To approach or to avoid : neurobiological mechanisms in social anxiety

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Chapter 1

General Introduction

Extensive animal research suggests that the Hypothalamus-Pituitary-Adrenal (HPA) system and the associated release of glucocorticoids (cortisol in humans) play an important role in the regulation of social motivational behavior. For example, in nonhuman primates elevated cortisol levels have been related to increased social submissiveness, fearful temperament and avoidance behavior in social situations (Kalin, Larson, Shelton, & Davidson, 1998; Sapolsky, 1990). Also in humans, the relation between HPA-function and withdrawal behaviors, particularly behavioral inhibition, has received a great deal of attention in the developmental literature (e.g., Kagan, Reznick, & Snidman, 1987; Schmidt et al., 1997; Spangler & Schieche, 1998). Such a relationship between HPA-function and social behavior is of particular relevance to patients with social anxiety disorder (SAD), which is characterized by extreme fear and avoidance of social situations, and for which childhood inhibition has been identified as a risk factor (for reviews see e.g., Hirshfeld-Becker, Micco, Simoes, & Henin, 2008; Rubin, Coplan, & Bowker, 2009). However, thus far little is known about the causal role of cortisol in the regulation of human social fear and avoidance behavior. The aim of this thesis is to gain more insight in the psychobiological mechanisms underlying social fear and avoidance behavior in humans, in particular socially anxious individuals, and the role of cortisol in the regulation of these processes.

In this introduction, I will start with a description of the main characteristics of social anxiety, and current knowledge about the role of information processing biases in this disorder. The next paragraph explains how these processes may be linked to behavior, including a discussion of the brain mechanisms involved in the regulation of motivational behavior and the role of individual differences. The second main part of this introduction focuses on the role of cortisol in the regulation of social motivational behavior. The introduction ends with an overview of the main predictions, the overall experimental approach, and an outline of the studies described in each of the remaining chapters of this thesis.

Fear and avoidance in social anxiety

Social anxiety disorder (SAD) is the most common anxiety disorder, with lifetime prevalence rates ranging from 7 to 13% in Western countries (see Furmark, 2002, for a recent review). SAD is characterized by extreme fear and avoidance of social situations (American Psychiatric Association [APA], 1994). Central to this disorder is the fear of behaving embarrassingly and being evaluated negatively by others. Cognitive behavioral models of social anxiety emphasize the role of information processing biases and avoidance or safety behaviors in the etiology and maintenance of this disorder. Two influential models (Clark & Wells, 1995; Rapee & Heimberg, 1997) both emphasize increased attention to threat as a critical factor in the maintenance of social fear. According to these models, socially anxious individuals are characterized by strong self-focused attention towards internal threat cues, such as dysfunctional assumptions about social evaluation and symptoms of physiological arousal (see Clark & Wells, 1995). In addition, Rapee and Heimberg (1997) suggested they show heightened vigilance to *environmental* cues related to potential negative evaluation, i.e., social threat.

Such preferential processing of external threat has been investigated in a wide range of cognitive-experimental studies, mainly through measurement of reaction times in response to threatening versus neutral stimuli in emotional Stroop, dot probe, or emotional spatial cueing tasks (see e.g., Bar-Haim, Lamy, Pergamin, Bakermans-Kranenburg, & Van IJzendoorn, 2007; Mobini & Grant, 2007, for recent reviews). The most widely used social threat stimuli in these tasks have been words (e.g., 'criticize') or pictures of human faces (e.g., angry compared to neutral or happy expressions). Results of these studies reliably demonstrated the existence of a threat-related attentional bias, in both clinical samples and individuals with high self-reported levels of social anxiety (see Bar-Haim et al., 2007). In addition, functional neuroimaging studies have shown hyperactive amygdala responses to threatening faces in patients with SAD (Phan, Fitzgerald, Nathan, & Tancer, 2006; Stein, Goldin, Sareen, Zorrilla, & Brown, 2002; Straube, Kolassa, Glauer, Mentzel, & Miltner, 2004). Thus, it seems that social anxiety is characterized by a hyperresponsive alert system, with an attentional bias towards socially threatening stimuli. In addition, some behavioral studies have provided evidence suggesting that this initial vigilance is followed by an avoidance of threat cues

in later, more strategic processing stages (e.g., Amir, Foa, & Coles, 1998; Mogg, Philippot, & Bradley, 2004; see also Mogg, Bradley, DeBono, & Painter, 1997).

