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The effects of cortisol administration on approach–avoidance behavior: An event-related potential study

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Abstract

We investigated the effects of cortisol administration (50 mg) on approach and avoidance tendencies in low and high trait avoidant healthy young men. Event-related brain potentials (ERPs) were measured during a reaction time task, in which participants evaluated the emotional expression of photographs of happy and angry faces by making an approaching (flexion) or avoiding (extension) arm movement. The task consisted of an affect-congruent (approach happy faces and avoid angry faces) and an affect-incongruent (reversed instruction) condition. Behavioral and ERP analyses showed that cortisol enhanced congruency effects for angry faces in highly avoidant individuals only. The ERP effects involved an increase of both early (P150) and late (P3) positive amplitudes, indicative of increased processing of the angry faces in high avoidant subjects after cortisol administration. Together, these results suggest a context-specific effect of cortisol on processing of, and adaptive responses to, motivationally significant threat stimuli, particularly in participants highly sensitive to threat signals.
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Keywords: Cortisol; Approach–avoidance; Facial expression; Action tendencies; Event-related potentials; Behavioral Inhibition Scale

Activity of the hypothalamus–pituitary–adrenal (HPA) axis is important in the regulation of adaptive stress responses such as the generation of active avoidance reactions (see Sapolsky et al., 2000). Stress leads to activation of the HPA system, resulting in the release of endogenous glucocorticoids such as cortisol. Particularly when measured in social situations, elevated cortisol levels have been found to be related to the manifestation of social submissiveness and avoidance behavior (Sapolsky, 1990). Despite the extensive literature on the relation between HPA-axis activity and avoidance behavior in animals, little is known about the role of cortisol in the generation of human avoidance behavior. In this study, we examined the effect of cortisol administration on avoidance reactions to threatening social stimuli (angry faces) in human participants. In addition, to gain more insight in the brain processes underlying these reactions, we measured event-related brain potentials (ERPs) during performance of an approach–avoidance task, specifically focusing on positive components related to emotional face processing.

The generation of active avoidance responses depends on a motivational network that involves various brain regions (see LeDoux, 2002; Rolls, 2000). When threat stimuli are processed by the amygdala, direct autonomic responses and primary motor reactions such as freezing are activated via connections to the brainstem. Moreover, motivational systems are activated that guide instrumental responses based on past learning or instantaneous decisions. The hippocampus and prefrontal cortex (PFC) play an important role in these motivational systems. The PFC is thought to integrate information on arousal (from brainstem centers) with context-relevant information (from the hippocampus) and with temporary contents of working memory (from PFC areas) in controlling motor

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responses (via connections with the motor cortex). The anterior cingulate (ACC) and orbitofrontal (OFC) regions of the PFC in particular are involved in these motivational systems, which enable approach and avoidance reactions to emotional stimuli (see LeDoux, 2002; Roelofs et al., in preparation; Rolls, 2000).

Rolls (2000) stressed the importance of processing of facial expressions by these motivational systems. Emotion has a communicative function, and faces constitute important signals of threat or appeasement in the social environment. In a series of lesion studies, Hornak et al. (2003) showed that in human participants both the OFC and the ACC are involved in emotion processing, including the identification of facial expression, social behavior, and subjective emotional state.

Angry facial expressions are commonly used as social threat stimuli in human research on threat processing. Neuroimaging studies have shown that viewing angry faces activates large parts of the above-mentioned motivational network, with the ACC, OFC, and amygdala in particular (for an overview see Adolphs, 2002; McClure et al., 2004; Strauss et al., 2005). In addition, transcranial magnetic stimulation of the medial PFC/ACC has been found to disrupt the processing of angry facial expressions (Harmer et al., 2001). Adolphs (2002) argued that whereas activation of the amygdala appears to depend on relatively passive or implicit processing of the emotion (such as in passive viewing paradigms), prefrontal regions may be activated more when participants are engaged in a cognitive task requiring explicit identification of the emotion, which in turn may inhibit the amygdala's activation.

ERP studies have also indicated that prefrontal motivational networks are involved in the processing of facial expressions. An enhanced positivity in response to emotional relative to neutral faces has been found over prefrontal areas as early as 120 ms after stimulus presentation (Eimer and Holmes, 2002) or between 160 and 215 ms (Eimer et al., 2003). This suggests that cortical circuits involved in the detection of emotionally significant events can be triggered rapidly by emotional facial expressions (Eimer et al., 2003; Pizzagalli et al., 1999; Sato et al., 2001). In addition, a more broadly distributed positivity (over parietal as well as frontal and central areas) has been observed beyond 300 ms (Eimer et al., 2003). In particular faces signaling threat (i.e. fearful or angry faces as opposed to happy or neutral faces) have been found to show these enhanced amplitudes in both early (e.g. 50–250 ms: Ashley et al., 2004; Bar-Haim et al., 2005; Schupp et al., 2004; Williams et al., 2006) and late positive components (300–500 ms: Schupp et al., 2004; Williams et al., 2006). Interestingly, recent studies reported the ERP effects of emotional expressions to be attention dependent (Eimer et al., 2003; Krolak-Salmon et al., 2001), suggesting they may reflect a greater allocation of attention to motivationally relevant input (Cuthbert et al., 2000).

In sum, a frontolimbic motivational network is involved in the processing of social threat stimuli and the generation of avoidance behavior. In the next section we explore how the stress hormone cortisol, which is thought to be important in the generation of adaptive stress responses (e.g. Sapolsky et al., 2000), may affect this network and, consequently, approach and avoidance behavior. It is well established that not only the hippocampus but also the PFC is a target structure for cortisol (e.g. Meaney and Aitken, 1985; Radley et al., 2004). Exogenously administered cortisol has been shown to affect prefrontal functions, such as working memory, in humans (for a review see Wolf, 2003). In addition, there is increasing evidence from animal studies that PFC mediated avoidance behavior and fearful temperament are positively correlated with high levels of cortisol (see e.g. Kalin et al., 1998a,b, 2000). De Kloet et al. (1999) emphasized that glucocorticoids influence information-processing systems conditionally, so that specific internal and external stimuli are more likely to elicit responses in the appropriate context. In this way, information processing is biased towards adaptive behavior that is most relevant to the situation.

Human studies on the relation between cortisol, the processing of social threat stimuli and avoidance behavior are scarce, but a recent study by Putman et al. (2007) suggested that acute (25 mg) cortisol administration enhanced preferential processing of angry faces in healthy young men. The results of this study showed a significant increase in memory bias for angry faces (i.e. enhanced spatial working memory performance compared to neutral faces) after cortisol administration compared to placebo. No such memory bias was found for happy faces. In addition, a study by Van Honk et al. (1998) in which angry and neutral faces were presented in a Stroop paradigm indicated that increased basal cortisol levels were associated with faster responses to angry faces, which was interpreted as reflecting (adaptive) avoidance. However, no studies so far have addressed the effects of cortisol administration on overt avoidance behavior.

