via the mediation of a chronic low-stage inflammatory process (Smoller et al., 2007). Immunological processes under stress in patients with PD may be considered the "missing link" in the explanation of the severity of the psychopathology and for the determination of the risk factors of occurring somatic comorbidities such as the increased risk of a myocardial infarct.

Methods:

Study sample

Recruitment of the study sample took place between August 2014 and March 2016. The patients were recruited from the department for psychotherapy and psychosomatic medicine at the university hospital Dresden, Germany. Participants with fluent German language knowledge and age between 18 and 65 years were included in the study. General exclusion criteria were a lifetime history of substance use disorder, psychotic or bipolar disorder, psychopharmacological or glucocorticoid-containing medication intake, severe medical illnesses (e.g. cancer, autoimmune diseases, diabetes), and pregnancy. The Structured Clinical Interview [SCID; First, Spitzer, Gibbon, and Williams (1995)] was conducted by trained interviewers for the assessment of *DSM-IV-TR* mental disorder diagnoses. Diagnostic assessment was confirmed by an experienced clinical psychologist. Patients with a primary diagnosis of PD with or without agoraphobia were included. Inclusion into the healthy control group was conducted on the basis that

participants reported no history of mental disorder in the SCID. The total sample included *n* = 32 PD patients with and without agoraphobia and *n* = 32 healthy controls. *N* = 4 (12.5%) showed a borderline, *n* = 12 (37.5%) a mild, *n* = 8 (25%) a moderate and *n* = 8 (25%) a severe disease severity according to the Panic & Agoraphobia Scale (PAS; Bandelow, 1999). All the study participants provided written informed consent.

Psychosocial stress induction and hormone sampling

The standardized protocol for the TSST was applied for the reliable induction of acute moderate psychosocial stress under laboratory conditions [for review: Foley and Kirschbaum (2010); (Kirschbaum, Pirke, & Hellhammer, 1993)]. In brief, the TSST requires a mock job interview (5 min) and a mental arithmetic task (5 min) of the participants to be performed in front of a mock selection committee. Women were tested exclusively in the luteal phase of their menstrual cycle. To account for circadian rhythm of cortisol and cytokine secretion, the TSST was performed not earlier than 2 pm in the afternoon. Subjective levels of distress were evaluated using the Primary Appraisal Secondary Appraisal Questionnaire (PASA; Gaab, 2009) prior to the TSST and a Visual Analogue Scale (VAS) following the TSST. Blood samples were collected via a venous catheter 15 min and 1 min prior to the TSST as well as 1 min, 10 min, 20 min, 30 min, 45 min, 60 min, 75 min, and 105 min after the TSST and stored at 4°C. For the determination of plasma cortisol concentrations, blood was collected in serum gel monovette (Sarstedt, Nümbrecht, Germany) and immediately centrifuged at 4°C and 3000 rpm for 10 min. Then, plasma was stored at -80°C and at -20°C before being assayed for cortisol. Plasma cortisol concentrations were determined using a commercially available radioimmunoassay kit with the Solid Phase Antigen Linked Technique (SPALT) with the LIAISON-Analyzer® (DiaSorin, S.p.A., Italy).

In a second run IL-6 (solely -1, +30, +105 min) and IL-10 (all collection time points) were determined using high-sensitive ELISA enzyme-linked immunosorbent assay (IBL International GmbH, Germany).

