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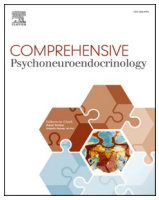

Preliminary results of anti-inflammatory cytokine concentrations predicting therapy outcome in panic disorder

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ABSTRACT

Background: Patients with panic disorder (PD) show alterations of the immune reactivity to acute stress, which could serve as a marker for effective treatment. Nevertheless, the effect of immune reactivity under acute stress before treatment on therapy outcome remains unclear.
Methods: A total of $N = 16$ PD patients performed the Trier Social Test. Blood sample collection of anti-inflammatory cytokine IL-10 accompanied the TSST. The Mobility Inventory was handed out for the assessment of avoidance behavior before and after treatment. Area under the curve with respect to the ground (AUC_G) and increase (AUC_I) were calculated for assessed cytokine levels and were used as predictors for therapy outcome in regression analyses.
Results: AUC_G significantly predicts avoidance behavior in company after treatment ($\beta = -0.007$, $p = .033$) but not avoidance behavior alone ($\beta = -0.003$, $p = .264$). AUC_I does not significantly predict therapy outcome.
Conclusion: Higher concentrations of anti-inflammatory cytokine IL-10 under acute stress before treatment predicts less avoidance behavior in company after therapy. Immune markers seem to play a crucial role in the maintenance of mental disorders such as PD. Underlying mechanisms and IL-10 as a marker for individualized treatments should be investigated in future studies.

1. Introduction

Panic disorder (PD) is a mental disorder characterized by acute, stressful panic attacks changing the behavior of those affected by leading to avoidance of situations or locations associated with panic attacks [1]. The influence of psychosocial stressors on the development of mental disorders might be explicable via changes in immune system functioning [2]. Cytokines are important proteins regulating the immune response to injuries, infections, and stressful events. The increased anti-inflammatory cytokine concentrations in PD under psychosocial stress has been established [3]. Whether these alterations in inflammation predict the well-established effect of exposure therapy on psychological symptoms in PD is unclear.

Due to the close relationship between the stress response and immune reactivity, recent studies focused on immune reactivity after treatment. It was shown that cognitive behavioral therapy (CBT) can influence immune parameters [4,5]. However, the findings are inconsistent and the role of anti-inflammatory cytokines such as IL-10 remains unclear. Since CBT focuses on coping and problem-solving skills that should reduce vulnerability to stress [6], the acute immune response to stress could serve as a marker for effective treatment. Therefore, the question arises whether the change in immune response to stress can be an active factor in the treatment of PD.

Pearlstein and colleagues (2020) provide the first evidence that the immune response to stress induction may serve as a predictor of CBT outcomes in individuals with affective disorders. They found significant correlations between chronic stress, inflammatory markers, and depression both before and after CBT. Cytokines measured before therapy predicted depressive symptoms after treatment. Individuals with chronic stress and high levels of inflammation were less likely to benefit from psychotherapy [7]. However, female patients with post-traumatic stress disorder (PTSD) and higher levels of

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anti-inflammatory cytokine under acute stress prior to therapy showed lower symptom burden after treatment [8].

To understand the predictive influence of immunoreactivity to psychosocial stress on treatment outcome in PD, the following study assessed IL-10 levels after acute stress induction before treatment as a predictor for therapy outcome (avoidance behavior) in PD patients.

2. Methods

2.1. Study sample

Patients were recruited in an outpatient facility. 36 patients were screened, 16 of whom were eligible for specialised treatment in the day clinic. Exclusion criteria were a lifetime history of psychiatric disorders, psychopharmacological or glucocorticoid-containing medication intake. The Structured Clinical Interview (SCID-IV) was conducted for the assessment of DSM-IV-TR mental disorder diagnoses. Patients with a primary diagnosis of PD with or without agoraphobia were included. Patients were in average $M = 35.13$ years old ($SD = 12.27$) and 56.3% were female. 56.3% of patients were unmarried, 37.5% were married. 56.3% of patients did smoke with a maximum of 10 cigarettes per day. Patients received a manualized exposure treatment by Lang et al. [9] in a day clinic for 6 weeks.

