To approach or to avoid : neurobiological mechanisms in social anxiety
Peer, J.M. van

Chapter 4

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.

Introduction

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, 2009a; 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., 2009a; De Kloet, et al., 2005; Holsboer & 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 increased threat processing (Mathews & Macleod, 1994) and threat avoidance (Roelofs et al., 2009a) 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 & 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 asses 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 & Mansell, 2004; Mathew & Ho, 2006; Mathews & MacLeod, 2005; Roelofs et al., 2009a).

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 & Mansell, 2004; Mathews & 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, Johnstone, & Gonsalvez, 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, Jedynak, Iwaki, & Skrandies, 2003; Eimer & Holmes, 2002; Williams et al., 2006), as well as modulation of later stages of ERP responses (Eimer & 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 & Miltner, 2006; Kolassa, Kolassa, Musial, & Miltner, 2007). Abnormalities in processing of angry faces were found in one of these studies (Kolassa & 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, Nielsen, & Green, 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 & 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 & Bargh, 1999; Rotteveel & 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.

Methods

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 4.1. 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 of psychotropic medication, use of corticosteroids in the 6 months prior to participation, use of cannabis more than once a week or use of any drugs other than cannabis in the 3 months prior to participation, and use of more than 3 glasses of alcohol or 20 cigarettes per day. Participants were instructed to minimize physical exercise, not to take large meals, chocolate or caffeine during the morning preceding the experiment, and not to eat, drink low pH drinks or smoke cigarettes in the hour before the start of the experiment, because these variables can affect saliva cortisol measures. All participants provided written informed consent prior to participation in the study, which was approved by the Medical Ethical Committee of the Leiden University Medical Center. Of the 21 patients tested, one had to be excluded because of missing reaction time data due to technical problems, leaving a total number of 20 participants (9 male, 11 female).

Table 4.1. 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[a]	36.3	6.2
Axis-1 comorbidity[b]		
Comorbid anxiety disorder[c]	N = 1*	
Current mood disorder[d]	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).
[a] NB n = 19 due to a missing value.
[b] Assessed using the Structured Clinical Interview for DSM-IV Axis-I Disorders (SCID-I).
[c] Including panic disorder, agoraphobia, specific phobia*, obsessive compulsive disorder, post-traumatic stress disorder and generalized anxiety disorder.
[d] Including current major depressive episode, mania, hypomania, dysthymic disorder, and bipolar disorder.

Participants were screened using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I: First et al., 1996) by a trained psychologist at the end of the first testing day to confirm diagnosis for social anxiety disorder and to exclude current major depressive disorder. Participants also completed Dutch versions of the Social Phobia and Anxiety Inventory (SPAI: Turner et al., 1989), the Beck Depression Inventory (Beck, Rush, Hollon, & Emery, 1979), the State-Trait Anxiety Inventory (Spielberger, 1983), and the Behavioral Inhibition and Behavioral Activation Scales (BIS/BAS: Carver & White, 1994). See Table 4.1 for questionnaire values.

Materials and procedure

For this study we used the same materials and procedure as reported by Van Peer et al. (2007). All participants were tested in a hydrocortisone (50 mg) and a placebo condition in a double-blind, within-subject crossover design. The order of cortisol or placebo administration was random and balanced over all participants. The two experimental sessions were 1 week apart. On the days of testing, participants

arrived at the laboratory at 12.15 p.m. After a short introduction, drugs were administered orally at 12.30 p.m., followed by a resting period of 1 h to allow for the cortisol to take effect. During this period, participants completed questionnaires and practiced with the response device for the approach-avoidance task, after which the electrodes for the electrophysiological measurements were placed. Subsequently, the experiment started with a short recording (~ 15 min) of the electroencephalogram (EEG) during rest, after which the approach-avoidance task was administered, followed by a number of additional cognitive tests of which the results will be reported elsewhere. During task performance, participants sat in an air-conditioned and sound-attenuated room in front of a computer monitor, and the experimenter sat in an adjacent room where the EEG apparatus was located.

Cortisol and subjective measures

Saliva samples were obtained using Salivette collection devices (Sarstedt, Rommelsdorf, Germany). Samples were obtained at four assessment points over a 165 min period, at respectively -5 min (T0), +60 min (T1), +120 min (T2), and +160 min (T3) with reference to capsule ingestion. Biochemical analysis of free cortisol in saliva was performed using a competitive electrochemiluminescence immunoassay (ECLIA, Elecsys 2010, Roche Diagnostics), as described elsewhere (Van Aken et al., 2003).

Self-reported mood (tension, fatigue, depression, anxiety, and activation at T0, T1, and T3) and motivation and concentration (directly before and after the AA-task) were rated on 100 mm visual analogue scales (VAS). In addition, state anxiety (STAI-state: Spielberger, 1983) was measured at T0 and T3.