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143 **Clinical assessment**

144 Five self-report questionnaires were handed out to the study participants for a clinical characterisation.
145 Overall, higher questionnaire scores indicate a higher disease severity. All questionnaires were handed out
146 in the German language version. (1) The global severity of PD was evaluated using the Panic &
147 Agoraphobia Scale (PAS; Bandelow, 1999) including the five sub-scales panic attacks, agoraphobia,
148 anticipatory anxiety, disability, and concerns about health. 13 items must be answered on a 4-point Likert
149 scale. (2) The agoraphobic Cognitions Questionnaire (ACQ; Chambless, Caputo, Bright, & Gallagher, 1984)
150 assessed the extent of fearful panic beliefs and catastrophic cognitions about panic and anxiety with 15
151 items to be answered on a 5-point Likert scale. (3) The Bodily Sensations Questionnaire (BSQ; Chambless
152 et al., 1984) assessed the extent of fear of bodily sensations that are associated with panic attacks. 17
153 items must be answered on a 5-point Likert scale. (4) The Mobility Inventory (MI; Chambless, Caputo, Jasin,
154 Gracely, & Williams, 1985) assessed the extent of agoraphobic avoidance behaviour, once when exposed
155 to fearful situation by himself and once when accompanied by another person. 26 items must be answered
156 on a 5-point Likert scale. (5) Depressiveness was evaluated with the Beck Depression Inventory II (BDI-II;
157 Beck, Steer, & Brown, 1996; Hautzinger, Keller, & Kühner, 2006) including 21 items that match the *DSM-*
158 *IV-TR* major depression criteria.

159

160 **Statistical analyses**

161 Group comparisons with respect to sociodemographic and clinical variables were evaluated using
162 univariate analyses of variance (ANOVA) for continuous variables and Chi-square test (χ^2) for dichotomous
163 variables. Blood cortisol and cytokine data were subject to log transformation to reduce the skewness
164 parameter. Group differences in the cortisol and cytokine responses (IL-6, IL-10, TNF-α) were assessed

using a 2 (group: PD patients, healthy controls) x 10 (time: -15, -1, +1, +10, +20, +30, +45, +60, +75, +105 min) ANCOVA for repeated measures with baseline values (-15, -1 min) as covariates and Greenhouse-Geisser corrections if necessary. Pearson correlations were conducted to test for an association between peak cytokine reaction and clinical variables. For cortisol analysis, data from two healthy controls were excluded due to outlying values of more than three standard deviations above the mean. All analyses were performed using SPSS, version 22 (IBM, Chicago, Illinois). The figures were created by Sigma Plot 11.0 (Systat Software Inc., Erkrath, Germany). The data in the figures are presented in original units.

Results

Study participants

The baseline characteristics of the study groups are described in Table 1. Groups were well matched with regard to sociodemographic variables (p's ≥ .070). As expected, PD patients scored significantly higher in the panic-specific questionnaires (p's ≤ .001) as well as in the self-reported depressiveness measured with the BDI-II (p ≤ .001).

Table 1

Sociodemographic variables and clinical self-report data of the study participants

	Panic disorder patients (n = 32)	Healthy controls (n = 32)	F/χ^2	p
Sociodemographic characteristics				
Females, n (%)[†]	20 (62.5)	20 (62.5)	0.000	1.000
Age in years	35.06 (10.43)	36.00 (11.01)	0.122	.728
Body mass index	23.29 (2.49)	22.51 (1.97)	1.938	.169
Smoking[†]	16 (50.0)	8 (25.0)	4.267	.070
Oral contraceptive use[†]	9 (45.0)	5 (25.0)	1.758	.320

Clinical self-report data (total scores)				
BDI-II [0-63]	10.78 (8.26)	4.31 (5.75)	13.218	.001***
PAS [0-52]	19.69 (9.68)	1.28 (2.43)	108.787	.000***
ACQ [0-4]	0.94 (0.54)	0.38 (0.34)	25.205	.000***
BSQ [0-4]	1.66 (0.75)	0.59 (0.48)	45.654	.000***
MI alone [0-4]	1.26 (1.00)	0.17 (0.35)	33.778	.000***
MI accompanied [0-4]	0.94 (0.97)	0.73 (0.17)	24.858	.000***

Note. BDI-II = Beck Depression Inventory II; PAS = Panic & Agoraphobia Scale; ACQ = Agoraphobic Cognitions Questionnaire; BSQ = Body Sensations Questionnaire; MI = Mobility Inventory.

