To approach or to avoid : neurobiological mechanisms in social anxiety

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Chapter 8

General Discussion

The aim of this thesis was to gain more insight in the psychobiological mechanisms underlying social fear and avoidance behavior in humans. *Chapter 1* described that avoidance behavior may play an important role in social anxiety. However, experimental studies investigating the behavioral as well as neurobiological aspects of avoidance tendencies in SAD were largely lacking. In addition, whereas animal studies suggest that cortisol plays an important role in the regulation of social motivational behavior, little was known about the effects of cortisol on the regulation of avoidance behavior in humans, or even about effects of cortisol on attentional processing of threat. Thus, the aim of this thesis was to gain more insight in the brain processes underlying threat processing and avoidance behavior in high socially anxious individuals, and to investigate how these processes are affected by cortisol.

In this final chapter, I will first present a summary of the studies described in *Chapters 2* to *7* of this thesis, followed by an integration of the main findings and a discussion of the strengths and limitations of these studies. The chapter concludes with suggestions for future research and implications for clinical practice.

Overview of findings

In *Chapter 2*, the predictions were tested that individuals characterized by high levels of behavioral inhibition show preferential processing of and stronger avoidance tendencies towards social threat cues, and that these processes are facilitated by cortisol. This was investigated by measuring the effects of cortisol administration in a sample of pre-selected high and low behaviorally inhibited/anxious students, using a placebo controlled within-subject design. Overt approach and avoidance responses 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 (AA-) task, Rotteveel & Phaf, 2004), and threat processing was measured by recording event-related potentials (ERPs) during task performance. The results of this study showed that cortisol administration significantly increased the AA congruency effects (i.e., relative faster avoidance compared to approach), in particular towards angry faces, in high but not low trait avoidant students. As reaction times for 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 (e.g., Roelofs et al.,

2009b), the increased AA congruency effect for angry faces is consistent with a relatively increased tendency to avoid threat. Moreover, the ERP results showed a significant effect of cortisol on social threat processing, again only in high trait avoidant participants. In these participants, cortisol administration resulted in a significant enhancement of processing of angry faces during avoidance behavior, as reflected by increased early (P150) and later (P3) midline positive ERP amplitudes. In line with our predictions, these findings suggest that cortisol administration results in a facilitation of processing and adaptive responses to motivationally significant threat stimuli, specifically in individuals that are highly sensitive to such threat cues.

The aim of the study presented in *Chapter 3* was to investigate the effects of endogenous cortisol increases on approach-avoidance behavior. Therefore, the Trier Social Stress Test (Kirschbaum et al., 1993) was administered to SAD patients, and performance on the AA-task in this psychosocial stress condition was compared to baseline using a within-subject design. The possible role of hypercortisolism in the failing regulation of social fear and fear behavior in SAD was investigated by directly relating stress-induced cortisol responses to overt avoidance responses to social threat cues. A sample of matched healthy participants and a sample of patients with Post-Traumatic Stress Disorder (PTSD) were included as control groups to investigate the specificity of the effects. This study showed three major findings: First, patients with SAD had larger cortisol responses to the social stress test as compared to healthy and PTSD control participants. Second, social stress elicited increased avoidance tendencies towards social threat stimuli in SAD, but not in PTSD patients and healthy controls. Third, the increased cortisol responses in the social stress condition were significantly correlated to the increase in social avoidance behavior in participants with SAD, over and above the effects of blood pressure and subjective anxiety. These findings provide evidence for a direct link between increased cortisol stress-responsiveness and social avoidance behavior in patients with SAD.

