



Pre-existent anxiety symptoms is associated with modified behavioral response during endotoxemia

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Introduction

- Experimental endotoxin administration is a well-established model to analyze the contribution of pro-inflammatory cytokines in the development of neuropsychiatric symptoms.
- Previous studies mostly focused on the effect of endotoxin on the development of behavioral alterations. The effect of inter-individual differences in pre-existent psychological state on the behavioral response remains unknown, and would require increased statistical power to be analyzed.

→ In the present study, we assessed whether pre-existent variability in psychological state is associated with the development of anxiety symptoms after endotoxin administration.

→ We combined data from multiple studies performed at two study sites to increase the statistical power.

Methods

Data from several studies performed at the Institute of Medical Psychology and Behavioral Immunobiology (Essen, Germany) and at Karolinska Institutet/Stress Research Institute (Stockholm, Sweden) were combined. All studies included healthy subjects without inflammatory or psychiatric condition and used a protocol of endotoxin administration (lipopolysaccharide at 0.4-0.8 ng/kg of body weight) in comparison to saline administration.

Plasma concentrations of interleukin-6 (IL-6) and tumor necrosis factor- α (TNF- α) were analyzed before and around 2, 3.5 and 6 hours after the endotoxin or saline administration. Standardized values (Z-scores) were used in order to reduce potential bias related to biological techniques. State anxiety symptoms were assessed at the same time points (2, 3.5 and 6 hours after the administration) using the State part of the State-Trait Anxiety Inventory (STAI). In addition, pre-existent anxiety and depression was assessed before the injection using the Trait part of the STAI and the Hospital Anxiety and Depression Scale (HADS).

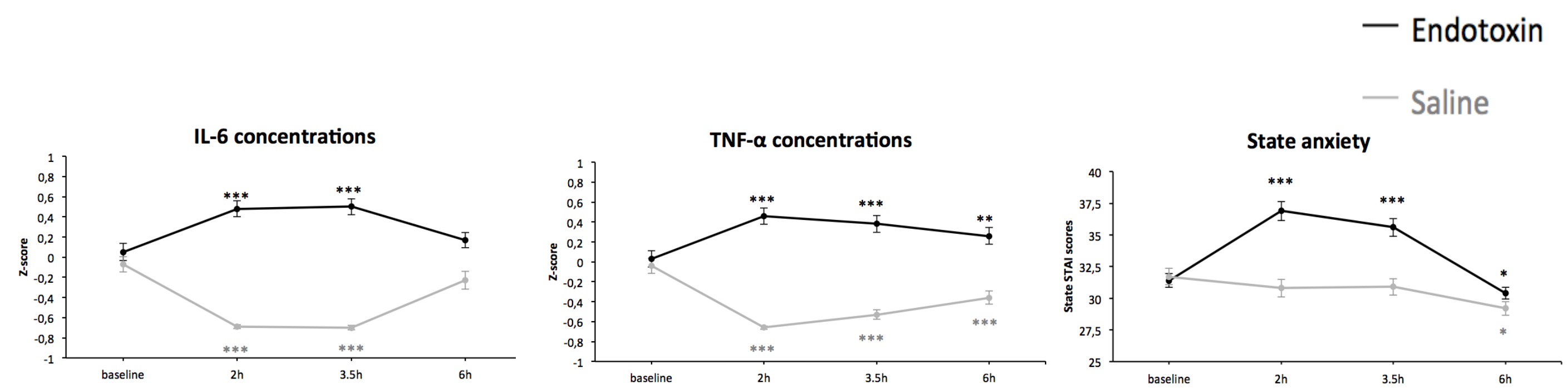
209 subjects were included. Of these, 90 received an endotoxin injection once, 41 a saline administration once, and 78 were injected twice (once with endotoxin and once with saline in a cross-over design with at least one week of wash-out). In total, the analyses are based on 168 occasions of endotoxin administration and 118 occasions of saline administration.