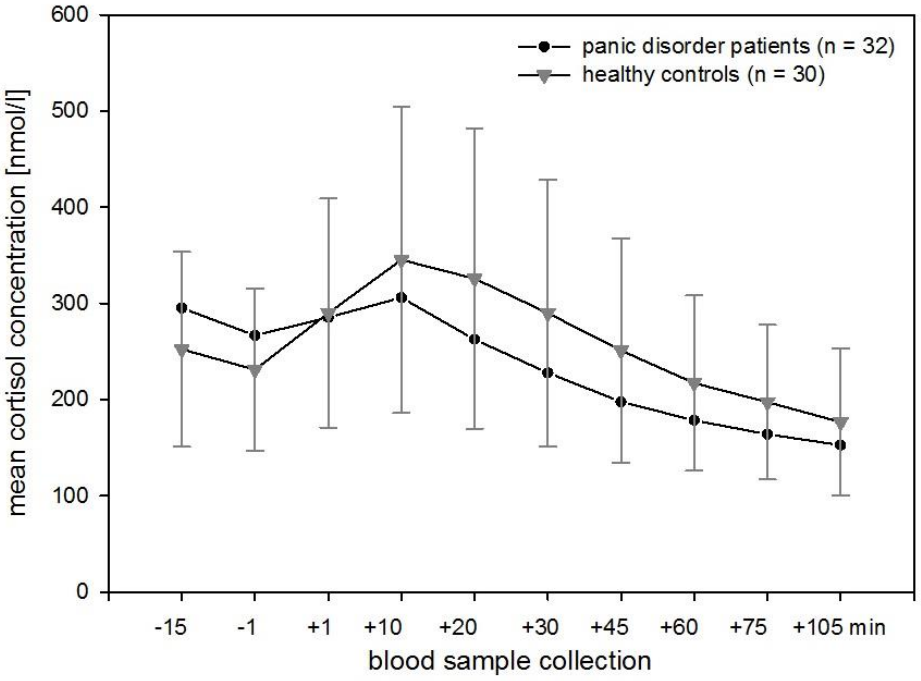
† χ^2-test.

*** $p \leq 0.001$.

Cortisol stress response

Figure 1 illustrates the cortisol stress response as a function of study group. Baseline cortisol levels did not differ between both groups (-15 min: $F_{1;61} = 1.263$, $p = .266$; -1 min: $F_{1;61} = 0.709$, $p = .403$). The repeated measures ANCOVA with baseline cortisol concentrations as covariates (-15 min, -1 min) revealed a significant main effect of time ($F_{2.562;148.590} = 6.940$, $p \leq .001$, $\eta^2 = 0.107$), a significant time x group interaction effect ($F_{2.562;148.590} = 3.258$, $p \leq .05$, $\eta^2 = 0.053$) as well as a significant main effect of group ($F_{1;58} = 6.083$, $p \leq .05$, $\eta^2 = 0.095$).

No significant differences in the subjective levels of distress were observed, neither for the PASA [mean (SD) for PD patients: 0.13 (1.30), for healthy controls: -0.43 (1.20), $F_{1;61} = 3.025$, $p = .087$] nor for the VAS scale [mean (SD) for PD patients: 49.68 (14.87), for healthy controls: 52.99 (12.33), $F_{1;61} = 0.900$, $p = .347$].



199

200 **Figure 1.** Mean (± SD) blood cortisol concentrations in response to the TSST of the PD patients and the
201 healthy controls.