Following the study in *Chapter 3*, the study presented in *Chapter 4* was conducted to more closely investigate the causal role of cortisol, as well as the neural processes involved in the regulation of social fear behavior in SAD. Furthermore, the same experimental procedure was used as in *Chapter 2*, to test whether the findings for the high anxious students in that study would generalize to a clinical population. Therefore, in this study the effects of cortisol administration on approach-avoidance behavior and

threat processing were investigated in a second sample of unmedicated patients with SAD, using a placebo-controlled within-subject design. The results showed a significant positive relation between levels of social anxiety and slowing of approach movements to angry faces, consistent with a relatively increased tendency to avoid threat in more anxious patients. In contrast to the findings of *Chapters 2* and *3*, we did not find significant effects of cortisol on behavior in this study. However, and most importantly, the results of the ERP analyses demonstrated a significant interaction of cortisol by social anxiety on early processing of emotional faces: Cortisol administration resulted in a significant increase in processing of emotional faces during avoidance compared to approach for patients with high levels of social anxiety, as reflected by increased midline P150 amplitudes. This effect was only significant for angry faces, although it did not differ significantly for happy faces. These results are largely in line with the findings of *Chapter 2*, and suggest that the mechanism of early threat processing which is enhanced by cortisol in high trait avoidant healthy participants is similarly affected in patients with a clinical diagnosis of SAD. In addition, these findings suggest that the link between increased cortisol stress-responsiveness and social avoidance behavior in patients with SAD as found in *Chapter 3* may be mediated by causal effects of cortisol on early threat processing.

In *Chapter 5* the hypothesis was tested that patients with SAD show increased early processing of angry faces regardless of whether this is required for task performance, and even under conditions of restricted stimulus awareness. Furthermore, as effects of cortisol have been shown to be context-dependent, I investigated whether the cortisol-induced increases in threat processing, as found in previous chapters, are contingent on the stimuli being task-relevant. In this study, the effects of cortisol administration on RT and ERPs were measured in patients with SAD during color-naming of masked and unmasked emotional faces in a modified emotional Stroop task, using a placebo-controlled within-subject design. This study showed two major findings: First, the ERP results showed an early processing bias for masked as well as unmasked social threat stimuli, reflected by increased P2 amplitudes for angry faces in the placebo condition. Second, this early threat bias significantly decreased (and disappeared) after cortisol administration in the masked task, and this cortisol-induced decrease in threat processing was stronger for participants with higher levels of social anxiety. These results provide evidence that, in line with the predictions, social threat stimuli

automatically attract more attention in patients with SAD at very early stages of information processing. They further suggest that cortisol administration significantly decreases the processing of social threat stimuli when they are task-irrelevant and presented under conditions of restricted awareness, which is in contrast to the effect of cortisol on threat processing when stimulus evaluation is explicit and relevant for the generation of overt avoidance responses, as described in *Chapter 2* and *4*. I will further discuss the implications of these findings with respect to the context-dependency of cortisol effects in a separate paragraph below.

In *Chapter 6* a more theoretical-methodological issue was explored, namely to which extent the approach-avoidance effects, as measured in previous chapters, depend on the actions of the participants themselves or may be mediated by a representation of relative distance between the participant and the stimulus. In a series of four reaction time experiments in healthy male and female students, I tested the effects of stimulus movements on the evaluation of happy and angry face stimuli. It was predicted that changes in relative distance due to stimulus movement would influence affective evaluation in a similar way as the approach and avoidance movements executed by the participant in the AA-task. In line with these predictions, the results of these experiments showed facilitation of affective categorization of emotional faces when stimulus movement was congruent with stimulus emotion, resulting in faster and more correct responses to approaching happy and withdrawing angry faces compared to approaching angry and withdrawing happy faces. These findings suggest that relative distance indeed plays an important role in AA congruency effects, and that these effects do not depend on the execution of movements by the participant.