Approach Avoidance task

In this affect-evaluation task (Rotteveel & Phaf, 2004; Van Peer et al., 2007), stimuli consisted of 60 grayscale photographs with happy and angry facial expressions (Ekman & Friesen, 1976; Matsumoto & Ekman, 1988; Lundqvist et al., 1998). Both the happy and the angry expression were taken from the same model (total of 30 models, 50% female). Each picture measured 12.4 cm × 8.9 cm ($h \times w$), and was presented against a black background at the center of a 15 in. computer screen at 70 cm viewing distance (see Figure 4.1).
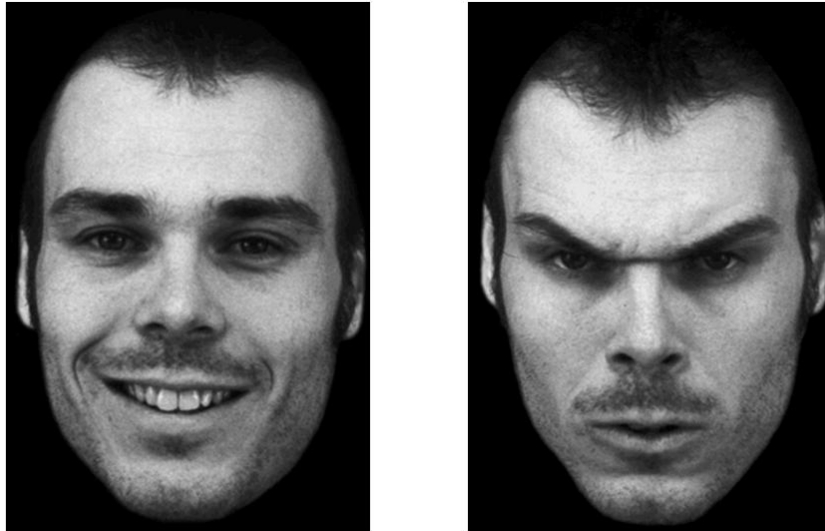
Figure 4.1. Examples of a happy and angry face stimulus used in the AA task.

Each trial started with the appearance of a central fixation point (100 ms), followed after an interval of 300 ms (black screen) by presentation of the stimulus (100 ms). The inter-stimulus-interval was randomized between 1500 and 2500 ms. Responses were registered by means of three buttons that were fixed to a vertical stand (see Rotteveel & Phaf, 2004, Figure 1) at the right side of the participant. Participants were instructed to push the "home" (middle) button loosely with the back of their right hand as long as no response was given, and to respond as fast and accurate as possible to the stimuli by releasing the home button and pressing one of the two response buttons (positioned 10.3 cm above and below the home button, allowing participants to simply flex or extend their arm in responding). After this, they had to return their hand to the home button.

Several studies (see e.g., Chen & Bargh, 1999; Rotteveel & Phaf, 2004; Solarz, 1960) have shown that arm flexion is associated with approach (as when pulling objects toward oneself), whereas arm extension is associated with avoidance (as when pushing something away). As a result, reaction times on the approach-avoidance task are typically faster when participants respond with arm flexion (approach) to positive stimuli and with arm extension (avoidance) to threatening stimuli (affect-congruent condition) than the other way around (affect-incongruent condition).

Participants received alternately an affect-congruent or an affect-incongruent instruction. The affect-congruent instruction indicated pressing the upper response button (arm flexion, approach movement) for happy faces and the lower button (arm

extension, avoidance movement) for angry faces. The affect-incongruent condition involved the opposite stimulus-response mapping (angry up, happy down). No reference was made in the instructions to congruence and incongruence, approach and avoidance, or arm flexion and extension.

The task consisted of four series of 60 trials, which were administered with either a congruent-incongruent-congruent-incongruent or an incongruent-congruent-incongruent-congruent order of instructions (counterbalanced across participants). Within each series all stimuli were presented once in a semi-randomized order (with a maximum succession of three happy or angry and three male or female pictures). Between each series participants performed an unrelated working memory task that served to ease the transition from affect-congruent to affect-incongruent instruction or vice versa. Each of the four series was divided into three blocks of 20 trials, with a short break (~30 s) between blocks, and was preceded by 20 practice trials of stimuli that were not included in the experimental series.

The task provided three behavioral measures: error rates (percentage incorrect responses) and two reaction time (RT) measures. The initiation time (IT) is the time between stimulus onset and the release of the home button. The movement time (MT) is the time between the release of the home button and the pushing of the response button.

