



## Cortisol-induced enhancement of emotional face processing in social phobia depends on symptom severity and motivational context

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### ABSTRACT

We investigated the effects of cortisol administration on approach and avoidance tendencies in 20 patients with social anxiety disorder (SAD). Event-related brain potentials (ERPs) were measured during a reaction time task, in which patients evaluated the emotional expression of photographs of happy and angry faces by making an approaching (flexion) or avoiding (extension) arm movement. Patients showed significant avoidance tendencies for angry but not for happy faces, both in the placebo and cortisol condition. Moreover, ERP analyses showed a significant interaction of condition by severity of social anxiety on early positive (P150) amplitudes during avoidance compared to approach, indicating that cortisol increases early processing of social stimuli (in particular angry faces) during avoidance. This result replicates previous findings from a non-clinical sample of high anxious individuals and demonstrates their relevance for clinical SAD. Apparently the cortisol-induced increase in processing of angry faces in SAD depends on symptom severity and motivational context.

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In a recent study, we investigated the effects of cortisol administration on threat processing and approach and avoidance behavior in a non-clinical sample of high and low anxious students (van Peer et al., 2007). The results of that study showed relatively faster avoidance behavior as well as enhanced positive amplitudes (P150 and P300) on midline electrodes during avoidance of angry faces after cortisol administration, indicating increased processing of threat stimuli during threat avoidance. Importantly, these effects were found only in high and not low anxious participants, suggesting a context-specific effect of cortisol on threat processing in participants highly sensitive to threat signals. These findings may be very relevant for patients characterized by strong avoidance tendencies and sensitivity to social threat, in particular patients with social anxiety disorder (SAD). Therefore, with the present study we aimed to replicate and extend these findings in a clinical group of patients with generalized SAD.

The stress hormone cortisol (corticosterone in animals) plays an important role in the regulation of social motivational behavior (e.g., Kalin et al., 1998a; Roelofs et al., 2005, 2007, 2009b; Sapolsky et al., 2000; Van Honk et al., 1998, 2000; van Peer et al., 2007). In addition,

dysregulation of cortisol levels is implicated in the development and maintenance of various mood and anxiety disorders (e.g., Roelofs et al., 2009b; De Kloet et al., 2005; Holsboer and Ising, 2008). However, studies investigating the effects of cortisol on cognitive–emotional processes have focused heavily on declarative memory (see Lupien et al., 2007 for a comprehensive review) and studies examining cortisol effects on threat processing and avoidance behavior in humans are scarce. Nevertheless, the results of some recent studies in healthy human subjects show that cortisol can affect threat processing and avoidance behavior, especially in high anxious individuals. Putman et al. (2007a) found acute cortisol administration in healthy participants to result in an increased performance bias for angry (compared to neutral) faces on a computerized object-relocation task, which was suggested to reflect a cortisol-induced increase in preferential processing of angry faces. In line with these results, in a study using a reaction time task to measure approach and avoidance responses to happy and angry faces, we found increased ERP amplitudes and relatively faster avoidance responses in reaction to angry faces after acute cortisol administration in high anxious healthy participants (van Peer et al., 2007). These results are in line with animal studies showing that high levels of cortisol are associated with increased fearful temperament and threat avoidance (Kalin et al., 1998a,b, 2000; Sapolsky, 1990), as well as with studies in humans showing

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increased threat processing (Mathews and Macleod, 1994) and threat avoidance (Roelofs et al., 2009b) in high anxious participants under stressful conditions.

The present study was set up as a follow-up of the study of van Peer et al. (2007) in a group of participants with clinical (social) anxiety. This study is particularly relevant in the light of recent studies (Aerni et al., 2004; De Quervain and Margraf, 2008; Schelling et al., 2006; Soravia et al., 2006) showing effects of acute glucocorticoid administration with potential implications for the treatment of anxiety disorders such as PTSD and (spider and social) phobia. The results of one of these studies (Soravia et al., 2006) showed that cortisone administration 1 h before exposure to a socio-evaluative stressor resulted in a reduction in self-reported phobic fear during anticipation, exposure and recovery of this stressor in social phobic patients. Although the authors proposed inhibition of aversive memory retrieval as a likely mechanism underlying this fear reduction, alternative processes such as an anxiolytic effect or modulation of other systems involved in the expression of fear may also play a role (see e.g., Putman et al., 2007b). Hence, it is important to assess the effects of cortisol administration on other key processes that have been implicated in the etiology and maintenance of anxiety disorders, such as attention towards threat stimuli and avoidance behavior (e.g., Bishop, 2008; Bögels and Mansell, 2004; Mathew and Ho, 2006; Mathews and Macleod, 2005; Roelofs et al., 2009b).

Evidence for the presence of preferential processing of threatening information in high anxious subjects is primarily based on behavioral studies showing impairments in interference paradigms, such as Emotional Stroop or dot probe tasks (e.g., Bögels and Mansell, 2004; Mathews and Macleod, 2005 for reviews). Another useful method to investigate this processing bias, however, is by recording event-related potentials (ERPs) from the scalp. Since ERPs are sensitive to both the extent (amplitude) and speed (latency) of cerebral processing, they can provide valuable information about early and rapid stages of attentional processing that is not reflected in behavioral measures (e.g., Bar-Haim et al., 2005; Thomas et al., 2007). Hence they provide suitable tools to examine more closely the claim that threatening stimuli are associated with enhanced attention in anxiety disorders, and to investigate the effects of cortisol administration on these processes.