Finally, in *Chapter 7* the prediction was tested that cortisol administration increases the strength of the relation between slow (delta or theta) and fast wave (alpha or beta) activity in the EEG, a pattern of brain activity that has been related to high self-reported levels of behavioral inhibition and anxiety. Recently, Schutter and Van Honk (2005) found a significantly increased slow-fast wave (delta–beta) correlation in participants with high compared to low endogenous basal cortisol levels, and suggested that cortisol can modify brain activity, increasing a pattern associated with anxious and inhibited motivational states. However, the cross-sectional design of their study precluded conclusive interpretations regarding the causal effects of cortisol on the correlation between delta and beta activity. Therefore, in this chapter I investigated the

effects of cortisol *administration* on this resting state EEG measure in a sample of pre-selected high and low behaviorally inhibited/anxious students, using a placebo-controlled within-subject design. As expected, I found significant correlations between delta and beta activity at midfrontal electrodes in high but not low behaviorally inhibited subjects in both conditions. In addition, in line with the predictions, cortisol tended to increase the delta-beta correlation compared to placebo, resulting in significant delta-beta correlations on all electrodes in high but not low behaviorally inhibited participants, and a (near) significant group difference at midfrontal and central electrodes.

Theoretical integration

As described in *Chapter 1*, in this thesis I aimed to test several predictions concerning social threat processing and avoidance in social anxiety, and the role of cortisol in the regulation of these processes. In the next section, I will first discuss the results of the studies presented in *Chapters 2* to *7* in relation to these predictions, followed by another important theme that emerged from these studies, i.e., the context-dependency of cortisol effects on early threat processing.

Increased threat processing in social anxiety

The first prediction in this thesis was that socially threatening stimuli receive early preferential processing by high socially anxious individuals. This prediction was clearly supported by the findings in *Chapter 5*, in which we found increased early positive ERP amplitudes in reaction to angry faces even under conditions of restricted stimulus awareness, and while threat processing was not required for task performance. The fact that this threat vigilance was reflected in the ERPs but not in the behavioral results is consistent with the findings of others (e.g., Kolassa & Miltner, 2006), and underlines the added value of using this psychophysiological measure in emotional Stroop tasks. Two other studies also provided evidence for increased processing of social threat, during the execution of overt avoidance responses in high trait avoidant/behaviorally inhibited students (*Chapter 2*) and patients with high levels of clinical social anxiety (*Chapter 4*), but only after cortisol administration and not in the placebo condition. A possible reason for the absence of enhanced threat processing in

high anxious participants under baseline conditions (i.e., after placebo administration) in these latter studies could be that the approach-avoidance task in these studies involved the *explicit* evaluation of the emotional valence of the stimuli, and because the emotional valence was relevant for goal-directed social motivational behavior in this task (i.e., the execution or inhibition of overt approach and avoidance responses). This may have increased the motivational significance of all stimuli (positive as well as negative) for the participants, diminishing the relative processing advantages for social threat cues in high anxious individuals.

Increased avoidance tendencies in social anxiety

The second prediction of this thesis was that individuals characterized by high levels of behavioral inhibition or social anxiety would show stronger avoidance tendencies in reaction to social threat cues. Consistent with this prediction, the results described in Chapter 4 showed a significant effect of social anxiety on reaction times, reflecting slower execution of approach responses to angry faces in patients with higher levels of social anxiety. However, under baseline conditions (i.e., after placebo administration or before stress induction) we did not find significantly increased threat avoidance in high compared to low trait avoidant participants (*Chapter 2*) or in patients with SAD compared to patients with PTSD or healthy controls (*Chapter 3*). Although this lack of group differences in avoidance under baseline conditions is consistent with some previous findings on the AA-task (Roelofs et al., 2005), others authors have recently reported significant differences between low and high socially anxious participants on approach-avoidance behavior (Heuer et al., 2007). Several methodological differences may account for these findings. First, the participants in the study of Heuer et al. (2007) were pre-selected on extreme high and low scores (highest and lowest 10% of the distribution) on the Liebowitz Social Anxiety Scale (anxiety subscale). The healthy control participants in *Chapter 3* of this thesis were unselected, and although participants in *Chapter 2* were pre-selected on a behavioral inhibition scale (BIS: Carver & White, 1994), these groups were less extreme (highest and lowest 33% of the distribution). Second, the task used by Heuer and colleagues included a zoom feature, creating the visual impression that the pictures were coming closer upon pulling a joystick (approach) and that they moved away upon pushing it (avoidance). As shown in *Chapter 6* of this thesis, this zooming effect can by itself (i.e., independent from the