202

203 *Cytokine response*

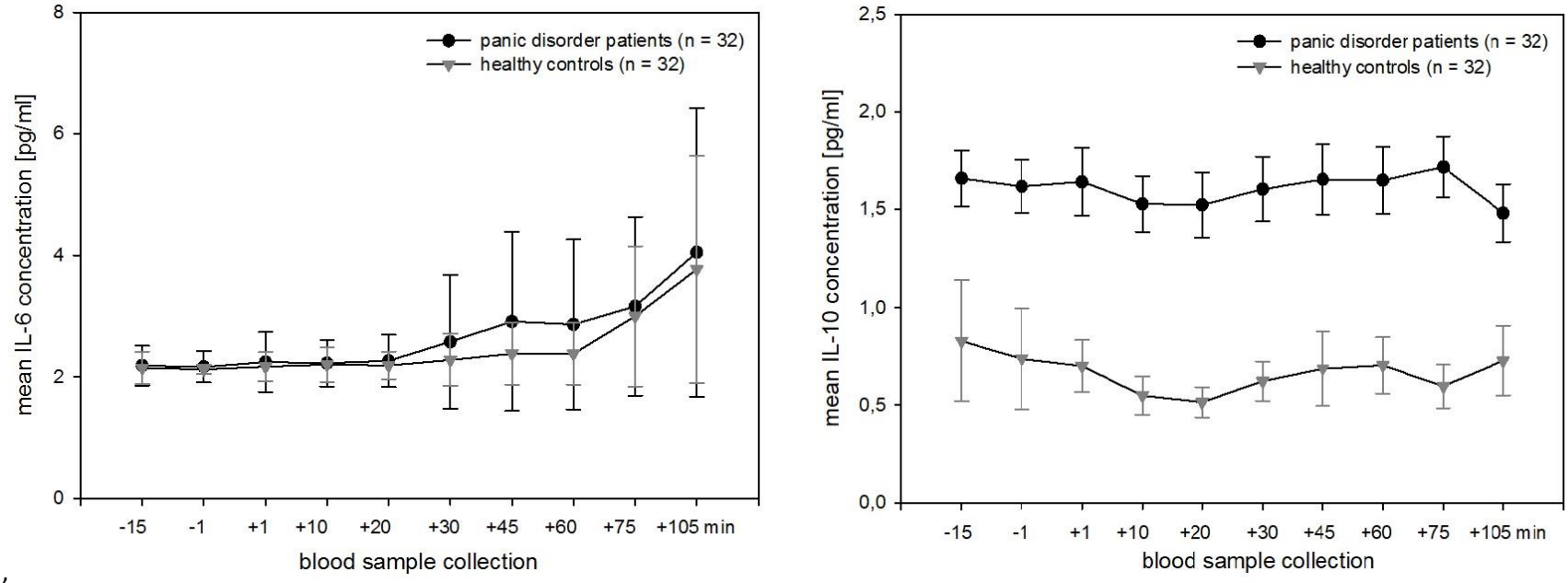
204 For the pro-inflammatory IL-6, there were no significant baseline differences in IL-6 concentration (*p*'s ≥
205 .288). The repeated measures ANCOVA revealed a non-significant trend for a main effect of time
206 ($F_{2.345;140.680}$ = 2.581, p = .070, η^2 = 0.041); neither a time x group interaction effect ($F_{2.345;140.680}$ = 0.520, p =
207 .624, η^2 = 0.009) nor a main effect of group ($F_{1;60}$ = 0.410, p = .525, η^2 = 0.007) were observed (see Figure
208 2).

209 For high-sensitive IL-6 assessment, a significant main effect of time ($F_{1.815;110.704}$ = 54.229, p = .000, η^2 =
210 0.471) emerged; neither a main effect of group ($F_{1;61}$ = 1.119, p = .294, η^2 = 0.018) nor a time x group
211 interaction effect ($F_{1.815;110.704}$ = 0.490, p = .596, η^2 = 0.008) were observed.

Regarding TNF-α, repeated measures ANCOVA failed to show a significant main effect of time ($F_{2.054;123.219}$ = 0.868, p = .425, η^2 = 0.014), time x group interaction effect ($F_{2.054;123.219}$ = 0.272, p = .768, η^2 = 0.005), or main effect of group ($F_{1;60}$ = 0.147, p = .703, η^2 = 0.002; see Figure 2). Groups did not differ in baseline TNF-α concentration (p's ≥ .179).

For the anti-inflammatory IL-10, repeated measures ANCOVA showed a significant main effect of time ($F_{5.476;328.544}$ = 2.240, p = .045, η^2 = 0.036), a significant time x group interaction effect ($F_{5.476;328.544}$ = 2.839, p = .013, η^2 = 0.045), and a significant main effect of group ($F_{1;60}$ = 13.902, p = .000, η^2 = 0.188). PD patients demonstrated higher baseline IL-10 concentrations (p's ≤ .001).

Pearson correlational analysis revealed a relationship for the peak IL-6 concentration significantly with the PAS global disease severity (r = .372, p = .036) and at trendlevel with the BDI-II depressiveness (r = .328, p = .067).



223 ,

224 **Figure 2.** Mean (± SD) blood cytokine concentrations (left: IL-6; right: IL-10) in response to the TSST of the PD patients and the healthy controls.