But what about behavior? In addition to fear and sensitivity to social threat, a second main characteristic of SAD is avoidance of social situations. Because such avoidance behavior reduces the opportunity to habituate to or reappraise a feared situation, or to learn to cope with the anxiety, it is considered to be a major maintaining factor of anxiety symptoms in the long-term (e.g., Clark & Wells, 1995). In contrast to attentional processes, however, avoidance behavior has not been a major focus of experimental research. The present thesis aims to start filling in this gap, with a main focus on overt social avoidance behavior.

Motivational systems regulating approach and avoidance behavior

Many authors have emphasized a close relationship between affective evaluations and action tendencies (e.g., Chen & Bargh, 1999; Frijda, Kuipers, & Ter Schure, 1989; Lang, Bradley, & Cuthbert, 1990, 1992). According to these views, positive and negative emotions and evaluations are strongly linked to approach and avoidance behavior, respectively, and this association is mediated by distinct appetitive and aversive motivational systems in the brain. For example, Gray (e.g., 1987; Gray & McNaughton, 2000) proposed a behavioral activation system (BAS) which responds to incentives, regulates movements towards goals, and is associated with the experience of positive affect. On the other hand, a behavioral inhibition system (BIS)[1] responds to threat, resulting in the inhibition of behavior (or avoidance) and is associated with the experience of negative affect (see e.g., Carver, Sutton, & Scheier, 2000, for an overview of similar theories).

Importantly, it has been suggested that individuals differ in the relative sensitivity or activation of these motivational systems, resulting in a predisposition to engage in either approach or avoidance behavior, and a proneness to react to reward or threat, and to experience positive or negative affect. To assess these individual differences, Carver and White (1994) created self-report scales (the BIS-BAS scales),

[1] Note that in a recent revision of this theory (Gray & McNaughton, 2000) the regulation of responses to aversive stimuli is now ascribed to the Fight-Flight-and Freezing system instead of the BIS, whereas the BIS is a conflict detection and resolution device that inhibits ongoing behavior (see also Smillie Pickering, & Jackson, 2006).

which have been widely used in experimental research. Extreme activation or de-activation of either of these systems has also been related to vulnerability for psychopathology. For example, hypo-activation in the approach system has been associated with depression (see e.g., Davidson, 1998), whereas hyperactivity of the behavioral inhibition system has been associated with anxiety (e.g., Gray & McNaughton, 2000). In this thesis, I will investigate avoidance behavior in both healthy individuals with high versus low self-reported levels of behavioral inhibition (BIS) and patients with SAD.

Brain mechanisms underlying emotion processing and motivational behavior

The processing of emotional stimuli and the regulation of the associated approach and avoidance responses involves a complex circuitry involving various cortical and subcortical brain regions. A first important structure in this network is the amygdala (for a review see e.g., Phelps, 2006) which receives input about the emotional significance of a stimulus quickly and prior to awareness (e.g., Morris, Öhman, & Dolan, 1998; Whalen et al., 1998). It has been suggested that projections from the amygdala to sensory cortical regions (Amaral, Behniea, & Kelly, 2003; Anderson & Phelps, 2001; Vuilleumier, Richardson, Armony, Driver, & Dolan, 2004) are able to facilitate further attentional and perceptual processes, resulting in increased cortical attention and vigilance in situations of danger (e.g., Whalen, 1998). Furthermore, direct and indirect output connections from the amygdala activate motivational systems, which enable goal-directed approach and avoidance reactions to emotional stimuli. The prefrontal cortex (PFC), in particular the anterior cingulate (ACC) and orbitofrontal (OFC) regions, plays an important role in these motivational systems (see e.g., Blair & Cipolotti, 2000; Hornak et al., 2003; Kringelbach & Rolls, 2003; LeDoux, 2002; Roelofs, Minelli, Mars, Van Peer, & Toni, 2009; Rolls, 2000). Davidson and colleagues (see e.g., Davidson, 2004) proposed that specialized neural substrates for behavioral approach and withdrawal systems are lateralized in the left and right prefrontal cortex, respectively. Support for this notion comes from EEG studies showing a relation between baseline measures of prefrontal activation asymmetry and individual differences in dispositional mood, affective reactivity, and temperament. In these studies, relative left-sided prefrontal activation has been associated with more positive affect, increased reactivity to positive stimuli, and relatively higher levels of self-reported behavioral activation (BAS),