Electrophysiological recording and data analyses

The electroencephalogram (EEG) was recorded from 19 scalp locations according to the international 10–20 system and referred on-line to C3/C4. An average earlobe reference was derived off-line. Vertical electro-oculogram (EOG) was recorded bipolarly from the supraorbital and the infraorbital ridge of the right eye, and horizontal EOG from the outer canthi of both eyes. The ground electrode was located at Fpz. EEG impedances were kept below 5 kΩ. The EEG and EOG signals were digitized at 500 Hz and segmented off-line (using Brain Vision Analyzer software,version 1.05, Brain Products GmbH, 1998–2004) into 1000 ms epochs, from 200 ms before to 800 ms after stimulus onset. Single trials were corrected for the effects of eye blinks and eye movements using a standard procedure (Gratton et al., 1983). Data were filtered digitally with a 0.01 Hz high-pass filter (24 dB/oct roll-off) and a 35 Hz low-pass filter (12 dB/oct). Artifact rejection was performed by removing epochs with activity below

0.50 μV and amplitudes exceeding ±75 μV in the C3, C4, Cz, F3, F4, Fz, P3, P4, and Pz electrode channels (average 1.2% of total dataset).

Separate averages were computed for happy and angry faces as a function of arm movement (approach/flex or avoid/extend). Based on the results of our previous study (Van Peer et al., 2007) analyses focused on the P150 and P300 components at midline electrodes (Fz, Cz, Pz). Peak amplitudes of these components were identified as local maximum relative to baseline in two successive time windows: P150 (the first major positive wave occurring 120–200 ms post-stimulus) and P300 (second major positive wave, 270– 400 ms). Time windows for peak detection were based on visual inspection of the grand average ERPs, averaged across all participants and categories. Incorrect responses and responses with ITs < 150 ms or > 1000 ms (total 4.7% of trials) were excluded from the RT and ERP analyses. Error rates were consistently low in all conditions (M = 3.0 ±1.8 %) and are therefore not reported.

The influence of cortisol administration on subjective measures, salivary cortisol, AA-task performance, and ERP peak amplitudes were tested with repeated measures analyses of variance (ANOVAs rm) using the Statistical Package for the Social Sciences (SPSS 14.0, SPSS Inc., 1989–2005). Since previous studies have shown that both ERPs related to processing of threatening faces (see e.g., Bar-Haim et al., 2005; Holmes et al., 2008) and the effects of cortisol on approach-avoidance tendencies (Van Peer et al, 2007; Roelofs et al., 2005) can be moderated by individual differences in anxiety, we included social anxiety (SPAI social phobia score) as a continuous variable (ANCOVA) in our behavioral and ERP analyses (see Judd et al., 2001). Significant effects including this variable were further investigated by calculating Pearson correlations between this factor and the within-subject effects. All statistical analyses employed a two-tailed alpha of .05. Effect sizes are reported as proportion of explained variance (partial eta squared [η^2]). The Greenhouse-Geisser correction was used when appropriate (epsilon [ε]).

Results

Cortisol and subjective measures

Salivary cortisol (nmol/L) measures (see Table 4.2) were skewed and therefore log transformed before statistical analysis. The results of a 2 × 4 ANOVA rm with

Table 4.2. Mean free salivary cortisol levels (nmol/L) after placebo and cortisol administration relative to time of capsule intake (t = 0)

Time (min)	Placebo		Cortisol	
	M	*SD*	*M*	*SD*
-5	9.7	3.5	9.7	3.6
+60***	8.3	2.7	294.2	213.5
+120***	7.3	2.5	230.0	186.5
+165***	6.7	2.4	151.2	155.1

Note: N= 17 due to missing values (unreliable saliva measurements n=2) and missing data AA-task (*N*=1). *** placebo vs. cortisol p<.001

Condition (placebo, cortisol) and Time (T0, T1, T2, T3) yielded a significant interaction of Condition × Time ($F(3,48)$ = 78.47, p = .000, η^2 = 0.83). This result indicates that, as expected, salivary cortisol levels did not differ between conditions before capsule intake (T0: $F(1,17)$ = .01, p = .92), but were significantly increased after cortisol administration compared to placebo from one hour after capsule intake until the end of the experiment (T1: $F(1,16)$ = 147.85, p = .000; T2: $F(1,17)$ = 214.16, p = .000; T3: $F(1,17)$ = 124.08, p = .000). Note that the AA-task was administered between T1 and T2 (i.e., between one and two hours after capsule intake).

To investigate effects of cortisol administration on subjective mood (data not shown) we conducted separate ANOVAs rm with Condition (placebo, cortisol) × Time for STAI-state (T0, T3) and VAS tension, fatigue, depression, anxiety, and activation (T0, T1, T3). Results showed no significant main or interaction effects of Condition on STAI-state anxiety, VAS tension, fatigue, depression, or anxiety (all F< 2.4, p > .14). We did find a significant main effect of Condition on VAS activation ($F(1,18)$ = 7.65, p = .013). However, follow up analyses revealed that reported activation was higher in the placebo than the cortisol condition before capsule intake (T0: $F(1,18)$ = 9.59, p = .006). Consequently, to control for pre-drug differences in activation level we performed an additional analysis using the pre-drug activation level (average of T0 in placebo and cortisol condition) as a covariate. The results of this analysis revealed no difference between conditions in post-drug activation levels ($F(1,17)$ = 0.26, p = .62), indicating that cortisol administration did not affect mood.