A systematic and objective method to study human avoidance behavior was provided by Solarz (1960) and Chen and Bargh (1999), consisting of a reaction time task in which individuals evaluate the emotional valence of positive and negative word stimuli by making arm movements (arm flexion or extension) that are either congruent or incongruent with their intuitive action tendencies. Rotteveel and Phaf (2004) extended this paradigm to the nonverbal domain, using pictures of happy and angry faces (the approach–avoidance (AA) task). Affect-congruent movements involve arm flexion (approach) in response to a positive stimulus (happy face) and arm extension (avoidance) in response to a negative stimulus (angry face). Affect-incongruent movements involve reversed mapping instructions (from stimulus valence to arm movement) that conflict with participants' intuitive action tendencies (i.e. to approach positive and avoid negative stimuli). With this paradigm a congruency effect is typically found, indicating faster responses for affect-congruent arm movements compared to affect-incongruent arm movements (see also Chen and Bargh, 1999; Markman and Brendl, 2005; Solarz, 1960).

Using this AA task, Roelofs et al. (2005) found an effect of stress-induced cortisol responses on the congruency effects. Participants with relatively high stress-induced cortisol responses (high CR) showed increased AA congruency effects when tested in baseline conditions, but no significant congruency effects during stress. In contrast, for low CR participants the congruency effects were only significant during and not before stress. Thus, the results of this study showed a significant

interaction of cortisol response and stress on approach–avoidance tendencies as measured by the AA task. However, the effects of high stress-induced cortisol levels could not be disentangled from the influence of individual differences in stress responsiveness or the effect of the social stress context. Therefore, the present study aimed to further investigate the effects of high cortisol levels on approach–avoidance tendencies, by studying the effects of cortisol administration on behavioral responses (particularly threat avoidance) in the AA task.

In addition, to investigate the effects of individual differences in threat sensitivity on behavioral responses to the threat signaling angry faces in the AA task, we compared participants with high scores to participants with low scores on a self-report measure of threat sensitivity (the Behavioral Inhibition Scale (BIS): Carver and White, 1994). Individuals with high scores on this scale (high BIS participants) can be characterized as anxiety prone, and tend to avoid threat (Carver and White, 1994). Compared to low BIS participants, we expected high BIS participants to be particularly responsive to social threat cues and to show relatively increased avoidance tendencies to the angry faces.

To test the effects of cortisol on these avoidance reactions, we administered the AA task to both participant groups after placebo and cortisol (hydrocortisone) administration. Because high cortisol levels have been associated with context-relevant adaptive responses (De Kloet et al., 1999; Sapolsky et al., 2000), biased processing of angry faces (Putman et al., 2007), and increased avoidance responses to threat (Buss et al., 2003; Kalin et al., 1998a,b, 2000; Van Honk et al., 1998), we expected cortisol administration to result in relatively increased avoidance reactions to angry faces on the AA task. Furthermore, we hypothesized that this effect would be especially strong for the high BIS subjects, given their increased sensitivity to these social threat cues. Such increased threat avoidance in the AA task can be either manifested by an increase in the effect of arm movement (faster avoidance than approach movements) for angry faces, or an increase in the effect of emotional expression for avoidance reactions (faster avoidance of angry than happy faces).

The second purpose of this study was to investigate brain processes associated with these effects using ERPs, with specific focus on components involved in emotional face processing and action monitoring. ERP components of particular interest were the previously mentioned positive waves that have been found over the prefrontal cortex between 120 and 250 ms post-stimulus, and the more broadly distributed positive wave observed beyond 300 ms (e.g. Eimer et al., 2003; Schupp et al., 2004). In line with our behavioral expectations, we expected cortisol administration to result in increased amplitudes of these components especially in the high avoidant (high BIS) participants during avoidant reactions to angry faces.[1]

A final component of interest was the N2, a frontocentral negative wave arising 200–350 ms post-stimulus. The N2 has been found to be increased in high conflict conditions, when incompatible response tendencies are simultaneously activated, and is suggested to reflect action monitoring (e.g. Van Veen and Carter, 2002), a function served by the medial prefrontal cortex (Ridderinkhof et al., 2004). In the AA task such response conflict may be elicited by affect-incongruent trials where the executed response is hypothesized to be in conflict with the participants' intuitive response tendency (i.e. to approach happy and avoid angry faces) (see Chen and Bargh, 1999; Rotteveel and Phaf, 2004). This study allows exploring whether the AA task indeed elicits significant N2 effects and whether cortisol administration may affect action monitoring during the generation of approach–avoidance responses.

To summarize our major predictions, we expected that cortisol administration would result in a facilitation of threat avoidance in high BIS participants. In addition, these behavioral effects were expected to be accompanied by increased amplitudes of ERP components involved in emotional face processing (in particular social threat). Finally, we explored whether cortisol administration would also increase action monitoring in high BIS participants.

1. Methods

1.1. Participants

Forty male students recruited from the University of Leiden participated in the experiment for financial (i.e. €40) or course credit. To create two extreme groups that differed in threat sensitivity, we selected a priori 20 students with low scores (≤16) and 20 students with high scores (≥21) on the Behavioral Inhibition Scale (BIS: Carver and White, 1994, see trait measures). Cutoff scores for these groups were based on the lower third and the upper third of the distribution of BIS scores (range 9–28, $M = 18.5$, S.D. = 3.6) in a sample of 153 male students.

Participants in this study were screened with the General Health Questionnaire (GHQ-12 ($M = 1.45$, S.D. = 1.69): Goldberg, 1978; Dutch version: Koeter and Ormel, 1991) and a biographic questionnaire to exclude any psychiatric disorder, clinical significant medical disease, past head injury with loss of consciousness >5 min, and use of medication. Inclusion criteria were right-handedness, normal or corrected-to-normal vision, age 18–30, and body-weight 60–85 kg. 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 measurements. 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.

1.2. Materials and procedure

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 (i.e. a capsule) was random and balanced within the high and low BIS groups. The two experimental sessions were 1 week apart. On the days of testing, participants arrived at the laboratory at either 12.15 or 2.15 p.m. After a short introduction, drug administration followed at 12.30 or 2.30 p.m., respectively. After ingestion of the capsule, a resting period of 1 h followed 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

[1] In contrast, the face-specific N170 component, which can be recorded over posterior temporal areas, has been found to be relatively insensitive to emotion processing and is predominantly associated with structural encoding of faces (see e.g. Ashley et al., 2004). We therefore had no predictions regarding this component with relevance to approach and avoidance behavior.