whereas more relative right frontal activation has been related to more negative affect, increased reactivity to negative stimuli, and relatively higher levels of behavioral inhibition (BIS) (see e.g., Davidson, 1998; Sutton & Davidson, 1997; Tomarken, Davidson, Wheeler, & Doss, 1992; Wheeler, Davidson, & Tomarken,1993) .

Interestingly, in primates many of the areas involved in this emotional-motivational network are highly sensitive to emotional facial stimuli, which underscores the important role of these networks in social interaction (see e.g., Rolls, 2000). Functional neuroimaging studies in humans have shown that viewing angry or fearful faces activates the ACC, OFC, and amygdala in particular (for an overview see Adolphs, 2002; McClure et al., 2004; Strauss et al., 2005). Furthermore, several of these areas have been shown to be hyperresponsive to threatening emotional expressions in socially anxious individuals compared to healthy controls (e.g., Phan et al., 2006; Stein et al., 2002; Straube et al., 2004). In addition, increased subcortical and decreased cortical activity have been found in SAD during (anticipation of) public speech (Lorberbaum et al., 2004; Tillfors et al., 2001), which is consistent with the notion that one function of the PFC is to modulate or inhibit amygdala activity (for a review see e.g., Phelps, 2006), and suggests a failure in prefrontal inhibition of amygdala driven fear responses in SAD.

In the next section, I will describe how the stress hormone cortisol may affect this network and, consequently the processing and regulation of emotions and motivational behavior.

Hormones and behavior: role of the HPA-axis and cortisol

Role of the HPA-axis in response to stress

The HPA-axis consists of the hypothalamus, the pituitary gland, and the adrenal gland. Together with the sympathetic nervous system, this system plays a primary role in the stress-response (see e.g., De Kloet, Joëls, & Holsboer, 2005; Sapolsky, Romero, & Munck, 2000, for reviews). In reaction to the perception of a stressor, the hypothalamus releases cortisol-releasing factor (CRF), which triggers the release of ACTH in the pituitary. This, in turn, causes adrenal secretion of glucocorticoids (GC, cortisol in humans). Finally, negative feedback mechanisms cause elevated GC concentrations to inhibit subsequent HPA activity, to prevent the stress-response from overshooting. GC are important for the regulation of adaptive stress responses. For example, they increase

activity of the sympathetic nervous system and enhance the mobilization of energy sources that are needed for action (e.g., fight or flight). In contrast, they inhibit parasympathetic functions that are unnecessary in the context of immediate threat, such as growth, reproduction, and inflammation. In addition to these actions during acute stress, both basal and stress-induced GC serve preparative functions to prime the defense mechanisms for responses to future stressors (Sapolsky et al., 2000).

Glucocorticoids can easily cross the blood–brain barrier (e.g., Herbert et al., 2006) and access the brain where they bind to receptors. There are two types of GC receptors in the brain: mineralocorticoid receptors (MR) and glucocorticoid receptors (GR) (e.g., De Kloet, 1991; De Kloet, Oitzl, & Joëls, 1999). GCs have higher affinity (i.e., bind more readily) to MRs than to GRs, resulting in a predominant occupation of MRs when GC levels are in basal ranges, whereas GRs are occupied only at the peak of the circadian cycle or when cortisol levels are elevated due to stress (e.g., De Kloet et al., 1999) or exogenous administration of cortisol. These receptors are also differentially distributed in the brain. The MR receptor is exclusively present in the limbic system, whereas the GR receptor is present in both subcortical and cortical structures, with a preferential distribution in the prefrontal cortex. GC effects on cognitive function are mediated by the relative activation of MR and GR receptors (De Kloet, 1991; De Kloet et al., 1999; Lupien, Maheu, Tu, Fiocco, & Schramek, 2007).