Behavioral results

Initiation times (IT)

For the initiation times we found the expected congruency effect: A significant Emotion × Arm movement interaction ($F(1,18)$ = 5.64, p = .029, η^2 = .24) showed that patients were faster in initiating affect-congruent (approach happy: M = 495 ± 62 ms; avoid angry: M = 509 ± 59 ms) than affect-incongruent arm movements (avoid happy: M = 524 ± 68 ms ; approach angry: M = 521 ± 64 ms). In contrast to our expectations, this AA congruency effect was not modulated by cortisol administration (Condition × Emotion × Arm movement: $F(1,18)$ = 1.05, p = .31). For Social anxiety we found a significant main effect, reflecting faster initiation times for patients with higher levels of social anxiety ($F(1,18)$ = 6.59, p = .019, η^2 = .27, R = -0.52), but no modulation of the AA congruency effect (Emotion × Arm movement × Social anxiety: $F(1,18)$ = 2.48, p = .13). The results showed no other significant effects on initiation times (All F< 1.83, p >.19).

Movement times (MT)

There was a main effect of Emotion ($F(1,18)$ = 4.80, p = .042), indicating faster movement times for happy than angry faces. In line with the results on initiation times, this effect was modulated by a trend towards an interaction of Emotion × Arm movement ($F(1,18)$ = 3.62, p = .073, η^2 = .17), suggesting that patients tended to be faster in executing affect-congruent (approach happy: M = 189 ± 89 ms; avoid angry: M = 184 ± 74 ms) than affect-incongruent arm movements (avoid happy: M = 188 ± 68 ms; approach angry: M = 199 ± 77 ms). In addition, we found a significant interaction of Emotion × Social anxiety ($F(1,18)$ = 5.60, p = .029), as well as an interaction of Emotion × Arm movement × Social anxiety ($F(1,18)$ = 5.39, p = .032, η^2= 0.23). Follow up analyses to determine the nature of this interaction revealed a significant interaction of Emotion × Social anxiety for approaching ($F(1,18)$ = 10.70, p = .004, η^2 = .37) but not for avoiding arm movements ($F(1,18)$ = .048, p = .83). Calculation of the Pearson correlation between the social anxiety levels and the emotion difference score (MT angry minus MT happy) for approach movements showed that the direction of this relation was positive (R = 0.61; for avoidance R = 0.05), indicating that high levels of social anxiety were associated with significantly longer movement times for approach of angry compared to happy
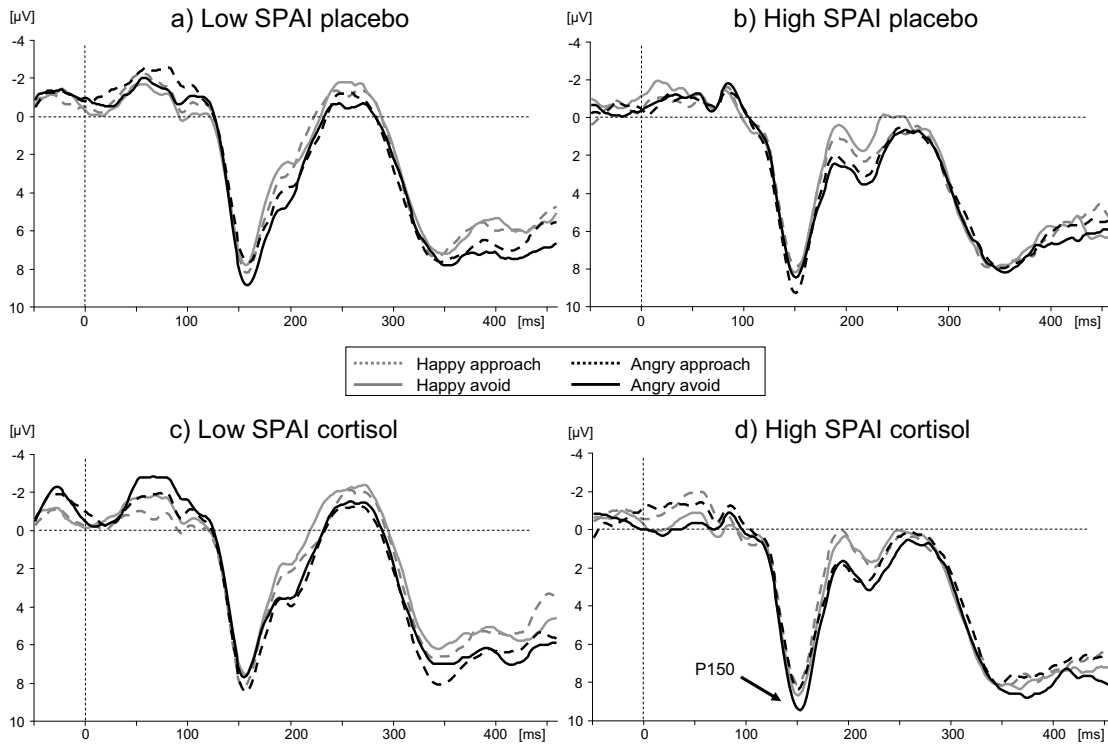
Figure 4.2. Stimulus synchronized grand average ERP waveforms at Pz electrode. To show the effects of cortisol and social anxiety, waveforms are presented separately for the placebo (upper panel) and cortisol (lower panel) conditions, and for patients with relatively low (left) and patients with relatively high (right) social anxiety scores. For presentation purposes, patient groups are formed based on a median split on SPAI social phobia scores (Median = 130.3, N = 10 in each group). Note that in the statistical analyses social anxiety was included as a continuous measure and not as a group factor. Results showed a significant Condition by Arm movement by Social anxiety interaction, reflecting relatively increased P150 amplitudes for avoidance compared to approach after cortisol administration in patients with higher levels of social anxiety. This effect was most strong (and only significant) for angry faces.