ERP responses during processing of emotional material have been extensively studied using pictures of human faces, due to their social significance and affective salience (e.g., Bradley et al., 1997; Rolls, 2000). Results of these studies in healthy human subjects have shown very rapid effects (i.e., <250 ms post-stimulus) suggesting early preferential processing of threat-related emotional faces (Ashley et al., 2004; Bar-Haim et al., 2005; Eger et al., 2003; Eimer and Holmes, 2002; Williams et al., 2006), as well as modulation of later stages of ERP responses (Eimer and Holmes, 2002; Schupp et al., 2004; Williams et al., 2006).

Considering the suitability of the ERP technique to study processing of emotional material, studies using ERPs to investigate threat processing in anxiety disorders are surprisingly scarce. Two recent studies investigated these processes using an emotional facial Stroop task in a clinical sample of patients with social anxiety disorder (Kolassa and Miltner, 2006; Kolassa et al., 2007). Abnormalities in processing of angry faces were found in one of these studies (Kolassa and Miltner, 2006), but not in the other (Kolassa et al., 2007). However, both studies focused only on occipito-temporal electrodes, and did not report on the early and late midline positive components described above, which are considered among the components most consistently demonstrating emotional expression ERP effects (see Holmes et al., 2008 for a review). Indeed, in a recent study Bar-Haim et al. (2005) found

increased early positive (P2) amplitudes at the vertex for angry faces in high anxious compared to low anxious healthy participants, indicating enhanced early threat processing. Similarly, in our previous study we found the most pronounced effects of cortisol on threat processing in high anxious students on these early and late positive amplitudes (P150 and P300) at the vertex (van Peer et al., 2007). For these reasons we focused on the P150 and P300 midline components in the present study.

In specific, we investigated the effect of acute cortisol administration on threat processing and behavioral avoidance in individuals with social anxiety disorder. Approach and avoidance reactions were assessed in reaction to positive and threatening social stimuli (i.e., happy and angry faces) using a reaction time affect-evaluation task (the approach-avoidance task, Rotteveel and Phaf, 2004), and threat processing was measured by recording event-related potentials during task performance. The approach-avoidance task provides a reliable tool to investigate overt avoidance behavior (see e.g., Chen and Bargh, 1999; Rotteveel and Phaf, 2004; Solarz, 1960) and has been shown to be sensitive to social anxiety and cortisol manipulations in healthy populations (Heuer et al., 2007; Roelofs et al., 2005; van Peer et al., 2007). Based on earlier findings with high anxious healthy participants (van Peer et al., 2007) we expected relatively increased avoidance (i.e., slower approach or faster avoidance responses) and enhanced processing (i.e., increased early (P150) and later (P300) positive ERP amplitudes) of angry faces after cortisol administration.

## 1. Methods

### 1.1. Participants

Twenty-one unmedicated patients with SAD participated in the experiment for financial compensation (i.e., €40 and traveling expenses). Demographic variables and group characteristics are presented in Table 1. Patients were recruited at the outpatient anxiety departments of three community mental health centers and through advertisements on Internet forums. Inclusion criteria were: a primary diagnosis of generalized SAD (according to DSM-IV criteria) and a total score >60 at the Liebowitz Social Anxiety Scale (Liebowitz, 1987), right-handedness, normal or corrected-to-normal vision, and age 18–55 years. Exclusion criteria were current diagnosis of major depressive disorder, pregnancy or breast-feeding, clinical significant medical disease, past head injury with loss of consciousness >5 min, use

**Table 1**  
Patient characteristics ( $n = 20$ ).

Measure	M	SD
Age (years)	32.8	10.2
BMI	22.2	3.2
BDI	12.2	6.1
LSAS fear	42.1	8.0
LSAS avoidance	36.3	10.0
LSAS total	78.4	16.2
SPAI social phobia	131.0	21.0
SPAI agoraphobia	26.8	10.9
SPAI difference	104.2	21.6
STAI trait	50.6	8.1
BIS	25.1	3.3
BAS total <sup>a</sup>	36.3	6.2
Axis-1 comorbidity <sup>b</sup>		
Comorbid anxiety disorder <sup>c</sup>	$N = 1$	
Current mood disorder <sup>d</sup>	$N = 0$	
Past major depressive episode	$N = 7$	

Note: (scale range between parentheses). BMI, body mass index; BDI, Beck Depression Inventory (0–63); LSAS, Liebowitz Social Anxiety Scale (fear 0–72, avoidance 0–72, total 0–144); SPAI, Social Phobia and Anxiety Inventory (social phobia 0–192, agoraphobia 0–78); STAI, State-Trait Anxiety Inventory (20–80); BIS, Behavioral Inhibition Scale (7–28); BAS, Behavioral Activation Scale (13–52).

<sup>a</sup> NB  $n = 19$  due to a missing value.

<sup>b</sup> Assessed using the Structured Clinical Interview for DSM-IV Axis-I Disorders (SCID-I).

<sup>c</sup> Including panic disorder, agoraphobia, specific phobia<sup>†</sup>, obsessive compulsive disorder, post-traumatic stress disorder and generalized anxiety disorder.

<sup>d</sup> Including current major depressive episode, mania, hypomania, dysthymic disorder, and bipolar disorder.

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