Cortisol and social motivation

Animal studies suggest that GC play an important role in the regulation of social motivational behavior. For example, studies in nonhuman primates have shown that elevated GC levels are related to the manifestation of increased submissiveness and avoidance behavior in social situations (Sapolsky, 1990). There are also some indications that patients with SAD have increased cortisol stress responses (Condren, O'Neill, Ryan, Barrett, & Thakore, 2002; Furlan, DeMartinis, Schweizer, Rickels, & Lucki, 2001), although this was not confirmed in other studies (Levin et al., 1993; Martel et al., 1999). In addition, relatively increased right PFC activity, which is related to fearful temperament and behavioral inhibition, has been associated with higher cortisol levels in rhesus monkeys (Kalin et al., 1998a; Kalin, Shelton, & Davidson, 2000) and human infants (Buss et al., 2003). The PFC is an important target structure for GC (e.g., Meaney & Aitken, 1985; Radley et al., 2004), and exogenously administered cortisol has been

shown to affect prefrontal functions such as working memory in humans (for reviews see Wolf, 2003; Lupien et al., 2007). Together, the relation between HPA-axis function and social behavior on the one hand, and the effects of cortisol on prefrontal brain areas involved in the regulation of social behavior on the other hand, give rise to the hypothesis that cortisol plays an important role in the prefrontal regulation of social fear behavior.

To summarize, cortisol and avoidance behavior may play an important role in social anxiety. However, experimental studies in social anxiety have predominantly focused on emotion processing and attention, and studies investigating avoidance behavior are largely lacking. Furthermore, little is known about the effects of cortisol on prefrontal regulation of avoidance behavior in humans, or even about effects of cortisol on cognitive and emotional processes other than memory (see Lupien et al., 2007, for a review), such as attentional processing of threat. Two recent studies using an emotional Stroop task indicated that increased basal cortisol levels (e.g., Van Honk et al., 1998), and high cortisol levels due to cortisol administration (Putman, Hermans, Koppeschaar, Van Schijndel, & Van Honk, 2007) were associated with relative attentional avoidance of threat. However, the effect of cortisol on *overt* avoidance *behavior* in humans remains unexplored. It is relevant to gain more insight in these mechanisms, not only to increase our understanding of the role of HPA-axis dysfunctions in the etiology and maintenance of social anxiety, but also because the administration of cortisol has recently been proposed as a treatment for SAD (Soravia et al., 2006).

Outline of this thesis

Main aim, predictions and general methodology

The aim of this thesis is twofold: First, I want to gain more insight in the brain processes underlying threat processing and avoidance behavior, especially in high socially anxious individuals. Second, I will investigate how these processes are affected by cortisol. The following hypotheses will be tested:

1. Threatening stimuli, in particular angry faces, receive preferential processing by high socially anxious individuals, and such vigilance occurs in early processing stages.
2. Individuals characterized by high levels of behavioral inhibition or social anxiety show stronger avoidance tendencies in reaction to social threat.
3. Threat processing and avoidance are facilitated by high levels of endogenous or exogenous cortisol.

Overall, these predictions will be investigated using the following methods:

First, a computerized reaction time (RT) paradigm is applied to measure approach and avoidance responses in reaction to social stimuli. In this task (the approach-avoidance (AA)-task, e.g., Rotteveel & Phaf, 2004), participants evaluate the emotional expression of photographs of happy and angry faces by making an approaching (flexion) or avoiding (extension) arm movement. The AA-task consists of an affect-congruent condition, involving approach movements to happy faces and avoidance movements to angry faces and an affect-incongruent condition in which the instruction is reversed. Typically, reaction times are faster in the affect-congruent than the affect-incongruent condition, reflecting the general tendency of participants to approach pleasant and avoid unpleasant stimuli (see e.g., Chen & Bargh, 1999; Rinck & Becker, 2007; Roelofs, Elzinga, & Rotteveel, 2005; Rotteveel & Phaf, 2004; Solarz, 1960). Although such a computer task constitutes an artificial and highly simplified environment compared to 'real-life' social interactions, it ensures a direct and objective measure of behavior, and also makes it possible to measure brain activity during task performance.