Conclusion

- These data suggest that inter-individual differences in anxiety or depression symptoms prior to administration do not appear to explain the extent of mood impairments during endotoxemia, at least in non-patient samples.
- The variation of pre-existent anxiety symptoms was, however, related to a modified mood response with a faster and stronger decline after the peak of symptoms.

Results

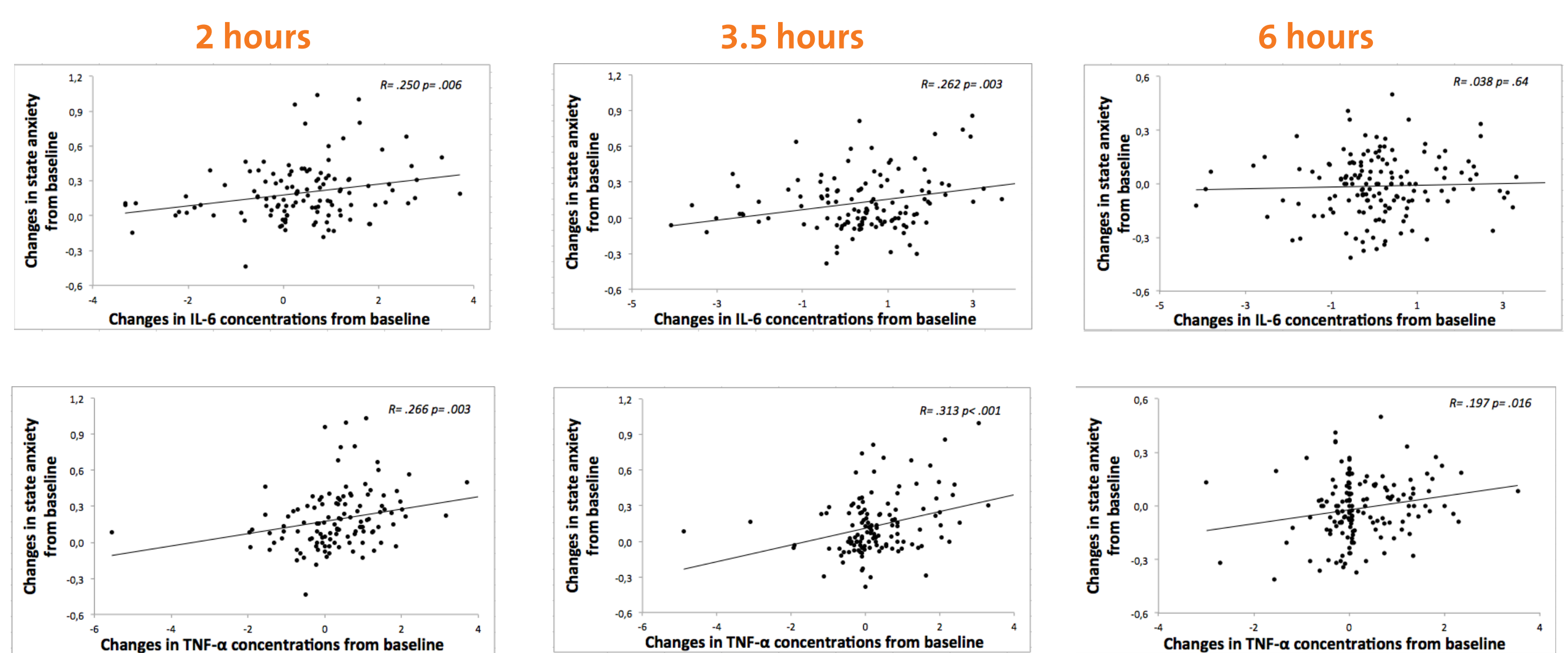
Effect of endotoxin administration on systemic cytokine concentrations and anxiety state



Systemic concentrations of IL-6 and TNF- increased after endotoxin administration. Six hours after the administration, TNF- concentrations remained significantly higher than baseline levels.

The endotoxin administration also induced a transient increase in anxiety symptoms, which returned below baseline values at six hours after the administration. Anxiety symptoms were also below baseline levels six hours after the saline administration.