All participants provided written informed consent. The study procedure was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the Medical Faculty, Technische Universität Dresden, Germany (EK#7012006).

2.2. Psychosocial stress induction and hormone sampling

The standardized protocol for the Trier Social Stress Test (TSST) was applied for the reliable induction of acute moderate psychosocial stress requiring a mock job interview (5 min) and a mental arithmetic task (5 min) of the participants, which are performed in front of a mock selection committee [10]. Women were tested exclusively in the luteal phase of their menstrual cycle. To account for the circadian rhythm of cytokine secretion, the TSST was performed not earlier than 2 p.m. in the afternoon. Blood samples were collected via a venous catheter 15 and 1 min prior to the TSST as well as 1, 10, 20, 30, 45, 60, 75 and 105 min after the TSST and stored at 4 °C. IL-10 concentrations were determined using highly-sensitive ELISA enzyme-linked immunosorbent assays (IBL International GmbH, Germany).

2.3. Clinical assessment

The Mobility Inventory [11] was handed out before and after treatment assessing the extent of agoraphobic avoidance behavior accompanied and alone. 26 items describe different situations, such as restaurants, supermarkets or trains and are answered on a 5-point Likert scale with '1 – never avoid' to '5 – always avoid'. Internal consistency (Cronbach's alpha) in this sample was $\alpha = 0.96$ for MI alone and $\alpha = 0.97$ for MI accompanied.

2.4. Statistical analyses

IL-10 values were subjected to ln-transformations because of skewness [12]. Differences in subjective symptom burden (MI) before vs. after therapy were calculated using paired t-tests. Values for AUC_G, AUC_I (Pruessner et al., 2003) and pre-treatment scores were used as predictors for therapy outcome in regression analyses. R^2 greater than $|0.26|$ indicate a high goodness-of-fit [13].

3. Results

When correlating MI scores before and after therapy, significant correlations for MI alone and accompanied before therapy ($r = 0.593$; $p < .05$), MI accompanied before therapy and MI alone after therapy ($r = 0.657$, $p < .01$), MI alone and accompanied after therapy ($r = 0.580$, $p < .05$) were found.

Pre- and post-treatment scores for MI alone (pre: $M = 1.14$, $SD = 0.95$; post: $M = 0.26$, $SD = 0.34$) and accompanied (pre: $M = 1.08$, $SD = 1.01$; post: $M = 0.33$, $SD = 0.38$) differed significantly with less avoidance behavior after treatment (alone: $t(1, 15) = 4.16$, $p < .001$, $d = 1.04$; accompanied: $t(1, 15) = 3.00$, $p = .009$, $d = 0.75$).

Table 1 shows results of the regression analyses. The regression model for avoidance behavior in company shows a good model fit with $R^2 = 0.27$. AUC_G significantly predicts avoidance behavior in company after treatment (see Fig. 1) but not avoidance behavior alone. AUC_I does not significantly predict therapy outcome.

Table 1
Prediction of avoidance behavior after treatment by IL-10 concentrations before treatment under acute stress.

	MI accompanied_e				
			Model fit		
	β	SE	F	p	R^2
AUCG IL-10	−0.007*	0.003			
AUCI IL-10	−0.001	0.002	2.83	.083	.27
MI accompanied_b	0.153	0.086			
	MI alone_e				
			Model fit		
	β	SE	F	p	R^2
AUCG IL-10	−0.003	0.003	1.72	.301	.13
AUCI IL-10	0.002	0.002			
MI alone_b	0.184	0.087			

Note. AUC_G = Area under the curve with respect to the ground; AUC_I = Area under the curve with respect to increase; MI = Mobility Inventory; b = pre-treatment scores; e = post-treatment scores; R^2 = adjusted R^2.
*p < .05.

