1. Introduction

The aim of the presented research project was to combine knowledge on stress, stress hormones and their influence on the brain and further examine their possible beneficial effect in the clinical setting. The project consisted of the following two parts: first, we examined possible beneficial effects of cortisone administration in a standardized socio-evaluative stress situation in patients with social phobia. The second part comprised the clinical relevance of the anxiolytic effect of cortisone treatment, in comparing the clinical sample to a control sample to measure the extent of the beneficial effect.

Social phobia (also known as social anxiety disorder) is characterized by fear and avoidance of social situations in which scrutiny by others or embarrassment may occure (APA, 1994). Even the anticipation of such a situation can initiate fear reaction that is associated with physical (e.g. sweating, blushing), cognitive (e.g. “I’m not good enough”) and behavioral (e.g. avoiding eye contact, wearing black shirts, so that sweating is not visible) symptoms (Stangier & Fydrich, 2002a). When confronted with a fearful situation, the characteristic negative self-evaluative thoughts are associated with memories of past social failures, negative beliefs of how they will perform and the expectation of rejection by others (D. M. Clark & Wells, 1995; M. Clark & Ehlers, 2003; R. Rapee, Heimberg, RG, 1997; Ronald M. Rapee, McCallum, Melville, Ravenscroft, & Rodney, 1994). Instead of focus on external stimuli in such situation, social phobics mostly focus on themselves and shift their attention towards internal threat stimuli such as their own anxiety response, and this preoccupation interferes with their ability to process the situation and other people’s behavior (Bogels & Mansell, 2004b; D. M. Clark & Wells, 1995). There is evidence of poorer recall of information regarding the social interaction in social phobics compared to non-anxious controls (Daly, Vangelisti, & Lawrence, 1989; Hope, Heimberg, & Klien, 1990; Kimble & Zehr, 1982), but no differences are detected in the free recall of environmental

information (Mellings & Alden, 2000). Because information-processing biases have been systematically observed, a cognitive-behavioral treatment of social phobia which attempt to correct information-processing biases is the method of choice.

Previous work indicates that an acute elevation of glucocorticoid levels impairs retrieval of hippocampal dependent, episodic memory and autobiographical memory, a subcategory of the episodic memory (Buss, Wolf, Witt, & Hellhammer, 2004; D.J.-F. De Quervain, Roozendaal, Nitsch, McGaugh, & Hock, 2000; Wolf, 2003). A recent imaging study in healthy humans (D.J.-F. De Quervain et al., 2003) and a study in rats with intra-hippocampal infusions of glucocorticoid receptor agonist (Roozendaal, Griffith, Buranday, de Quervain, & McGaugh, 2003) demonstrate that the medial temporal lobe is involved in mediating these effects of glucocorticoid on memory retrieval. Therefore, a clinical study examined whether the administration of cortisone could also have beneficial effects in the way that high levels of cortisol may reduce fearful or traumatic episodic memories (Aerni et al., 2004). The results demonstrate that low-dose cortisone treatment (10 mg/day) over a time period of a month reduced cardinal symptoms of post-traumatic stress disorder, such as reliving the trauma.

The current project focused on the experienced anxiety of patients with social phobia when confronted with a phobic stimulus. 21 male patients who fulfilled the criteria for social phobia and 22 healthy control subjects participated in the Trier Social Stress Test (TSST), a standardized socio-evaluative stress test consisting of an unprepared interview for a job and a mental arithmetic task in front of an audience. Half of the subjects received 25 mg cortisone orally one hour before the stress test. During the 3 hours of the test procedure several physiological and psychological parameters were measured. To examine the physiological stress response, salivary cortisol was collected 5 times during the course of the study and heart rate was monitored continuously. General well-being, attention processes and different dimensions of anxiety, such as

physical discomfort, avoidance and state anxiety were repeatedly measured. To exclude possible interruptions of the stress reaction, only medication free man who smoked less than 15 cigarettes were included in the study.

The results revealed that 25 mg cortisone before the confrontation with a phobic stimulus reduced cardinal symptoms of social phobia, such as anxiety, physical discomfort and avoidance in patients suffering from social phobia. Even the heart rate did not arise significantly in the cortisone treated group when confronted with a phobic stimulus, while the placebo group showed a significant acceleration.