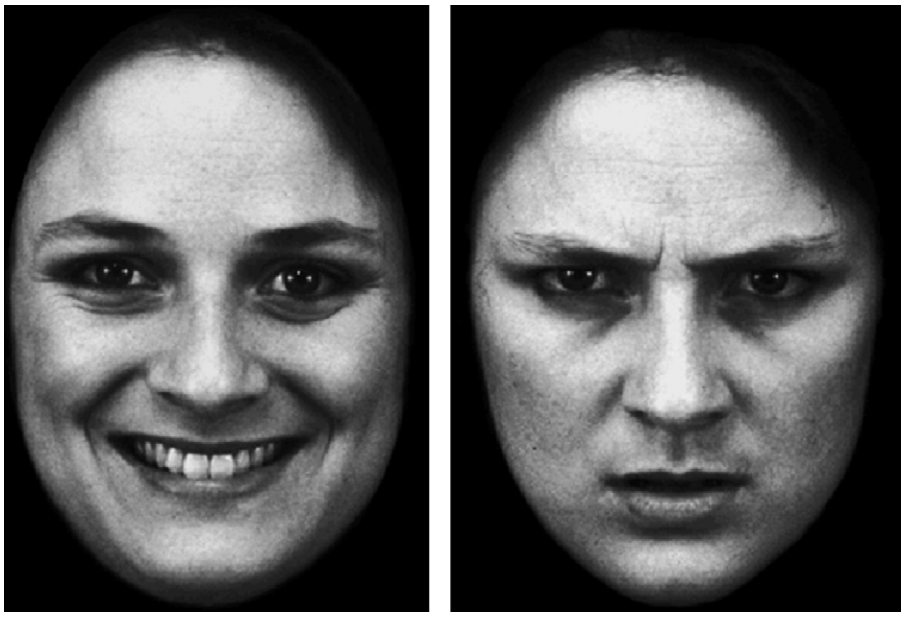

Fig. 1. Examples of a happy and angry face stimulus used in the AA task.

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.

1.3. Approach–avoidance task

In this affect-evaluation task (Rotteveel and Phaf, 2004), 60 pictures with facial expressions from Ekman and Friesen (1976), Matsumoto and Ekman (1988), and Lundqvist et al. (1998) served as stimuli. Half of the pictures were taken from female and the other half from male models (total of 30 models). Pictures consisted of grayscale photographs presented against a black background (see Fig. 1). To minimize variation in physical parameters unrelated to emotional expression, both the happy and the angry expression were taken from the same model. In addition, each face was trimmed to exclude the hair and non-facial contours, and adjusted to match for size, brightness and contrast. Each picture measured 12.4 cm × 8.9 cm ($h \times w$), and was presented at the center of a 15 in. computer screen at 70 cm viewing distance, resulting in a 10.1° × 7.3° visual angle.

The start of an individual trial was indicated by the appearance of a central fixation point (lasting 100 ms). After an interval of 300 ms the stimulus was presented for 100 ms. The time interval between successive stimuli was randomized between 1500 and 2500 ms. Pictures were presented using the Wesp Experimentation Stimulus Program (version 1.98 WESP XP, Molenkamp, University of Amsterdam, 2002).

Responses were registered by means of three buttons (of 16 cm^2) that were fixed to a vertical stand (see Rotteveel and Phaf, 2004, Fig. 1). Participants sat to the left of the stand, allowing them to respond with their right hand. For the resting position participants were instructed to push the home button (fixed in the middle) loosely with the back of their right hand as long as no response was given. The height of this button was set for each participant individually, such that the angle between their forearm and upper arm was 110° in the resting position. In this position both the biceps and the triceps were equally tensed. The response buttons were positioned above and below the home button (at a distance of 10.3 cm). This allowed participants to simply flex or extend their right arm in responding without the need for precise aiming at the response buttons.

Participants were verbally instructed to evaluate the facial expressions (i.e. happy or angry), and to respond as fast and accurate as possible to the stimuli by releasing the home button and pressing one of the response buttons. After this, they had to return their hand to the home button. Participants received alternately an affect-congruent or an affect-incongruent instruction. The affect-congruent instruction indicated pressing the upper response button (i.e. arm flexion) for happy faces and the lower button (i.e. arm extension) for angry faces. In the affect-incongruent condition the mapping of the facial expression to the response buttons was reversed. 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. Within each series all stimuli were presented once in a semi-randomized order (with a maximum of three happy or angry and three male or female pictures in succession). Half of the participants started with a series with an affect-congruent instruction, followed by a series with an affect-incongruent instruction, another affect-congruent instruction series, and a final affect-incongruent instruction series. The other half of the participants received the reversed order of instructions. Between each series participants performed an unrelated working memory task (digit span or spatial memory) 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. IT constitutes an index of central processes reflecting stimulus evaluation, response selection and programming the execution of movements, and is relatively independent of MT, which reflects the magnitude of the neuro-muscular response (Fitts, 1954). The influence of affect on the reaction times is therefore primarily expected in IT, rather than MT (see Rotteveel and Phaf, 2004; Solarz, 1960). Incorrect responses and RTs that deviated more than 2.5 S.D. from the individual RT averages per cell (cells defined by cortisol condition × emotion × arm movement) were excluded from the RT analyses.

1.4. Electrophysiological recording and analysis

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. Signals were processed off-line using Brain Vision Analyzer software (version 1.05, Brain Products GmbH, 1998–2004). Codes synchronized to stimulus presentation and response were used to allow off-line averaging of epochs associated with specific stimulus and response types. The epoch ran for 1000 ms, beginning 200 ms prior to stimulus onset, aligned to a 100 ms prestimulus baseline. Single trials were corrected for the effects of eye blinks and eye movements using a standard procedure (Gratton et al., 1983). Data were subsequently filtered digitally with a 0.1 Hz high-pass filter, a 35 Hz low-pass filter (both with a roll-off of 12 dB/oct) and a 50 Hz notch filter. After baseline correction, trials including amplitude values larger than ±75 μV, a difference >100 μV between the lowest and the highest amplitude within the segment, a period >100 ms with activity <0.50 μV, or a difference >50 μV between two subsequent sampling points were considered artifacts and were excluded from analyses (9% of total dataset). We analyzed stimulus-locked data only for trials with correct responses with reaction times between 150 and 1000 ms, computing averages for each category (defined by emotion × arm movement). After rejection of artifacts and incorrect responses a mean number of 49.7 trials (S.D. = 9.4) per category was left for each participant in each cortisol condition for further analysis. To facilitate peak detection, individual averages per category were low-pass filtered at 12 Hz before peaks were identified and measured. The following stimulus-locked ERP components (peak amplitudes relative to baseline) were identified at electrodes F3, Fz, F4, C3, Cz, C4, P3, Pz, and P4: N1 (the first major negative wave occurring 30–130 ms post-stimulus), followed by P150 (the first major positive wave occurring 120–200 ms post-stimulus), N2 (180–300 ms), and P3 (270–400 ms). Time windows for peak detection were based on visual inspection of the grand average ERPs, averaged across all participants and categories.

1.5. Trait measures

As described above, participants were assigned to two groups based on their score on the Behavioral Inhibition Scale (BIS).[2] This seven-item self-report scale measures sensitivity to signals of threat and was shown to have good reliability (BIS/BAS: Carver and White, 1994). Items are statements that reflect a concern over the possibility of a bad occurrence or a sensitivity to such events when they do occur, and each item is rated on a four-point scale, with a maximum total score of 28. The Behavioral Activation Scale (BAS) consists of a total of 13 items measuring sensitivity to reward. In addition, we administered questionnaires measuring trait anxiety (State Trait Anxiety Inventory (STAI): Spielberger, 1983; Dutch version: Van der Ploeg, 2000) and social anxiety (Social Phobia and Anxiety Inventory (SPAI): Turner et al., 1989; Dutch version: Bögels and Reith, 1999), as well as the temperament subscales of the Temperament and Character Inventory (TCI), which contains a Novelty Seeking and Harm Avoidance subscale that have been related to behavioral activation and behavioral inhibition, respectively (Cloninger et al., 1994; Dutch version: De la Rie et al., 1998).