movement executed by the participant) result in significant approach-avoidance effects, and may thus be expected to increase these effects compared to a static stimulus as used in this thesis. Finally, in contrast to the AA-task used in this thesis, participants in the study of Heuer and colleagues responded to a neutral dimension (puzzles versus faces) instead of the stimulus emotion. Such indirect (implicit) measurement of the effects of emotional expressions has been argued to be more sensitive to individual differences in automatic processing and less affected by cognitive control mechanisms (e.g., De Houwer, 2006) compared to explicit evaluation. However, because of the zoom feature and the explicit instruction to the participants to pull the joystick towards themselves or push it away from themselves, the concepts of approach and avoidance are arguably not implicit in the AA-task of Heuer et al. (2007), whereas they are implicit in our task version.

Thus, we found evidence for increased avoidance tendencies in high anxious participants, sometimes at baseline but most evidently in a context of a (endogenous or exogenous) cortisol challenge. These findings not only provide experimental support for behavioral observations of avoidance tendencies in SAD (e.g., Alden & Bieling, 1998; Horley, Williams, Gonsalvez, & Gordon, 2003), but also shed light on the conditions in which these avoidance tendencies are most pronounced. This latter aspect will be discussed in the next section.

Cortisol facilitates social avoidance

The third and final main prediction in this thesis was that threat processing and avoidance would be facilitated by high levels of endogenous or exogenous cortisol. The findings of the studies in *Chapters 2*, *3* and *4* largely support this prediction. *Chapter 2* showed an increase in AA congruency effects after cortisol administration in high trait avoidant participants, consistent with a relatively increased avoidance tendency. In addition, the findings of *Chapter 3* demonstrated that social stress elicited increased avoidance tendencies toward social threat in patients with SAD, and moreover that this increased tendency to avoid threat was directly related to the stress-induced cortisol levels in these patients.

With regard to threat processing, *Chapters 2* and *4* provided evidence for facilitated processing of social threat stimuli in high behaviorally inhibited/anxious healthy participants (*Chapter 2*), as well as patients with high levels of clinical social

anxiety (*Chapter 4*). Interestingly, cortisol only increased threat processing during the execution of avoidance responses. This suggests that cortisol facilitates avoidance perhaps by facilitating motivated attention to threat.

By contrast, the findings of *Chapter 5* showed that cortisol administration significantly *decreased* processing of social threat stimuli when they were task-irrelevant and presented under conditions of restricted awareness. Thus, in line with the findings of *Chapter 4*, in *Chapter 5* cortisol administration specifically affected early positive ERP amplitudes for angry faces, and the magnitude of this effect was related to severity of social anxiety in both studies, but the *direction* of the cortisol effect was reversed. As both of these studies were conducted in the same participant sample and during the same experimental procedure, the contrasting findings are most likely explained by task-related differences, of which the task or goal-relevance of the stimuli may be an important factor (see *Chapter 5* for a more detailed discussion of task differences). Eimer and Holmes (2007) proposed that early midline positive ERP effects reflect higher order processing that is task dependent and relevant for the adaptive intentional control of behavior. As noted above, in the AA-task used in *Chapters 2* and *4*, evaluation of the emotional valence of the stimuli was explicit and relevant for goal-directed social motivational behavior. In contrast, in the emotional Stroop task in *Chapter 5*, the emotional valence of the stimuli was task-irrelevant and required inhibition, as the task goal was to quickly identify the stimulus color. Considering the above, the findings that cortisol administration facilitated processing of social threat stimuli during the execution of affect-congruent avoidance responses (*Chapters 2* and *4*), whereas it decreased processing of these stimuli when they interfered with the task goal (*Chapter 5*, see also Putman et al., 2007b; Oei et al., 2009), suggest that cortisol administration affects processing of motivationally significant threat stimuli in a goal-relevant and adaptive manner. This is consistent with the notion that glucocorticoid effects on cognition are generally adaptive, and facilitate behavior that is most relevant to the situation (De Kloet et al., 1999). In the next section, I will further discuss these findings in light of the view that the effects of cortisol on cognitive-emotional processing are context-dependent.