faces. Follow-up analyses of the Movement × Social anxiety interaction separately by emotion were not significant (Happy: $F(1,18) = 3.24$, $p = .089$; Angry: $F(1,18) = 0.85$, $p = .37$). We did not find any significant effect of cortisol administration on movement times (all $F < 0.91$, $p > 0.34$).

ERP results

Figure 4.2 presents grand average ERPs at Pz electrode (where the effects were most pronounced) on trials with approach and avoidance responses in reaction to happy and angry faces.

P150 amplitude

For the P150 on midline electrodes we found a significant interaction of Condition × Arm movement ($F(1,18) = 6.97$, $p = .017$), which was further modulated by a significant
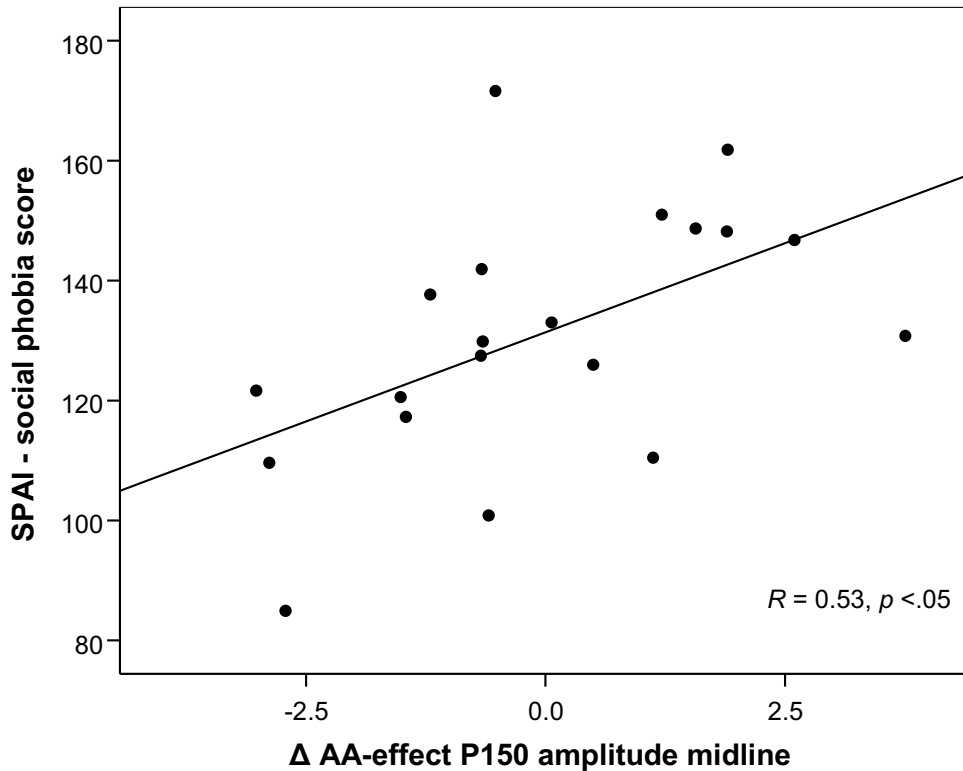
Figure 4.3. Correlation between social anxiety (SPAI- social phobia scale) and cortisol-induced change in P150 amplitude for avoidance compared to approach (i.e. [Δ Avoid-Approach cortisol] minus [Δ Avoid-Approach placebo]). Positive numbers for the ΔAA-effect indicate larger P150 amplitudes on midline electrodes (Fz, Cz, Pz) for avoidance than approach in the cortisol condition, compared to the placebo condition. The scatterplot shows that high levels of social anxiety are associated with increased P150 ΔAA-effects after cortisol administration, indicating an increase in processing of emotional faces during avoidance compared to approach.