1.6. 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 10 cm visual analogue scales (VAS). In addition, state anxiety (STAI-state: Spielberger, 1983) was measured at T0 and T3.

1.7. Statistical analyses

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). All statistical analyses described employed a two-tailed alpha of .05. Effect sizes are reported as proportion of explained variance (partial eta squared [η^2]). Reaction times of two participants (both from the low BIS group) were not registered due to technical problems. These participants were excluded from all analyses, resulting in a total number of 18 subjects in the low BIS group.

2. Results

2.1. Trait measures

Table 1 presents the mean values for the low and the high BIS groups on the trait measures. As expected, and due to our selection procedure, groups differed significantly on BIS-scores ($F(1, 36) = 177.87$, $p < .001$, $\eta^2 = 0.83$). In addition, the high BIS group scored significantly higher on several anxiety measures: trait anxiety (STAI-T: $F(1, 36) = 30.18$, $p < .001$, $\eta^2 = 0.46$), social anxiety (SPAI total: $F(1, 35) = 11.31$, $p < .01$, $\eta^2 = 0.26$) and harm avoidance (TCI-HA: $F(1, 36) = 26.01$, $p < .001$, $\eta^2 = 0.42$). The groups did not differ significantly in age, body mass index or any of the other trait measures (all $p > .10$).

2.2. Cortisol and subjective measures

2.2.1. Salivary cortisol

Salivary cortisol (nmol/L) measures (see Table 2) were skewed and therefore log transformed before statistical analysis. The results of a 2 (group: low BIS, high BIS) × 2 (cortisol: placebo, cortisol) × 4 (time: T0, T1, T2, T3) ANOVA rm yielded a significant interaction of cortisol × time ($F(3, 102) = 188.92$,

Table 1
Trait scores for low BIS and high BIS groups

Measure	Low BIS		High BIS	
	M	S.D.	*M*	S.D.
Age	20.4	1.7	19.9	1.4
BMI	21.4	1.6	21.6	1.7
BIS***	14.0	2.1	22.1	1.7
BAS total	37.9	4.4	37.9	3.4
STAI-trait***	29.6	4.9	37.6	4.1
SPAI total**	40.4	17.5	57.8	13.0
TCI				
Harm avoidance***	4.1	3.4	9.4	3.0
Novelty seeking	9.5	4.2	8.9	3.4
Reward dependence	8.7	2.5	10.0	2.7
Persistence	1.8	1.6	2.2	1.2

Note: BMI = body mass index; BIS = Behavioral Inhibition Scale; BAS = Behavioral Activation Scale; STAI = State Trait Anxiety Inventory; SPAI = Social Phobia and Anxiety Inventory; TCI = Temperament and Character Inventory.
** $p < .01$.
*** $p < .001$.

[2] The BIS/BAS scales of Carver and White (1994) were developed on the basis of the reinforcement sensitivity theory (RST: e.g. Gray, 1982). Note that due to a recent revision of this theory (Gray and McNaughton, 2000) the BIS scale, designed to measure threat sensitivity, is likely associated with the Fight Flight and Freezing System in the revised RST (Smillie et al., 2006).

Table 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	S.D.	*M*	S.D.
−5	8.9	3.2	9.1	2.8
+60***	6.8	1.7	161.7	145.1
+120***	6.7	3.5	122.5	55.0
+165***	6.5	2.6	112.4	50.2

Note: $N = 36$ due to missing values of two participants.
*** $p < .001$.

$p < .0001$, $\eta^2 = 0.98$). This result indicates that, as expected, unbound levels of cortisol did not differ between conditions before capsule intake (T0: $F(1, 35) = 0.44$, $p = .51$), but were significantly increased after cortisol administration compared to placebo from 1 h after capsule intake (T1: $F(1, 35) = 320.48$, $p < .0001$, $\eta^2 = 0.90$) until the end of the experiment (T2: $F(1, 34) = 846.67$, $p < .0001$, $\eta^2 = 0.96$; T3: $F(1, 35) = 1265.77$, $p < .0001$, $\eta^2 = 0.97$). There were no significant differences in salivary cortisol values between groups.

2.2.2. Subjective measures

To investigate group differences in subjective mood during task administration and effects of cortisol administration on mood, we conducted separate ANOVAs rm with group (low BIS, high BIS) × cortisol (placebo, cortisol) × time for STAI-state (T0, T3) and VAS (T0, T1, T3) tension, fatigue, depression, anxiety, and activation. Results showed significant main effects of group on STAI-state anxiety ($F(1, 36) = 8.49$, $p < .01$, $\eta^2 = 0.19$) and VAS tension ($F(1, 36) = 7.23$, $p < .05$, $\eta^2 = 0.17$) indicating higher scores for the high BIS group (STAI-S: $M = 33.5$; TEN: $M = 2.7$) compared to the low BIS group (STAI-S: $M = 28.8$; TEN: $M = 1.9$). In addition, VAS anxiety scores tended to be higher for high BIS ($M = 1.6$) compared to low BIS ($M = 1.3$) participants ($F(1, 36) = 4.06$, $p = .051$, $\eta^2 = 0.10$). There were no significant main or interaction effects of cortisol on mood.

2.3. Behavioral results

To investigate the influence of cortisol administration and trait avoidance on performance of the AA-task we conducted separate 2 (group: low BIS, high BIS) × 2 (cortisol: placebo, cortisol) × 2 (emotion: happy, angry) × 2 (arm movement: approach (flex), avoid (extend)) ANOVAs rm on error rates and reaction times (MT and IT).[3] For all behavioral measures we will first present results concerning the AA congruency-effect (i.e. the emotion × arm movement interaction) and subsequently the effects of group and cortisol on this congruency effect.

[3] We performed two additional analyses, with session (first day, second day) and stimulus gender (male, female) as additional factors. Since both analyses revealed no significant effects of these factors on the emotion × arm movement interaction, we have further left them out of the analyses.

2.3.1. Error rates

As to be expected in the AA-task (see Rotteveel and Phaf, 2004), a significant emotion × arm movement interaction ($F(1, 36) = 5.77$, $p < .05$, $\eta^2 = 0.14$) showed that participants made more errors (%) during affect-incongruent arm movements (avoid happy: $M = 7.2$; approach angry: $M = 8.8$) than affect-congruent arm movements (approach happy: $M = 5.3$; avoid angry: $M = 7.8$). There were no effects of group or cortisol on these congruency effects (all $p > .16$).

2.3.2. Initiation times (IT)

Also for the IT (in ms), we found the expected AA congruency effect. A significant emotion × arm movement interaction ($F(1, 36) = 21.05$, $p < .0001$, $\eta^2 = 0.37$) showed that participants were faster in initiating affect-congruent (approach happy: $M = 486$; avoid angry: $M = 500$) than affect-incongruent arm movements (avoid happy: $M = 506$; approach angry: $M = 511$). The effects of group or cortisol on this emotion × arm movement interaction were not significant.