4. Discussion

This study assessed the predictive role of anti-inflammatory cytokine IL-10 for therapy outcome of PD patients. The concentration of IL-10 under acute stress predicted accompanied avoidance behavior after treatment with higher levels of IL-10 predicting less avoidance behavior but IL-10 levels did not predict avoidance behavior alone. These results are in line with past studies showing an effect of cortisol levels under acute stress before treatment on avoidance behavior accompanied after treatment but not on avoidance behavior alone [14]. One explanation could be, that PD patients tend to use more safety behavior when confronting themselves with anxiety-inducing situations on their own, which is more difficult to control during treatment and favors the maintenance of the symptoms. A favorable effect of high IL-10 concentrations before therapy for treatment outcome was already found in a past study with PTSD patients [8]. These results strengthen the assumption of immune response to acute stress as an active factor in the treatment of PD and other mental disorders. In past studies, an association of inflammation, anxiety symptoms and the connectivity between amygdala and ventromedial prefrontal cortex, crucial for emotion regulation, was found [15]. Cytokine concentrations could thereby influence the function and connectivity of these brain areas and in turn affect therapy outcome. As the present and a past study [8] shows effects of the anti-inflammatory cytokine IL-10 on therapy outcome, it might be beneficial for treatment outcome and could serve as a marker for identifying personalized interventions.

As the sample size of this study is rather small and includes male and female patients, this study provides only preliminary results and future studies should further assess the effect of the immune system on therapy outcome and its interaction with crucial areas of the CNS in a larger

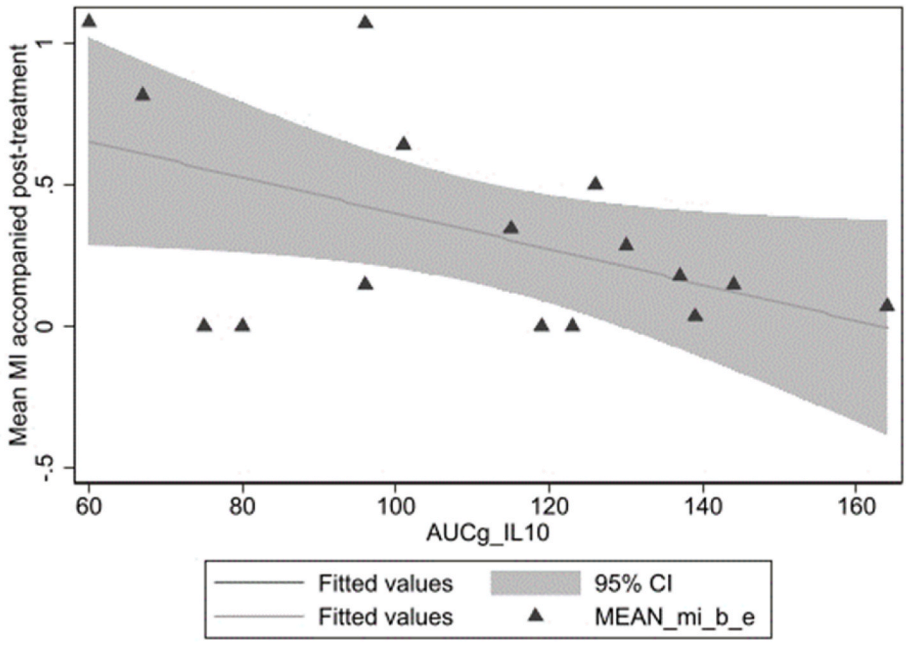

Fig. 1. Prediction of post-treatment avoidance behavior in company by AUC_G IL-10 before treatment.
Note. AUCg = area under the curve with respect to the ground; IL-10 = Interleukin 10; MI = Mobility Inventory; CI = confidence interval.

sample.

This study is to the best knowledge of the authors the first study showing predictive effects of anti-inflammatory cytokines on therapy outcome in PD patients with higher levels of IL-10 under acute stress predicting less avoidance behavior after treatment.

CRediT authorship contribution statement

Vanessa Renner: Data curation, Formal analysis, Methodology, Writing – original draft. **Rupert Conrad:** Supervision, Writing – review & editing. **Clemens Kirschbaum:** Formal analysis, Resources, Supervision, Writing – review & editing. **Thomas Lorenz:** Conceptualization, Resources, Supervision, Writing – review & editing. **Katja Petrowski:** Conceptualization, Investigation, Project administration, Supervision, Writing – original draft, Writing – review & editing, Funding acquisition.

Declaration of competing interest

No conflict.

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Further reading

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