Second, brain activity (in the form of event-related potentials) is recorded from the scalp during task performance to get more insight in the neural processes associated

with threat processing and avoidance behavior. Event-related potentials (ERPs) provide a continuous and high temporal resolution measure of both the speed (latency) and intensity (amplitude) of cerebral processing and are therefore very suitable for a refined investigation of biases in different information processing stages. Resting state EEG is also measured, to investigate individual differences in (and cortisol effects on) baseline motivational brain states.

Third, effects of cortisol on threat processing and behavior are investigated through experimental manipulation of endogenous cortisol levels (with a psychosocial stress task) as well as through acute administration of exogenous cortisol. Because many factors interact with endogenous cortisol levels during stress-induction (e.g., arousal, social stress context, and individual differences), the emphasis in this thesis lays on exogenous administration in order to investigate the causal role of cortisol.

Finally, I investigated these processes not only in healthy participants characterized by high versus low levels of trait avoidance/inhibition, but also in two samples of patients with a clinical diagnosis of SAD. Student samples with high self-reported, but non-clinical, levels of social or trait anxiety are widely used in anxiety research, and can provide a valuable contribution to the understanding of basic processes implicated in anxiety disorders. Nevertheless, studies in clinical populations are necessary to draw conclusions about the generalizability of these findings as well as the clinical significance of these processes.

Overview of chapters

Chapter 2 describes a first study testing the predictions that a) individuals characterized by high levels of behavioral inhibition show preferential processing of and stronger avoidance tendencies towards social threat cues, and b) that these processes are facilitated by cortisol. This is investigated by measuring the effects of cortisol administration on the AA- task in a sample of pre-selected high and low behaviorally inhibited/anxious students, using a placebo-controlled within-subject design. Furthermore, event-related potentials (ERPs) are measured during task performance to gain more insight in the brain processes associated with threat processing and approach and avoidance reactions.

Chapter 3 investigates the effects endogenous cortisol increases on approach-avoidance behavior. Therefore, the Trier Social Stress Test (Kirschbaum, Pilke, &

Hellhammer, 1993) is administered to SAD patients, and performance on the AA-task in this psychosocial stress condition is 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 is investigated by directly relating the stress-induced cortisol responses to AA-task performance. A sample of matched healthy participants and a sample of patients with Post-Traumatic Stress Disorder (PTSD) are included as control groups to investigate the specificity of the effects.

Following the study in *Chapter 3*, the study in *Chapter 4* aims to get a better understanding of the *causal* role of cortisol, as well as of the neural processes involved in the regulation of social fear behavior in SAD. Furthermore, the same experimental procedure is used as in *Chapter 2*, to test whether the findings in high inhibited/anxious healthy participants generalize to a clinical population. Therefore, in this study the effects of cortisol administration on performance of the AA-task are measured in a second sample of patients with SAD, using a placebo controlled within-subject design, and with ERPs measured during task performance.

In *Chapter 5* the hypothesis is 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 investigate whether the effects of cortisol on threat processing are similar when the stimulus emotion is implicit (task-irrelevant), compared to when stimulus emotion is explicit and task relevant, as in the AA-task. In this study, the effect of cortisol administration on reaction times and ERPs is 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 is conducted in the same participant sample as *Chapter 4*.

In *Chapter 6*, a more theoretical-methodological issue is 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 (e.g., Neumann & Strack, 2000). In a series of four reaction time experiments, the effects of stimulus movements on the evaluation of happy and angry face stimuli are investigated in healthy male and female students. It is predicted that changes in relative distance due to stimulus

movement exert similar effects on affective evaluation as the approach and avoidance movements executed by the participant in the AA- task.

Chapter 7 describes the effects of cortisol administration and individual differences in trait avoidance/behavioral inhibition on resting state brain activity that has been associated with approach and avoidant motivational states.

Finally, *Chapter 8* presents an overview and integration of the findings of the *Chapters 2* to *7*, and a discussion of the strengths and limitations of these studies. The chapter concludes with suggestions for future research and implications for clinical practice.