We did, however, find a significant three-way interaction of group × cortisol × arm movement ($F(1, 36) = 15.03$, $p < .0001$, $\eta^2 = 0.29$). Separate ANOVAs for the high and low BIS group showed a significant cortisol × arm movement interaction for the high BIS group ($F(1, 19) = 16.11$, $p < .001$, $\eta^2 = 0.46$), but not for the low BIS group ($F(1, 17) = 2.25$, $p = .15$) (see Fig. 2). The significant results for the high BIS group were due to a significant effect of cortisol on the approach movement ($F(1, 19) = 5.76$, $p < .05$, $\eta^2 = 0.23$), indicating that approach reactions were slowed after cortisol administration in high BIS participants. The cortisol × emotion × arm movement interaction was not significant in the high BIS group ($F(1, 19) = 0.38$, $p = .55$), indicating that the cortisol × arm movement interaction was not different for happy and angry faces. However, because we had specific hypotheses about this effect for angry faces, we additionally checked whether the cortisol × arm movement interaction for the high BIS group would hold when tested for responses to angry faces only. The results indeed showed the cortisol × arm movement interaction in the high BIS group to be significant for angry faces ($F(1, 19) = 10.30$, $p < .01$, $\eta^2 = 0.35$). Interestingly, this effect was not significant for happy faces (cortisol × arm movement: $F(1, 19) = 2.16$, $p = .16$). In addition, due to the slowing of approach reactions after cortisol administration, the congruency effect for angry faces (i.e. faster avoidance than approach) was only significant for the high BIS group in the cortisol condition (arm movement: $F(1, 19) = 8.84$, $p < .01$, $\eta^2 = 0.32$) and not the placebo condition ($F(1, 19) = 0.17$, $p = .69$) (see Fig. 2).

Thus, in line with our hypotheses, cortisol administration affected approach–avoidance congruency effects especially to angry faces in high BIS participants. Although the results indicated that this effect did not differ significantly between happy and angry faces, the effect was only significant for angry, and not for happy faces.

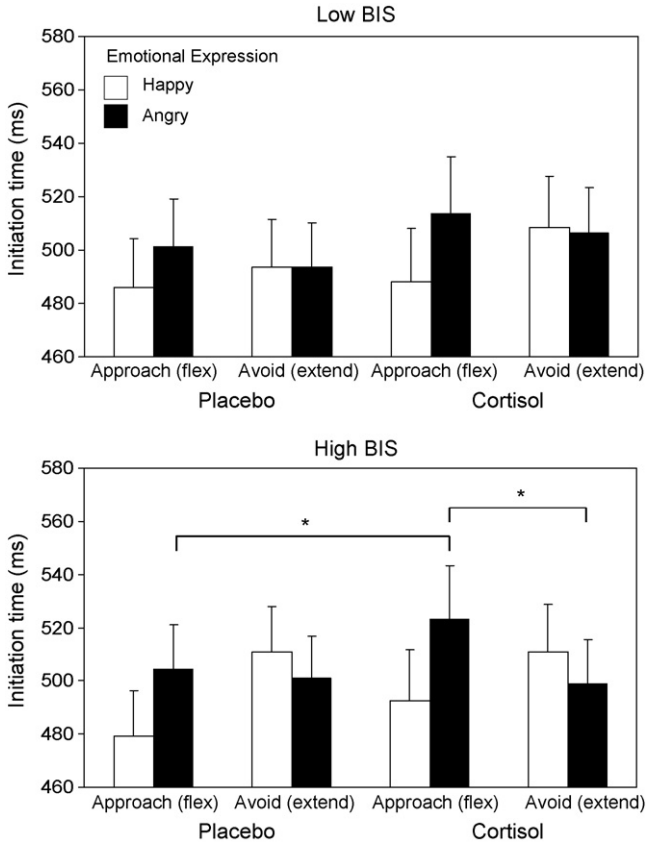

Fig. 2. Mean initiation times (in ms) on the AA task for the low BIS (upper panel) and high BIS (lower panel) group after placebo and cortisol administration. Cortisol administration resulted in a significant slowing of approach, but not avoidance, movements in the high BIS group only. This effect was significant for angry faces, but not for happy faces. The congruency effect for angry faces (i.e. faster avoidance than approach) was only significant in the high BIS group after cortisol administration. Error bars indicate the standard errors of the means. $^*p < .05$.

2.3.3. Movement times (MT)

Like the error rates and IT, the MT (in ms) showed a significant emotion × arm movement interaction ($F(1, 36) = 8.48$, $p < .01$, $\eta^2 = 0.19$) indicating faster execution of affect-congruent (approach happy: $M = 138$; avoid angry: $M = 134$) than affect-incongruent arm movements (avoid happy: $M = 140$; approach angry: $M = 142$). There were no effects of group or cortisol on these congruency effects in MT.

2.4. Event-related potentials

The data from the Cz electrode appeared most representative for the three midline electrodes (Fz, Cz, Pz) and are presented in Fig. 3. The general morphology of the waveform at these midline electrodes included a prominent, early negative peak at 100 ms (N1), followed by a positive wave at 150 ms (P150), a second negative wave at 230 ms (N2) and a final positive wave at 350 ms (P3). As shown in Fig. 3, event-related peaks were pronounced.

Baseline-to-peak amplitudes were analyzed with separate 2 (group: low BIS, high BIS) × 2 (cortisol: placebo, cortisol) × 2 (emotion: happy, angry) × 2 (arm movement: approach (flex), avoid (extend)) × 3 (electrode: Fz, Cz, Pz)[4] ANOVAs rm for N1, P150, N2, and P3. As for the behavioral results, we will focus on the AA congruency-effects (i.e. the emotion × arm movement interaction) and the effects of group and cortisol on this interaction.

2.4.1. P150

For P150 peak amplitude, we found a significant four-way interaction of group × cortisol × emotion × arm movement ($F(1, 36) = 4.94$, $p < .05$, $\eta^2 = 0.12$). Follow up analyses to determine the nature of this interaction showed that the emotion × arm movement interaction was only significant for the high BIS group in the cortisol condition ($F(1, 19) = 6.50$, $p < .05$, $\eta^2 = 0.26$) (see Fig. 4, panel A). It was not significant for the high BIS group in the placebo condition ($F(1, 19) = 0.17$, $p = .69$), nor was it significant for the low BIS group in either the cortisol condition ($F(1, 17) = 1.88$, $p = .19$) or the placebo condition ($F(1, 17) = 0.42$, $p = .53$). Further analyses of this emotion × arm movement interaction for the high BIS group in the cortisol condition revealed that the effect of arm movement was significant for angry faces ($F(1, 19) = 9.93$, $p < .01$, $\eta^2 = 0.34$), but not for happy faces ($F(1, 19) = 0.68$, $p = .42$). This indicates that only in response to angry faces P150 amplitude was significantly higher (i.e. more positive) when these participants made an avoidant arm movement, than when they made an approaching arm movement. Thus, consistent with the behavioral (IT) results, we found significant congruency effects (i.e. approach versus avoidance) for the high BIS group in the cortisol condition for angry faces only. Also, the P150 amplitude of high BIS participants in the cortisol condition was significantly higher in response to angry compared to happy faces only for avoidant arm movements (emotion: $F(1, 19) = 14.15$, $p < .001$), and not for approaching arm movements ($F(1, 19) = 0.00$, $p = .99$).