3-way interaction of Condition × Arm movement × Social anxiety[1] ($F_{(1,18)}$ = 6.99, p = .016, η^2 = 0.28). Follow-up analyses showed that this finding reflects a significant Arm movement × Social anxiety interaction after cortisol administration ($F_{(1,18)}$= 6.39, p = .021, η^2 = 0.26) but not after placebo ($F_{(1,18)}$ = 1.52, p = .23). In addition, the interaction of Condition × Social anxiety was marginally significant for avoidance movements ($F_{(1,18)}$ = 3.99, p = .061), but not significant for approach movements ($F_{(1,18)}$ = 0.36, p = .56). The significant 3-way interaction indicates that the effect of cortisol administration on P150 amplitude during avoidance compared to approach correlated significantly with the patients' social anxiety levels. Pearson correlations between social

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[1] A second analysis for P150 and P300 amplitude was conducted with F3, F4, C3, C4, P3, and P4 as additional electrodes, and with laterality (left, midline, right) as an additional factor. This analysis only showed one significant interaction with laterality for P150 amplitude, i.e. Condition x Arm movement x Social anxiety x Laterality (F(2,36) = 3.42, p=.046, ε = 0.96, η^2 = 0.16). Post hoc testing revealed that the interaction of Condition x Arm movement x Social anxiety was most pronounced at the midline electrodes, and only marginally significant at the left (F(1,18) = 3.06, p=.097) and right lateral electrodes (F(1,18) = 3.23, p=.089). Therefore, only results of midline electrodes are presented.

anxiety levels and the cortisol-induced change in P150 amplitude for avoidance compared to approach (i.e., [P150 amplitude avoid - approach cortisol] minus [P150 amplitude avoid - approach placebo]) showed that the direction of this correlation was positive ($R = 0.53$), indicating that patients with higher social anxiety levels showed a larger cortisol-induced increase in P150 amplitude for avoidance compared to approach (see Figure 4.3). We found no significant interaction with Emotion (all $F < 2.3$, $p > .14$), suggesting that this effect was not significantly different for happy and angry faces. However, since we specifically expected effects for processing of threat, we conducted a planned comparison to investigate whether this effect would hold when testing angry faces separately. Indeed, the effect was most strong and significant for the angry faces ($R = 0.52$, $p = .019$) whereas it was not significant for happy faces ($R = 0.19$, $p = .42$).

We found no significant effects on P300 midline amplitudes (all $F < 2.14$, $p > .16$).

Discussion

The aim of the present study was to investigate the effects of cortisol administration on threat processing and approach and avoidance behavior in a clinical sample of patients with generalized social anxiety disorder. In line with earlier findings of a very similar study 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.

First, our behavioral results showed the expected emotion by arm movement interaction (congruency effect) in reaction times, indicating that the patients were faster in initiating affect-congruent (approach happy, avoid angry) than affect-incongruent (approach angry, avoid happy) arm movements, consistent with the findings of several previous studies in healthy participants (Roelofs et al., 2005; Rotteveel & Phaf, 2004; Van Peer et al., 2007). In contrast to our expectations and previous findings (Van Peer et al., 2007), however, we did not find an effect of cortisol administration on initiation times in the present study. Since the experimental procedure was the same as in our previous study it is difficult to account for the current absence of this effect, although it could be due to the heterogeneity of the current sample compared to the relatively homogeneous male sample of our previous study.

For the movement times the emotion by arm movement interaction was modulated by the severity of patients' social anxiety. Post hoc testing revealed that the execution of approach movements to angry faces (compared to happy faces) was significantly slower for patients with higher levels of social anxiety. Reaction times for affect-incongruent responses, such as approaching an angry face, reflect the costs of inhibiting an intuitive response tendency, i.e., to avoid the angry face, in favor of the instructed response (Roelofs et al.,2009b). This slowing of approach responses towards angry faces is therefore consistent with a relatively increased tendency to avoid threat in patients with higher levels of social anxiety.

Most importantly, results of the ERP analyses showed a significant interaction of cortisol by social anxiety on early positive (P150) amplitudes: Cortisol administration resulted in a significant increase in P150 amplitudes during avoidance compared to approach of emotional faces for patients with high levels of social anxiety. This result is largely in line with our previous finding of enhanced P150 amplitudes during avoidance of angry faces after cortisol administration in high trait avoidant healthy participants (Van Peer et al., 2007). Although the lack of a significant interaction with stimulus emotion in the present study implies that this effect was not significantly different for happy and angry faces, the effect was still significant when tested for the angry (but not the happy) faces separately. This is in line with the findings of our previous study, as well as with other studies showing sensitivity to social threat in patients with social anxiety (see e.g., Bishop, 2008; Bögels & Mansell, 2004; Mathew & Ho, 2006; Mathews & MacLeod, 2005).