Because the socio-evaluative stress test was not a fearful situation for healthy control subjects, the described anxiolytic (fear reducing) effect was not detected in the control sample. It is important to highlight that acute cortisone treatment in patients with social phobia reduces symptoms like anxiety, physical discomfort and avoidance behavior to an amount that the experience of these symptoms comes down to the range of normal non-anxious persons. For this reason the hypothesis of an inhibition of specific fearful memories through an exogenous elevated cortisol level was approved. Furthermore, cortisone administration increased later recall of room-related details of the stressful situation only in patients with social phobia. This cortisone effect presumably resulted from an enlarged focus of attention under reduced anxiety through the elevation of the cortisol levels rather than from a specific memory effect because recall of person-related details remained unaffected. The administration of 25 mg cortisone did not cause any side effects or change in existential orientation. Therefore, repeated administration of cortisone of this dose is safe and might have beneficial effects combined with behavioral confrontation therapy.

2. Theoretical Background

This chapter includes the basic constructs of the present work. They are structured in the specification of social phobia, the elucidation of stress and stress hormones as well as their modulation of cognitive functions.

2. 1. Social phobia and social anxiety disorders

The expression “social phobia” (phobie des situations socials) was introduced by Janet (1903) on the beginning of the 20th century. He described patients who feared being observed while speaking, playing the piano, or writing. Looking back in history, syndromes of shyness, social anxiety, and social avoidance had been described as early as the time of Hippocrates (as quoted in (Marks, 1969), who reported this case: “through bashfulness, suspicion, and timorousness, will not been seen abroad; … He dare not come in company, for fear he should be misused, disgraced, overshoot himself in gestures of speeches…. He thinks every man observed him….” (p.362)

2.1.1. Diagnostic criteria, differential diagnostic and comorbidity

The Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) (Association, 1994) defines social phobia as ‘a marked and persistent fear of one or more social performance situations in which the person is exposed to unfamiliar people or to possible scrutiny by others. The individual fears that he or she will act in a way (or show anxiety symptoms) that will be humiliating or embarrassing’. The fear must be seen as excessive or unreasonable by the patient, lead to avoidance of feared situations or cause anticipatory anxiety, and significantly interfere with the patient’s social or occupational life. The fear

or avoidance must not be the direct effect of any substance or general medical condition. Further persons with social phobia experience excessive fear of being humiliated or judged negatively in social or performance situations by others.

Social phobia is characterized by the presence of physical, cognitive, and behavioral symptoms. The physical symptoms reported by many persons with social phobia include, shaking, sweating, blushing, palpitations, nausea, and diarrhoea (Brunello et al., 2000; Stangier & Fydrich, 2002a). Studies using physiologic measures show that these patients react with increased arousal on exposure to their feared stimuli including increased heart rate and blood pressure and decreased habituation of skin conductance responses (Beidel, Turner, & Dancu, 1985; Turner, 1986). As a consequence of the fear and the physical reactions, activities such as eating, drinking, writing or speaking in public, expressing opinions in a group, and talking to members of the opposite sex or to an authority figure or stranger may actively be avoided to evade the perceived negative evaluation of others (Neal et al., 2001).

The reticence that is characteristic of social phobia inhibits many patients from volunteering relevant information (e.g. go to a physician, teacher, etc). In addition, some patients, who have built their lives around avoiding their feared situations, may also have trouble recognising and reporting areas of functioning in which they are impaired. In other words, some patients see their functional limitations as ‘just the way I am’. For these reasons, it is important to be systematic and comprehensive in evaluating social phobia symptoms and the extent of related impairment. Because of the broad spectrum of disability related to social phobia, many experts feel today that it would be preferable to refer social phobia with the DSM-IV synonym, ‘social anxiety disorder’ (Brunello et al., 2000; Michael R. Liebowitz, Heimberg, Fresco, Travers, & Stein, 2000).

2.1.1.1. Subtypes of Social Phobia

Another diagnostic distinction is made by subclassifying social phobia into generalized or non-generalized type. In generalized social phobia, which is the most debilitating, the patient fears most social interactions and situations (APA, 1994). However, the DSM does not explicitly define the number and type of social situations that comprise the generalized subtype. As a result, various research groups have developed slightly different operational definitions for generalized social phobia and the residual subgroup, which has made it difficult to directly compare empirical studies (Stefan G. Hofmann, Heinrichs, & Moscovitch, 2004). The non-generalized type of social phobia usually involves fears of public performance or speaking, when scrutiny is inevitable.