2.4.2. P3

For P3 amplitude, the group × cortisol × emotion × arm movement ANOVA rm yielded a significant three-way interaction of group × cortisol × arm movement ($F(1, 36) = 5.13$, $p < .05$, $\eta^2 = 0.13$) and a significant three-way interaction of cortisol × emotion × arm movement ($F(1, 36) = 4.13$, $p < .05$, $\eta^2 = 0.10$). Although post hoc analyses of the first interaction did not reveal significant effects, post hoc analyses for the cortisol × emotion × arm movement interaction showed the following effects: The emotion × arm movement interaction was significant in the cortisol condition ($F(1, 36) = 5.78$, $p < .05$, $\eta^2 = 0.14$), but not in the placebo condition ($F(1, 36) = 0.00$, $p = .98$). In the cortisol condition, the P3 amplitude for avoidant arm movements was significantly higher

[4] A second analysis for each component 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 confirmed the conclusion based on visual inspection that there were no laterality effects involving emotion × arm movement. Therefore, only results of midline electrodes are presented.

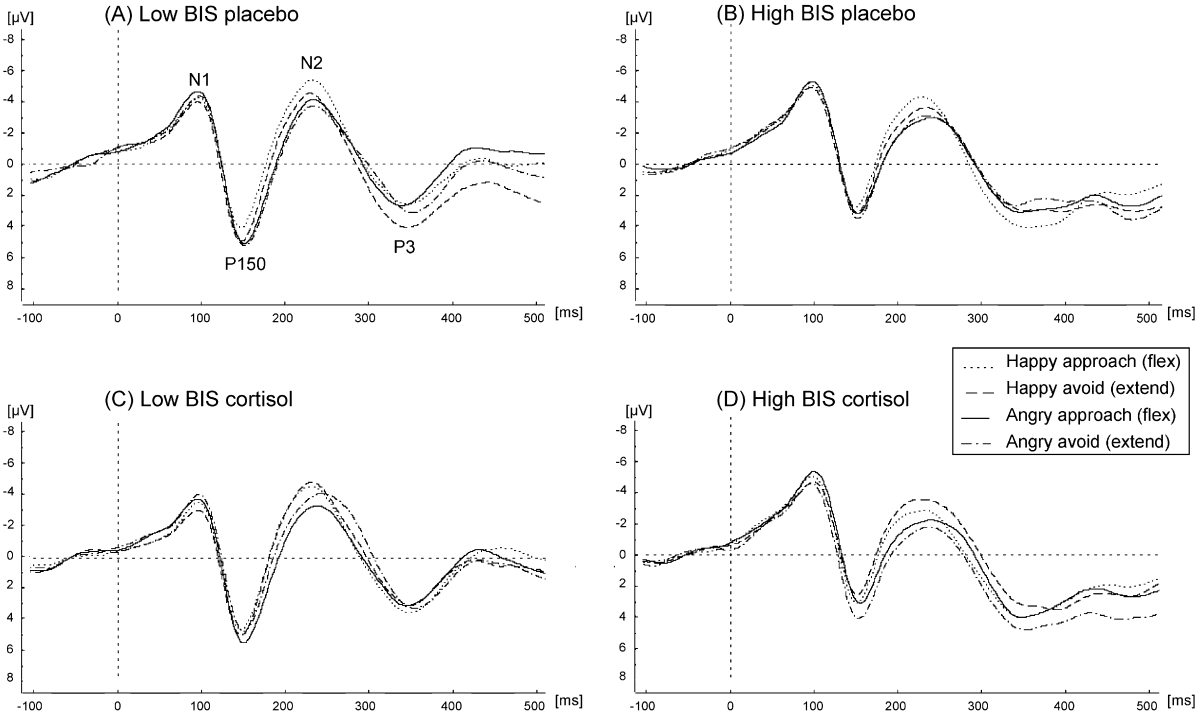

Fig. 3. Stimulus synchronized event-related potential (ERP) waveforms at Cz for the low BIS (panels A and C) and high BIS (panels B and D) groups after placebo (panels A and B) and cortisol (panels C and D) administration. Stimulus onset was at $t = 0$. Lines represent the categories defined by the emotional expression of the stimuli and the arm movement of the response.

(i.e. more positive) in response to angry faces than in response to happy faces (emotion: $F(1, 36) = 8.85$, $p < .01$, $\eta^2 = 0.20$). The four-way *group* × cortisol × emotion × arm movement interaction was not significant ($F(1, 36) = 0.02$, $p = .88$), indicating that this effect did not differ between groups. However, because we had specific hypotheses about the congruency effects after cortisol administration in the high BIS participants, we additionally checked whether the emotion × arm movement interaction in the cortisol condition would hold when tested in the high BIS group only. The results indeed indicated that the emotion × arm movement interaction in the cortisol condition was significant for the high BIS group only ($F(1, 19) = 4.67$, $p < .05$, $\eta^2 = 0.20$). Interestingly, it was not significant for the low BIS group ($F(1, 17) = 1.45$, $p = .25$), nor was it significant for either group in the placebo condition (low BIS: $F(1, 17) = 0.57$, $p = .46$; high BIS: $F(1, 19) = 0.72$, $p = .41$). Follow up analyses indicated that, in line with the P150 results, for the high BIS group in the cortisol condition the effect of Emotion was significant for avoidant arm movements ($F(1, 19) = 12.67$, $p < .003$, $\eta^2 = 0.40$), but not for approaching arm movements ($F(1, 19) = 0.86$, $p = .37$). Thus, P3 amplitudes were significantly higher in response to angry faces than in response to happy faces only when an avoidant arm movement was made by high BIS individuals in the cortisol condition (see Fig. 4, panel B).

2.4.3. N1 and N2

We did not find a significant emotion × arm movement interaction for N2 amplitude ($F(1, 36) = 0.15$, $p = .70$), indicating that N2 amplitude was not increased for affect-incongruent arm movements (avoidance of happy faces and approach of angry faces) compared to affect-congruent arm movements (approach of happy faces and avoidance of angry faces).

Although we did not have specific expectations about possible effects of cortisol and group on congruency effects for the N2, visual inspection of Fig. 3 suggested that N2 amplitudes showed similar effects as P150 and P3. This may suggest a general effect of cortisol administration on ERP amplitudes in the high BIS group. Indeed, significant N2 congruency effects were found in the high BIS group after cortisol administration only (emotion × arm movement: $F(1, 19) = 11.55$, $p < .01$, $\eta^2 = 0.38$) (see Fig. 4, panel C). Thus, although the effects of cortisol administration on the N2 congruency effects were not significant in the four-way ANOVA (group × cortisol × emotion × arm movement: $F(1, 36) = 2.38$, $p = .13$), the N2 effects showed trends in the same direction as the IT and positive ERP wave results. As expected we found no other significant effects involving emotion and arm movement on negative waves (N1: all $p > .20$).