Increased amplitudes of early (as well as late) positive midline ERP components in reaction to threat-related emotional faces have been consistently reported in studies in healthy participants, and are generally interpreted as reflecting increased allocation of processing resources to motivationally significant stimuli (Bar-Haim et al., 2005; Eimer & Holmes, 2002; Eimer et al., 2003; Williams et al., 2006). Furthermore, Bar-Haim et al. (2005) found enhanced P2 amplitudes to angry faces in high compared to low anxious healthy participants, indicating that early threat processing is modulated by trait anxiety level (although cf. Holmes et al., 2008; Moser, Huppert, Duval, & Simons, 2008). The results of our studies suggest that this process is sensitive to cortisol administration, resulting in enhanced processing of social threat in high socially anxious participants. This is in line with behavioral findings indicating increased preferential

processing of angry faces after cortisol administration (Putman et al., 2007a). Most importantly, the present study is the first to show an effect of cortisol administration on threat processing in a clinical sample of patients with generalized social anxiety disorder.

Although the timing of the ERP effect in the present study suggests that early stages of information processing are involved, it most likely does not reflect pre-attentive classification processes (Eimer & Holmes, 2007). Instead, such an early midline positive ERP effect is proposed to reflect higher order and attention-dependent processing in neocortical areas, where representations of emotional content are generated in a strategic and task-dependent fashion for the adaptive intentional control of behavior (Eimer & Holmes, 2007). Recent findings by Amodio & Potanina (2008) support this notion by showing that the P200 component reflects motivated attention to cues related to response control. Interestingly in this respect is our finding, in the present as well as our previous study (Van Peer et al., 2007), that after cortisol administration in high anxious participants the P150 amplitude in reaction to angry faces was significantly higher for avoidance compared to approach movements. This implies that the effect of cortisol administration on early threat processing is also modulated by the behavioral response mode, suggesting that early processing is indeed related to behavioral control mechanisms. In our design, affect-congruent and affect-incongruent responses were blocked in separate instruction conditions, which may have resulted in priming of response-congruent stimulus processing.

Together our findings suggest that cortisol-induced enhancement of emotional face processing depends on symptom severity and motivational context in SAD. There are, however, some limitations that should be discussed. First, the present study aimed to replicate and extend previous findings in high anxious healthy participants (Van Peer et al., 2007) to patients with clinical SAD, and therefore we did not include an additional non-anxious control group. The current within-subject design allowed us to control for individual differences in symptom severity, which proved to be an important moderating factor. Nevertheless, a matched control group would have offered more information regarding the specificity of the effects of cortisol on threat processing for social anxiety. We cannot draw conclusions about this specificity based on the present study. The results of previous studies of our group, investigating the effects of cortisol on approach-avoidance in high versus low anxious healthy participants (Van Peer et al.,

2007) and in patients with SAD versus patients with PTSD and healthy controls (Roelofs et al., 2009a), however do suggest that the association of high cortisol levels with increased social avoidance tendencies may be specific to high socially anxious individuals.

Second, in contrast to our expectations and previous findings (Van Peer et al., 2007), we did not find an effect of cortisol on the behavioral results in the present study. As we suggested above, this could be due to the heterogeneity of the current sample compared to the relatively homogeneous male sample of our previous study. On the other hand, modulation of ERP components in absence of behavioral effects has been reported by several other authors (see e.g., Bar-Haim et al., 2005; Holmes et al., 2008; Thomas et al., 2007) and it has been suggested that ERPs may provide a more sensitive measure of attentional biases compared to reaction times. In addition, early positive ERP components in particular have been associated with enhanced attentional vigilance for threat-related material in high anxious participants (e.g., Bar-Haim et al., 2005; Holmes et al., 2008). In both of our studies, the effects of cortisol administration on ERP components related to threat processing were more pronounced on these early (P150) compared to later (P300) amplitudes.

Together, our findings suggest that a mechanism of early threat processing -that is enhanced by cortisol in high anxious healthy participants- is similarly affected in patients diagnosed with generalized SAD. Although the present study is the first ERP study on cortisol administration in SAD and the results should be replicated to allow definite conclusions, these findings may have some valuable methodological and clinical implications.

First, it underscores the usefulness of the ERP methodology as a sensitive measure for both the study of attentional processes in anxiety (e.g., Bar-Haim et al., 2005; Thomas et al., 2007) and the study of the effects of cortisol on motivational processes.