Relationship between endotoxin-induced increase in systemic cytokine concentrations and anxiety state

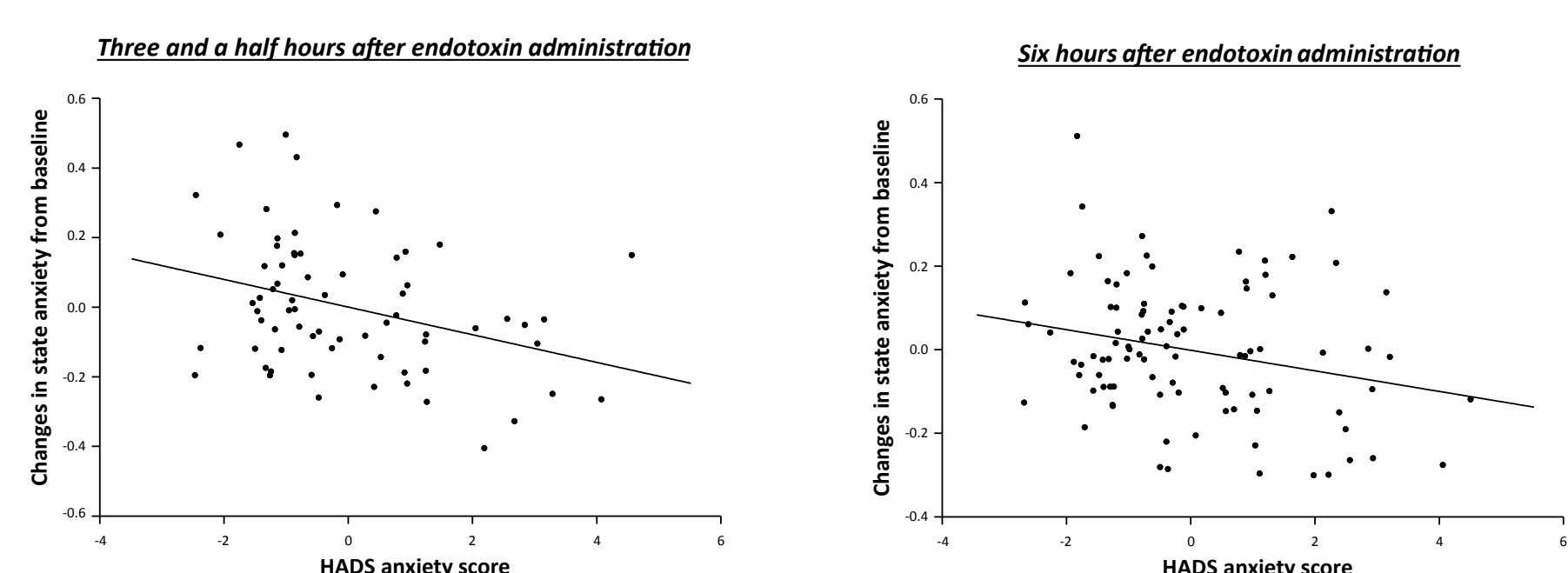


Higher increase in IL-6 and TNF- concentrations was associated with stronger development in anxiety symptoms up to 6 hours after the LPS administration.

Association of pre-existent psychological state with the development of anxiety symptoms after endotoxin administration

Dependent variables	R ² =R ²	β	p
Two hours after LPS administration			
HADS anxiety	.107	-.194	.18
HADS depression	.107	.178	.16
Trait anxiety	.107	.027	.85
Three and a half hours after LPS administration			
HADS anxiety	.281	-.408	.007
HADS depression	.281	.089	.50
Trait anxiety	.281	.230	.14
Six hours after LPS administration			
HADS anxiety	.140	-.324	.02
HADS depression	.140	.125	.32
Trait anxiety	.140	.056	.68

Linear regression analyses controlled for age, sex, BMI, LPS dose and study design



Higher levels of pre-existent anxiety symptoms (HADS) were associated with a stronger reduction in state anxiety symptoms after the peak of symptoms, at 3.5 hours and 6 hours after the endotoxin administration.