3. Discussion

With the present study we aimed to investigate the influence of cortisol administration on approach and avoidance behavior towards positive and negative social stimuli in high and low avoidant participants (i.e. scoring high or low on the Behavioral Inhibition Scale (BIS)). The second aim was to investigate the associated brain processes using ERPs, with specific focus on components involved in emotional face processing and action

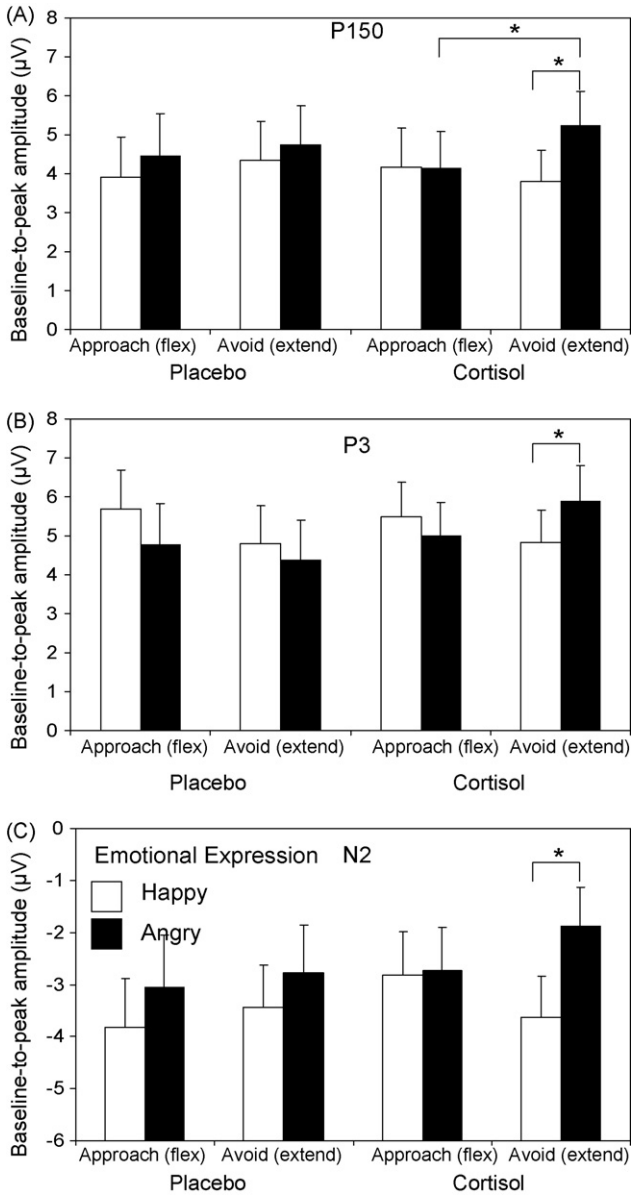

Fig. 4. Baseline-to-peak amplitude (in μV) for P150 (panel A), P3 (panel B), and N2 (panel C) ERP components for the high BIS group after placebo (left) and cortisol (right) administration. All three components show a significant emotion × arm movement interaction in the high BIS group after cortisol administration only, with most positive amplitudes in response to angry faces when an affect-congruent avoidance response (arm extension) is made. Note that for the N2 component (panel C) the values of the *y*-axis are inverted, such that consistent with panels A and B a higher bar indicates a more positive amplitude. Error bars indicate the standard errors of the means. $*p < .05$.

monitoring. Compared to low BIS participants, we expected high BIS participants to show relatively increased threat avoidance, and we expected that cortisol administration would result in a facilitation of this threat avoidance. In addition, these behavioral effects were hypothesized to be accompanied by increased amplitudes of ERP components involved in motivational processes. Our results were largely in line with our expectations, showing cortisol administration in high BIS participants to result in enhanced AA congruency effects in both initiation times and positive ERP amplitudes for angry faces. Below, these behavioral and ERP results will be first discussed separately. Thereafter, these results will be integrated in the light of previous findings related to glucocorticoid effects on cognition and threat processing.

3.1. Behavioral results

First, consistent with previous findings (Chen and Bargh, 1999; Roelofs et al., 2005; Rotteveel and Phaf, 2004), this study showed the expected congruency effects, as reflected by faster initiation times (IT), faster movement times (MT) and less errors for affect-congruent (i.e. approach happy and avoid angry faces) compared to affect-incongruent (avoid happy and approach angry faces) arm movements.

In addition, in the high BIS, but not the low BIS group, cortisol administration resulted in a significant slowing of approach reactions (IT). In line with our expectations, this resulted in a significant increase of the approach–avoidance congruency effect for angry faces (faster avoidance than approach), but not for happy faces. However, these differential effects for valence should be interpreted with caution. The lack of a four-way interaction including the emotional valence of the faces suggests an inhibition of approach reactions to social stimuli, independent of stimulus valence. However, our present interpretation is supported by the ERP results (as will be discussed later), which do suggest a differential effect of cortisol administration on processing of happy and angry faces.

In spite of the fact that our groups were a priori selected on the basis of extreme high or low BIS scores, and differed significantly with respect to trait anxiety and social anxiety, they did not differ in approach–avoidance reactions in the placebo condition. This may be due to the fact that all participants were healthy students. It is also important to note that basal cortisol levels did not differ between high and low BIS participants. Apparently the approach–avoidance reactions of high and low BIS participants differed only after cortisol administration. These results are consistent with the findings of Roelofs et al. (2005), who also found no differences between high and low trait avoidant individuals (based on a post hoc median-split on BIS scores) on approach–avoidance behavior, independent of cortisol.

Finally, consistent with previous findings (Roelofs et al., 2005), we did not find significant effects of BIS group or cortisol on the error rates or the movement times (MT). This is not surprising, since participants generally make few errors in this task, and MT has been suggested to be predominantly affected by physical parameters of movement, and not by central cognitive processes (see Rotteveel and Phaf, 2004).

3.2. ERP results

The second purpose of this study was to investigate the brain processes associated with approach and avoidance of happy and angry faces. In line with the behavioral results, we found a significant effect of cortisol administration on ERPs for high BIS participants only. After cortisol administration P150 amplitude was highest (i.e. most positive) in reaction to angry

faces when high BIS participants made an avoidant arm movement. A similar effect was found on P3 amplitude, showing significantly higher positive amplitudes in reaction to angry as compared to happy faces when an avoidant arm movement was made by high BIS participants after cortisol administration. Although the lack of a four-way interaction including group (low BIS, high BIS) on P3 amplitude indicated that this effect did not differ significantly between groups, separate analyses for each group confirmed our specific a priori expectation that P3 amplitudes in reaction to angry faces would be particularly pronounced for high BIS participants after cortisol administration, given the increased motivational significance of threat stimuli for these participants.