Second, our findings suggest that it is important to take motivational processes into consideration when investigating effects of cortisol and anxiety on threat processing. A few recent studies have investigated ERPs related to threat processing in anxiety (Bar-Haim et al., 2005; Holmes et al., 2008; Kolassa & Miltner, 2006; Kolassa et al., 2007; Moser et al., 2008), and results thus far have been rather inconsistent (see Holmes et al., 2008 for a review). Our finding that after cortisol administration the P150

amplitude for angry faces was significantly higher for avoidance compared to approach movements suggests that it is important to take motivational behavior into account (see also Amodio & Potanina, 2008). This may help resolve inconsistencies not only in the ERP literature on emotional processing and anxiety, but also in the reported effects of cortisol administration on ERPs related to stimulus processing (Born, Hitzler, Pietrowsky, Pauschinger, & Fehm, 1988; Born, Kern, Fehm-Wolfsdorf, & Fehm, 1987; Hartmann et al., 1995; Hsu, Garside, Massey, & McAllister-Williams, 2003; Kopell, Wittner, Lunde, Warrick, & Edwards, 1970).

Third, the interaction with social anxiety in the present study indicates that it may be important to take individual differences in symptom severity into account when studying emotional processing in patient groups (see also Kolassa & Miltner, 2006; Roelofs et al. 2009a) as has been demonstrated earlier in samples of healthy participants (see Holmes et al., 2008; Roelofs et al., 2005; Van Peer et al., 2007).

Fourth, our finding that cortisol administration affects threat processing in a clinical sample of patients diagnosed with generalized SAD is important in light of the recent interest in cortisol administration as a possible treatment for anxiety disorders (see De Quervain & Margraf, 2008; Soravia et al., 2006). Our results indicate that in addition to memory processes or subjective fear responses, as put forward earlier by several authors (e.g., De Quervain & Margraf, 2008; Soravia et al., 2006), cortisol administration can also affect initial attention-related threat processing in social anxiety, which has been proposed as another important mechanism in the etiology and maintenance of this disorder (see e.g., Bögels & Mansell, 2004; Mathews & MacLeod, 2005 for reviews). At first sight our findings may seem in contrast with the findings of Soravia et al. (2006) which indicated a reduction in subjective fear in SAD after cortisol administration. There are, however, some important differences between the studies:

First, they focus on different aspects (phases) of emotional processing. Whereas Soravia et al. (2006) studied subjective fear responses (proposed to be mediated by retrieval of fear memory), the main effect of cortisol in our study was found on early attention processes (i.e., P150). It is presently unclear how enhanced early processing of threat cues, as reflected by ERPs, is exactly related to subsequent subjective fear responses. We suggest that enhanced early ERP amplitudes do not themselves indicate increased anxiety, but rather reflect increased vigilance or motivated attention to the threat stimuli (a view supported by studies where such increased attention to threat

occurred in the context of anger-related approach motivation -see e.g., Bertsch et al., 2008; Putman et al., 2007a). According to cognitive theories of anxiety, not only the initial vigilance but also subsequent higher order processes (e.g., coping behavior) are relevant for predicting emotional reactions to the threat stimuli (see e.g., Mathews & Mackintosh, 1998). For instance, if increased threat processing is followed by increased avoidance behavior, this can reduce immediate subjective anxiety (see the vigilance-avoidance hypothesis, e.g., Mogg et al., 1997), although in the long term this behavior may maintain anxiety by preventing reappraisal of the threat.

Another important difference between our studies is the context in which the effects of cortisol were studied. Whereas Soravia et al. (2006) studied the effects of cortisol administration during exposure to a stressful situation, in our study the testing situation was relatively relaxed. As shown by Tops, Van Peer, Wester, Wijers, & Korf (2006), the effects of cortisol administration are context-sensitive and can have opposite effects depending upon the stressfulness of the testing situation. Although the literature on this topic is scarce, there are several studies suggesting that cortisol administration in a stress context can lead to a reduction in negative mood and avoidance motivation (see e.g., Het & Wolf, 2007; Reuter, 2002; Soravia et al., 2006; Tops et al., 2006), whereas cortisol administration in absence of stress results in enhanced processing of threatening information and relatively increased avoidance motivation (see Putman et al. 2007a; Tops et al., 2005, 2006; Van Peer et al., 2007; cf. Buchanan, Brechtel, Sollers, & Lovallo, 2001). This notion that effects of cortisol administration are context-dependent is in line with extensive animal literature (see e.g., De Kloet et al., 1999; Lupien et al., 2007). More research is warranted to investigate the effects of cortisol administration on different phases of emotional processing and the effect of different experimental contexts.

To conclude, this study is the first to investigate the effect of cortisol administration on threat processing and avoidance in a clinical sample of patients with generalized social anxiety disorder, and shows that cortisol-induced enhancement of emotional face processing in these patients depends on symptom severity and motivational context.