Context-dependency of cortisol effects

The results of the studies in this thesis in which we investigated the neural

processes associated with threat processing and avoidance behavior (*Chapters 2*, *4*, and *5*) demonstrated particularly robust effects of cortisol on early positive midline ERP components, which have been associated with "motivated attention", or facilitated processing of motivationally significant stimuli, possibly due to re-entrant projections from the amygdala to cortical regions (Amaral et al., 2003; Anderson & Phelps, 2001; Vuilleumier et al., 2004, see also *Chapter 1*). Furthermore, these results indicated that the effects of cortisol on this process are most pronounced for motivationally significant information (social threat cues), are stronger in individuals for which this information is highly relevant to their personal concerns (high trait avoidant or socially anxious participants), and depend on the relevance of the stimuli to the task goal. Together, these findings suggest that the effects of cortisol on cognitive-emotional processing are context-dependent, i.e., the strength and the direction of the effects depend on factors such as the processing stage, motivational significance and personal relevance of the stimuli, and task goal. This notion that effects of cortisol on cognitive-emotional processing are context-dependent is not new, and has been widely studied in the field of memory research. These studies have shown that the strength and direction of the effects of cortisol on memory processes (i.e., enhancement or impairment) depend, among other things, on factors such as the processing stage (encoding, consolidation, retrieval or reconsolidation), the emotional value (emotionally arousing versus neutral) and task-relevance (related or unrelated to the source of stress/emotional arousal) of the to-be-remembered material (see e.g., Lupien et al., 2007 for an extensive review). Furthermore, based on extensive animal research, De Kloet et al. (1999) proposed that corticosteroid effects on cognition are mediated by mineralocorticoid and glucocorticoid receptors in the brain, and depend on the relative activation of these receptors in the various stages of information processing. They further emphasized that the context in which this corticosteroid-receptor activation takes place is crucial, and that in general the effects of corticosteroids influence information-processing such as to increase adaptive behavior that is most relevant to the situation. The results of the studies in this thesis are generally consistent with this notion, but are the first to show such context-dependent effects of cortisol on early attentional processing of threat as measured by ERPs.

Strengths, limitations, and suggestions for future research

Strengths

First, we used a computerized RT paradigm to measure approach and avoidance responses in reaction to social stimuli, which ensured a direct and objective measure of behavior, and also makes it possible to measure brain activity during task performance. The studies presented in this thesis are the first using this paradigm for the investigation of approach and avoidance tendencies in a selected sample of patients with clinical SAD.

Second, we used ERPs to investigate the neural processes underlying threat processing and avoidance. ERPs are a highly sensitive measure of temporal dynamics of neural processing, and especially suitable for the study of very early attentional processes, which are much harder to measure with purely behavioral paradigms (see also Bar-Haim et al., 2005; Thomas et al., 2007).

Third, effects of cortisol on threat processing and behavior were investigated not only through experimental manipulation of endogenous cortisol levels (with a psychosocial stress task, *Chapter 3*) but also through acute administration of exogenous cortisol (*Chapters 2* and *4*). Exogenous administration was used in order to investigate the causal role of cortisol, because many factors interact with endogenous cortisol levels during stress-induction (e.g., arousal, social stress context, and individual differences).