Increased amplitudes of early as well as late positive ERP components have been interpreted as reflecting increased allocation of processing resources to motivationally significant input (Eimer et al., 2003; Nieuwenhuis et al., 2005). The timing of the early effect in the present study (i.e. P150 amplitude) is in line with results of previous studies showing differential processing of faces signaling threat (i.e. fearful or threatening faces, 110–220 ms post-stimulus: e.g. Bar-Haim et al., 2005; Eimer and Holmes, 2002; Schupp et al., 2004; Williams et al., 2006), and suggests an effect on relatively early stages of information processing. Interestingly, data from single-neuron recordings in human ventromedial prefrontal cortex showed differential processing of threatening emotional face stimuli in the same time range (120–170 ms: Kawasaki et al., 2001), suggesting that early aspects of perceptual processing may be modulated via top-down influences, facilitating early identification of, and appropriate behavioral responses to, threat (see Bar, 2003).

The increased P3 amplitude in the present study is consistent with results of other studies indicating increased amplitudes of late positive components for emotionally negative or threat stimuli (e.g. Huang and Luo, 2006; Schupp et al., 2004), which are assumed to reflect more elaborate sustained perceptual processing of relevant emotional stimuli, via top-down influences from limbic and/or frontal areas (Eimer et al., 2003; Krolak-Salmon et al., 2001; Sato et al., 2001). Interestingly, we found enhanced P150 and P3 amplitudes for angry faces after cortisol administration only in high avoidant (high BIS) individuals, indicating that processing of angry faces after cortisol administration was specifically enhanced in individuals sensitive to threat. In addition, here the P150 amplitude for angry faces was significantly higher when an (affect-congruent) avoidance movement was made than when an (affect-incongruent) approach movement was made. This finding may be explained by the fact that the affect-congruent and affect-incongruent arm movements were blocked in separate instruction conditions, which may have strengthened the response mode within each condition, resulting in priming of affect-congruent stimulus processing.

On a more exploratory basis, we also tested whether the AA task could elicit significant N2 effects, reflected by increased amplitudes for affect-incongruent relative to affect-congruent arm movements. We did not find such effects. In other more frequently used paradigms involving congruent and incongruent stimulus–response mapping, such as Flanker or Stroop tasks, an N2 congruency effect is observed ubiquitously (see e.g. Yeung et al., 2004). A possible explanation for the discrepancy of our finding is related to the type of conflict that may be elicited by the AA task. In this task, the response conflict in incongruent trials is not the result of two competing endogenous responses elicited simultaneously by the stimulus, as is the case in Flanker and Stroop tasks, but results from a conflict between the instructed response and the intuitive response tendency elicited by the stimulus. Conflict or incompatibility in the AA task may therefore be represented at another level than in typical conflict tasks, and as a result it may not be reflected by increased N2 amplitudes. At present, the representational level at which action or conflict monitoring by the ACC takes place is still unclear (Van Veen et al., 2004).

3.3. Cortisol effects and threat sensitivity

Together, the behavioral and ERP findings showed cortisol administration to be associated with enhanced AA congruency effects in reaction to angry faces in high avoidant, but not low avoidant, individuals. However, whereas this effect was manifested in a slowing of affect-*incongruent* (approach) responses in behavior, ERPs showed enhanced positive amplitudes for affect-*congruent* (avoidance) responses.

The results of this study did not show a general effect of cortisol on approach and avoidance (AA) tendencies. Instead, the effects of cortisol administration on affect-congruent processing of, and initiation times to, angry faces in particular were mediated by individual differences in self-reported threat sensitivity (BIS). This finding may be viewed as consistent with the findings of Roelofs et al. (2005) who investigated the effects of stress-induced cortisol responses on AA behavior, using the same paradigm. In that study, the effects of stress-induction on approach and avoidance tendencies (IT) were found to be mediated by individual differences in cortisol responsiveness, which is possibly associated with individual differences in the tendency to perceive and respond to affective stimuli (Roelofs et al., 2005).

These results are also in agreement with the findings from animal studies showing that corticosteroid effects on cognition are context dependent, and are influenced by factors such as environmental input and concurrent information processing (De Kloet et al., 1999). People with high BIS scores are suggested to be especially responsive to threat cues (Carver and White, 1994) and thus may have a processing bias for threat-related facial expressions, as has been previously found with anxious individuals (e.g. Bar-Haim et al., 2005; Fox et al., 2002; Mogg and Bradley, 2002). This processing bias has been found to increase under stressful conditions (Mathews and Macleod, 1994), as well as after acute cortisol administration in healthy young males (Putman et al., 2007). In the present study, the effects of cortisol administration may have interacted with a processing bias of threatening stimuli in high BIS participants. This interpretation is in line with the results of a study by Cools et al. (2005), who found that a manipulation of serotonin function interacted with individual differences in BIS scores to bias the processing of threatening stimuli.

The present study is the first to show effects of cortisol administration on human approach–avoidance behavior, and several related questions remain unanswered. First, it remains to be explored whether the present findings are dose dependent. Second, the effects of cortisol administration in our study do not mimic the behavioral effects of high endogenous cortisol levels during stress, which were found to result in decreased approach and avoidance tendencies (Roelofs et al., 2005). This difference may be explained by the results of several recent studies (e.g. Roozendaal et al., 2004; Elzinga and Roelofs, 2005) suggesting that the impairing effects of cortisol on prefrontal functions depend on concurrent noradrenergic activation, which is present during stress, but not in our study. Interesting in this respect is that, consistent with the findings of the present study, Van Honk et al. (1998) found increased (basal) cortisol levels to be associated with increased avoidance of angry faces on an emotional Stroop task, when testing subjects in a non-stress condition. Taken together, these findings suggest an important role for the context in which cortisol levels are elevated. Future studies in which the effects of endogenous cortisol are attenuated, for example with the use of selective steroid receptor antagonists, may help to further assess the role of cortisol and the interplay with contextual effects in human cognition (De Kloet et al., 1999).

Third, since negative laboratory stimuli are routinely judged to be more arousing than positive laboratory stimuli, the differential effects of cortisol administration on angry faces may be due to either the valence or arousal qualities of these stimuli. We cannot differentiate between these factors in the present study. However, in all likelihood, valence and arousal together influence the motivational significance of these stimuli, to prepare the individual for rapid behavioral responses to stimuli that signal potential danger.

Finally, it should be noted that in order to avoid interactions with hormonal cycling in females, the findings of the present study were based on male participants only, and it remains to be tested whether similar effects emerge for females.

In conclusion, both the behavioral and ERP analyses showed that cortisol enhanced approach–avoidance congruency effects towards angry faces in high avoidant individuals only. ERP analyses showed that amplitudes of both early (P150) and late (P3) positive components were enhanced, suggesting increased processing of threat stimuli after cortisol administration. Together, these results suggest a context-specific effect of cortisol on processing of, and adaptive responses to, motivationally significant threat stimuli, particularly in participants highly sensitive to threat signals. These effects may be relevant for the study of stress and avoidance reactions in patients characterized by strong avoidance tendencies and sensitivity to social threat, such as patients with social anxiety disorder.

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