Discussion

This study analyzed pro- (IL-6, TNF-α) and anti-inflammatory (IL-10) cytokine activity in response to a laboratory psychosocial stress induction in PD patients in comparison to healthy control individuals. We found a significant time x group interaction effect both for cortisol and IL-10 release. Our main finding is that increased baseline and challenged anti-inflammatory IL-10 production was present in PD patients as compared to healthy individuals. No substantial group differences were observed for IL-6 and TNF-α. However, the peak IL-6 reaction correlated significantly with global panic disease severity. Secondly, the PD patients demonstrated lower challenged cortisol concentrations as compared to healthy volunteers.

In healthy individuals, adequate cortisol secretion under stress has the function to attenuate pro-inflammatory cytokine secretion (Padgett & Glaser, 2003). A reduced cortisol secretion would suggest increased pro-inflammatory and thus compensatory increased anti-inflammatory cytokine reactions. A previous investigation in PTSD patients found that a reduced cortisol availability under stress was accompanied by an increased pro-inflammatory cytokine reaction (Rohleder et al., 2004). Together, these findings suggest similar results for PD patients, because research extensively replicated a decreased cortisol reaction upon psychosocial (Petrowski et al., 2010; Petrowski et al., 2013; Wichmann, Kirschbaum, Böhme, et al., 2017; Wichmann, Kirschbaum, Lorenz, & Petrowski, 2017) and physiological stress (Graeff, Garcia-Leal, Del-Ben, & Guimarães, 2005), with no differences found in a direct comparison of PTSD and PD patients (Wichmann, Kirschbaum, Böhme, et al., 2017). In this study, we were able to replicate overall research finding of a cortisol hypo-responsiveness upon provocation in PD patients. However, contrasting with previous results, we were not able to detect significantly increased pro-inflammatory cytokine secretion in PD patients. Instead, we found increased baseline and challenged levels of the anti-inflammatory cytokine IL-10. Thus we agree with studies that also failed to find substantial differences in baseline pro-inflammatory cytokine levels (Koh & Lee, 2004; Rapaport & Stein, 1994; Van Duinen et al., 2008; Weizman et al., 1999), but conflict with

previous reports of both increased (Hoge et al., 2009) and decreased pro-inflammatory cytokine activity (Koh & Lee, 2004; Van Duinen et al., 2004).

It is assumed that cytokines with anti-inflammatory properties are compensatory released in response to an increased secretion of pro-inflammatory cytokines (Opal & DePalo, 2000). The TSST resulted in a significant increase of IL-6 both in the patients and healthy volunteers, which is in accordance with meta-analytic findings (Steptoe et al., 2007). However, in our patient sample we found no evidence for increased levels of pro-inflammatory cytokines in comparison to the healthy volunteers. A possible explanation might be that in PD patients other unmeasured cytokines with pro-inflammatory properties than those analyzed in this study resulted in an increase of the anti-inflammatory cytokine IL-10. For instance, IL-1RA and IFN-gamma were also found to respond to psychosocial stress induction (Steptoe et al., 2007). Further, the stage of disease might have an influence. PD is an episodic disease with episodes of remission and relapses. This sample included patients with a broad spectrum of disease severity ranging from mildly to severely affected patients. The correlational analysis showed that more severely affected patients, which represented only 25% of this study sample, demonstrated a greater peak level of the pro-inflammatory IL-6. This result suggests a greater pro-inflammatory activity in more severe cases, which have been reported for PTSD patients as well (von Känel et al., 2007). It is plausible that the concentration on either severely affected, mildly affected or remitted patients would have produced different results, eventually with greater levels of pro-inflammatory cytokines.