Finally, in the studies presented in this thesis, we investigated threat processing and social avoidance behavior in high and low trait avoidant healthy students as well as in patients with a clinical diagnosis of social anxiety disorder. Studies in such pre-selected student samples can provide a valuable contribution to the understanding of basic processes implicated in anxiety disorders, but subsequent studies in clinical populations are necessary to draw conclusions about the generalizability of the findings and the clinical significance of these processes. Furthermore, we carefully selected participants based on strict criteria. In the studies in *Chapters 4* and *5*, patients using psychotropic medication were excluded, because this can significantly affect brain activity. We also excluded patients suffering from a concurrent major depression, as previous studies have shown that the attentional bias for threat in these patients may be moderated by the presence of a comorbid depression (Musa et al., 2003). A disadvantage of such strict selection criteria is that the patients in these studies may comprise an atypical representation of social anxiety patients in the general population, which

restricts the generalizability of the present findings. In *Chapter 3* patients with medication or depression were not excluded, but we controlled for these effects in the analyses.

Limitations

The studies presented in this thesis have several limitations, which are discussed in detail in the respective chapters. Here, I would like to focus on the limitations that are most important to the studies in this thesis in general.

The most important limitation is that we did not use a healthy control group for the clinical sample in the studies in *Chapters 4* and *5*. Although this does not limit the interpretation of the findings in these studies, a matched control group would have offered more information regarding the specificity of the effects of cortisol on threat processing for social anxiety. The within-subject design that was used for cortisol administration in these studies did allow us to control for individual differences in symptom severity, which proved to be an important moderating factor with regard to the effects of cortisol on threat processing. The effects of cortisol were stronger in patients with higher levels of social anxiety in these studies, which does point at an increased sensitivity in high anxious patients. This is consistent with other studies (*Chapters 2* and *3*; see also Putman et al., 2007b), but future studies including a matched control group are necessary to draw definite conclusions about such increased sensitivity to cortisol in patients.

Second, although the results of the studies in this thesis together suggest that the effects of cortisol on early threat processing are context-dependent, we did not investigate all aspects of this context-dependency in a controlled manner. We did control factors such as personal relevance and motivational significance of the stimuli, but studies in which factors such as goal-relevance are systematically manipulated are necessary to further investigate this issue.

Third, the external validity of the approach avoidance task for social behavior in real-life situations is thus far only supported by relations with self-report measures. However, using a highly similar paradigm, approach and avoidance tendencies towards spiders in spider phobic individuals have been shown to be reliably related to performance in a behavioral assessment test (BAT), in which participants were asked to approach a large living spider (Rinck & Becker, 2007). This provides general support for

the external validity of this paradigm in phobic individuals, but more research is needed to directly test associations of the social version of this task with real-life social avoidance.

Finally, in some studies (*Chapters 3* and *5*) we did not find an effect of cortisol on behavioral results, although we did find effects on ERPs. Future studies in which vigilance or avoidance of threat can be demonstrated using RTs would be helpful as a confirmatory measure to strengthen conclusions regarding ERP effects (e.g., Holmes et al., 2009), and to further investigate how increased early threat processing is associated with subsequent processing and behavior.

Suggestions for future research

In addition to the suggestions for future research mentioned above, I would like to outline a number of areas of specific interest for the study of cortisol effects on threat processing and avoidance.

First, studies using neuroimaging techniques such as fMRI should further investigate the brain areas that play a crucial role in the regulation of social motivational behavior in SAD, and how activity in the social motivational brain network is modulated by cortisol.

Second, it would be interesting to investigate the effects of cortisol on other measures of avoidance behavior, such as eye movements (see e.g., Horley et al., 2003) or social interactions, to see whether our findings on the approach-avoidance task generalize to other situations.

Third, in contrast to exogenous administration of cortisol, manipulation of endogenous cortisol levels through social stress induction results is associated with a number of concurrent stress-responses, such as noradrenergic activation, which may interact with the effects of cortisol on prefrontal function, as suggested by the results of several recent studies (e.g., Roozendaal et al., 2004; Elzinga & Roelofs, 2005). Future studies in which the effects of endogenous cortisol are attenuated, for example with the use of selective steroid receptor antagonists (e.g., metyrapone), may help to further assess the causal role of endogenous cortisol and the interplay with contextual effects in social avoidance behavior (De Kloet et al., 1999).

Fourth, future studies investigating the effects of cortisol on emotional or social motivational processing should systematically investigate the effects of context.

Finally, in contrast to most previous studies investigating the effects of cortisol on cognitive-emotional processing (which have mostly focused on memory processes, see e.g., Lupien et al., 2007, for a review), our results showed effects of cortisol administration on very early attentional processing of negative emotional stimuli. It would be valuable to link these two areas of research and to implement measurement of ERPs in memory studies, to investigate whether the effects of cortisol on memory are possibly related to modulation of early processing of emotional information.

Clinical implications

First, it is important to note that the approach of this study was fundamental: We aimed to gain more insight in basic processes underlying fear and avoidance in social anxiety. As a result, our findings cannot be readily used for the treatment of this disorder. Nevertheless, some of our findings do have implications for clinical practice. For example, the demonstrated link between high stress-induced cortisol levels and increased social avoidance behavior in patients with SAD (*Chapter 3*) suggests that in order to achieve optimal benefits, i.e., to decrease avoidance and promote threat approach behavior, the level of stress during exposure therapy should be kept to a limit. In addition, individual glucocorticoid stress-sensitivity might be assessed to tailor and fine tune psychological and pharmacological interventions in patients with SAD.

Also the results of our cortisol administration studies are relevant for clinical practice, as glucocorticoid administration has been proposed as a treatment for anxiety disorders (SAD and PTSD; see e.g., De Quervain, 2008; Soravia et al., 2006). This practice is based on findings showing that pre-treatment with cortisol decreases subjective anxiety during exposure to social stress, which is suggested to be mediated by glucocorticoid inhibition of fear memory (Soravia et al., 2006). Although our results do not necessarily contradict these findings, they do show additional effects of cortisol on very early attention to threat, and suggest that the direction of these effects are sensitive to the task context (*Chapters 4* and *5*), and perhaps also the conditions under which cortisol is administered (e.g., with or without concurrent social stress, see *Chapter 4* for a more extensive discussion). This context-sensitivity, along with the finding that cortisol increased early threat processing during avoidance in high anxious individuals, also argues against a general anxiolytic (fear-reducing) effect of cortisol that as has been

proposed by some researchers (e.g., Putman et al., 2007b). Thus, we propose that more research is warranted to investigate the effects of cortisol administration on processes other than memory (and subjective anxiety), and that attention should be paid to task-factors and the situation in which cortisol is administered.

Finally, it is worthwhile to investigate whether avoidance tendencies can be trained away. The results of several recent studies (e.g., Amir, Weber, Beard, Bomyea, & Taylor, 2008; MacLeod, Rutherford, Campbell, Ebsworthy, & Holker, 2002; See, Macleod, & Bridle, 2009) suggest that individuals can be trained to direct their attention away from threatening stimuli in computer tasks, and that this training reduces trait anxiety scores and anxiety responses to a subsequent environmental stressor. These findings provide support for the notion that such attentional biases play a causal role in the etiology and maintenance of anxiety. It is an interesting question to investigate whether the same is true for behavioral avoidance tendencies.

To conclude

The aim of this thesis was to gain more insight in the psychobiological mechanisms underlying social fear and avoidance behavior in humans. Our findings provide support for the important role of early threat processing and avoidance behavior in social anxiety. The findings further confirmed our prediction that cortisol plays an important role in the regulation of social avoidance behavior. This prediction was largely based on animal research, and the studies presented in this thesis are among the first to provide evidence supporting such a role of cortisol in humans. Furthermore, the results of our studies suggest that the effects of cortisol on early threat processing (and avoidance) are influenced by factors related to the motivational context, such as motivational significance and personal relevance of the stimulus material, and the task-goal.

More research investigating the effects of cortisol on early attentional processes is warranted, to study how these are related to subsequent cognitive processes, behavioral responses and subjective anxiety, and to systematically investigate the context-dependency of these effects.