Accumulating evidence suggests that the HPA-axis progressively becomes hypo-responsive with chronic stress exposure/disease course (Fries, Hesse, Hellhammer, & Hellhammer, 2005). Although the cross-sectional design of this study does not allow longitudinal inferences, it is plausible that due to cytokine-HPA interactions, cytokine secretion also becomes altered with prolonged duration of disease. Chronic hormone and/or cytokine derangement might induce inflammation processes that eventually result in the development of somatic diseases. For instance, it is well known that inflammation contributes to atherosclerosis initiation and manifestation which is the main cause

for coronary artery disease (Hansson, 2005). Such mechanisms could represent one psychophysiological mechanism from PD diagnosis to cardiovascular outcomes (Gomez-Caminero, Blumentals, Russo, Brown, & Castilla-Puentes, 2005; Smoller et al., 2007). However, without the use of prospective designs the existence of such a mechanism remains speculative. Longitudinal studies are needed to confirm inflammation as missing link between PD and cardiovascular disease.

Strengths of this study are the simultaneous assessment of cortisol levels because stress hormones are known to impact immune response and its feedback functions. Previous studies often failed to assess stress hormone levels. Further we controlled for time of day and menstrual cycle phase for blood collection, which is important because some cytokines follow a circadian and monthly rhythm with secretion rates varying as a function of time of day and of luteal or follicular phase (Hermann et al., 2006; O'Brien et al., 2007; Vgontzas et al., 2005).

Some study limitations should be mentioned here. First, in some analyses there may have been limited power due to small sample size. Figure 2 suggests differences in challenged IL-6 concentrations, but ANCOVA failed to reveal a significant time x group interaction effect. Secondly, our results do not allow conclusions regarding cytokine levels in PD in relation to other anxiety or affective disorders. Future studies should make direct comparisons between the patient groups themselves. Further, it would be interesting to analyze reversibility of altered cytokine reactions. Future studies should include patients with recent onset and patients with a chronic or remitted course of disease. Since cytokine levels before the development of PD are usually unknown, prospective study designs are required. Last, residual confounding could have resulted from current life stress or early childhood maltreatment which was not assessed in this study, but is known to impact immune response (Carpenter et al., 2010; Maes et al., 1998).

To conclude, this study found evidence for increased anti-inflammatory activity in PD patients under baseline and psychosocial stress conditions. Results tentatively provide evidence for a low-grade inflammatory process in PD, possibly representing one mediating factor between PD and increased risk for cardiac outcomes. Findings are in need of replication in larger samples of in- and outpatients with

multiple cytokine assays and inflammatory markers. Meta-analytic strategies could also help to explain inconsistent findings.

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Programmspezifischer Teil

a) Wurden die im Antrag formulierten Forschungsziele erreicht oder gab es Änderungen? Wenn ja, welche?

Die im Antrag formulierten Forschungsziele wurden mit dem identischen Design, wie im Antrag vorgestellt, untersucht.

b) Welcher wissenschaftliche Zugewinn wurde durch den Verbund erzielt? Wurden strukturelle Maßnahmen ergriffen, durch die die Zusammenarbeit gestaltet und der Verbund gestärkt wurde?

Das Projekt hat zum einen (1) zum Aufbau der Expertise in der Arbeitsgruppe in der Psychoneuroendokrinologie unter Verwendung von High-Sensitive Elisa geführt. Diese High-Sensitive ELISA sind vor allem im Bereich der Stressforschung und bei Langzeitverläufen im Rahmen von chronischen unterschwelligen Entzündungen von besonderem Interesse. Diese Verfahren werden mittlerweile bei hochrangigen Journals als Goldstandard gefordert. Das Projekt hat zum anderen (2) methodische Probleme der ELISA zu Tage gebracht. Je nach ELISA-Kit wurden unterschiedliche Wertebereiche erreicht. Dies lag nicht am Labor des Uniklinikums, sondern ist ein Reliabilitätsproblem der ELISA -Herstellung. Daher wurden die Zweitproben zu einem weiteren Labor an der TU-Dresden

(Prof. Kirschbaum) geschickt. In diesem Labor konnten über Doppelanalysen diese Fehlwerte bereinigt werden. Angestoßen durch die Werte aus dieser Studie und den Erfahrungen durch die Zweitanalysen wurde ein weiteres Grundlagenprojekt in Kooperation mit Prof. Dr. Kirschbaum initiiert, in dem die beiden High-Sensitive- ELISA von den beiden Herstellern miteinander verglichen werden. Hierzu werden eine gesunde Stichprobe sowie zwei Patientenstichproben herangezogen. Anhand dieser Daten soll die Fehlerrate, Reliabilität, Sensitivität, Spezifität, Normwerte sowie Datenrange für die ELISA-Kits spezifiziert werden.
Die bisher erzielten Daten wurden in einer Publikation bei Psychoneuroendocrinology eingereicht sowie beim Internationalen Kongress der Psychoneuroendokrinologischen Fachgesellschaft vorgestellt (ISPNE, 2018).

c) In welcher Form fand eine thematische oder örtliche Schwerpunktsetzung statt?

Angeregt durch die Forschungsförderung und das vorliegende Forschungsprojekt fand eine örtliche Schwerpunktsetzung (TU-Dresden) bezüglich der Analytik aber auch bezüglich Erhebung von Zytokinen im psychophysiologischen oder Stressforschungsbereich statt. Ferner wird diese Expertise weiter ausgebaut, in dem in einem Grundlagenprojekt in Kooperation mit Prof. Dr. Kirschbaum die beiden High-Sensitive- ELISA von den beiden Herstellern miteinander verglichen werden. Anhand dieser Daten soll die Fehlerrate, Reliabilität, Sensitivität, Spezifität, Normwerte sowie Datenrange für die ELISA-Kits spezifiziert werden. Diese Informationen sind für jegliche zukünftige psychoneuroendokrinologische und Stressforschung von hoher Relevanz!

d) Wie schätzen Sie die internationale Sichtbarkeit der Forschergruppe ein?
Die internationale Sichtbarkeit der Ergebnisse ist hoch, da alle Ergebnisse international publiziert werden. Ferner wurden erste Ergebnisse auf dem internationalen ISPNE-Kongress in Irvine, CA 2018 präsentiert.

e) Durch welche Maßnahmen wurde der wissenschaftliche Nachwuchs gefördert?
Im Rahmen des Projektes konnte ein Masterstudent seine Qualifikationsarbeit absolvieren sowie drei Doktorarbeiten geschrieben werden.

f) Welche Maßnahmen zur Gleichstellung von Wissenschaftlerinnen und Wissenschaftlern wurden umgesetzt?
In dem Forscherteam und in den untersuchten Probanden befanden sich leider nur Männer und so konnte in diesem Projekt keine Maßnahme umgesetzt werden.

g) Ggf. Transferaspekte: Wurden aus Anwendungssicht Fortschritte gegenüber dem Stand der Technik erreicht und wenn ja, welche? Lassen sich daraus Folgeprojekte ableiten?

Angeregt durch die Forschungsförderung und das vorliegende Forschungsprojekt konnte eine örtliche Expertise in der Analytik aber auch in der Erhebung von Zytokinen im psychophysiologischen oder Stressforschungsbereich aufgebaut werden. Ferner wird diese Expertise weiter ausgebaut, in dem in einem Grundlagenprojekt in Kooperation mit Prof. Dr. Kirschbaum die High-Sensitive- ELISA von den beiden Herstellern miteinander verglichen werden. Anhand dieser Daten soll die Fehlerrate, Reliabilität, Sensitivität, Spezifität, Normwerte sowie Datenrange für die ELISA-Kit spezifiziert werden. Diese Informationen sind für jegliche zukünftige psychoneuroendokrinologische und Stressforschung auf internationaler Ebene von sehr hoher Relevanz.

Übersichten und Verzeichnisse

Promotionen:

Name, Vorname	Alter zum Zeitpunkt d. Promotion	Abschluss der Promotion in welcher Förderphase des Projektes
Tittel, Thomas	28	Abschluss geplant Ende 2018
Rohwerder, Max	26	Abschluss geplant Ende 2018
Yvonne Thomson	24	Abschluss geplant Ende 2018

Masterarbeiten:

Name, Vorname	Alter zum Zeitpunkt d. Masterarbeit	Abschluss der Promotion in welcher Förderphase des Projektes
Johanna Jurczyk	24	Ende 2018

Veröffentlichungen und Patente aus der Forschergruppe

Petrowski, K., Wichmann, S., & Kirschbaum, C. (submitted). Stress-induced pro- and anti-

inflammatory cytokine concentrations in panic disorder patients. Psychoneuroendocrinology.