2.1.1.2. Social phobia as a Continuum of Social Anxiety

Because social phobia and avoidance personality disorder (APD) share several diagnostic as well as experiental characteristics, it's evident that epidemiological studies show high rates of comorbidity, especially between generalized social phobia and APD (Grant et al., 2004; K.R. Merikangas & Angst, 1995; F. R. Schneier, Johnson, Hornig, Liebowitz, & Weissman, 1992; Tillfors, Furmark, Ekselius, & Fredrikson, 2004). Therefore it has been suggested by many authors, that social phobia and APD rather lie on a continuum of social anxiety, than being categorized in two independent disorders (Marteinsdottir, Furmark, Tillfors, Fredrikson, & Ekselius, 2001; K.R. Merikangas & Angst, 1995; Ronald M. Rapee & Spence, 2004; Stein, Torgrud, & Walker, 2000; Tillfors et al., 2004). As shown in figure 1 the range of social anxiety starts with normal shyness, including individuals who do not meet the criteria for social phobia yet, and ends with avoidance personality disorder which appears to be the most severe version associated with the greater disability (APA, 1994; Brunello et al., 2000). Merikangas and coworkers (2002) introduced a quasi-dimensional approach to classify social phobia, with

increasing severity of symptoms, avoidance, distress and/or impairment suggesting that this would be a more valid approach to define the manifestation of social phobia. The spectrum classification reflects the tendency for those individuals with social phobia that oscillate between the full diagnostic criteria and the subthreshold and symptom levels over time.

Tillfors et al. (2004) studied persons with social phobia and or with avoidance personality disorder (APD) out of a general population. The results show that the presence of comorbid APD in social phobics seems to predict a global functioning decrement independent of anxiety severity, in the way that that social- and work impairment, self-reported distress, and comorbidity increased with the severity.

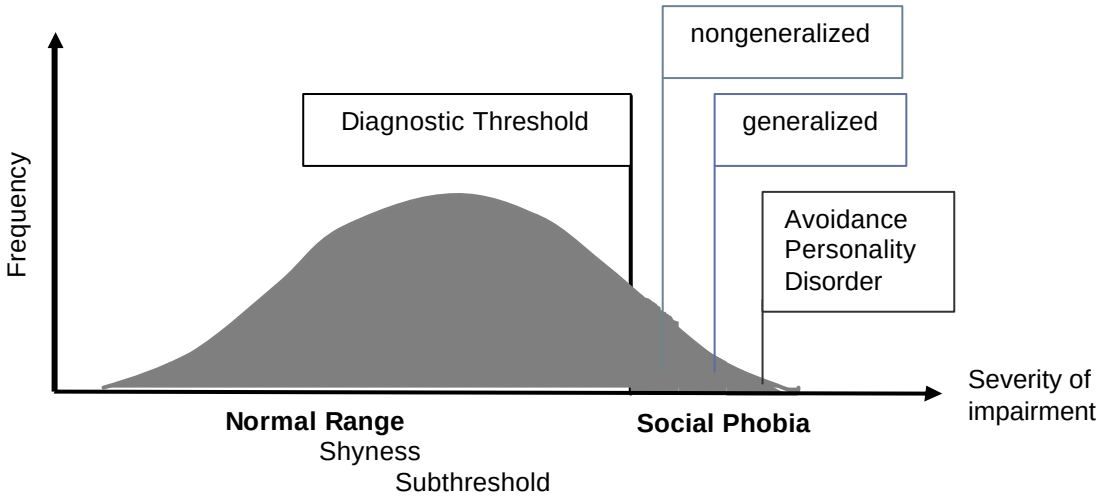

Figure 1: Continuity model of social anxiety (Stangier & Friedrich, 2000, pp.23)

2.1.1.3. Differential diagnostic

The most difficult differential diagnostic consideration in identifying patients with social phobia is the potential confusion with agoraphobia with and without panic attacks. This is due to the fact that agoraphobics can experience fear reactions in social situations and also avoid specific social situations (Brunello et al., 2000). However, agoraphobic patients avoid situations because they

fear having a panic attack or fear the loss of control in a crowd or social situation from which the patient may not easily escape. They may also fear social situation, which are difficult, embarrassing or impossible to exit. Compared to patients with panic attacks, social phobics don't have uncued spontaneous panic attacks, their anxiety is always coupled to social situations but sometimes takes the form of symptoms that resemble panic attacks (Brunello et al., 2000).

2.1.1.4. Comorbidity

Other mental disorders commonly occur together with social phobia. On average, 80% of patients with social phobia met diagnostic criteria for another lifetime condition, demonstrating that comorbidity tends to be the rule rather than the exception (K.R. Merikangas & Angst, 1995; F. R. Schneier et al., 1992). The relatively early onset of social phobia suggests that it could be an etiological factor, or at least a vulnerability marker of risk, for developing other disorders. It is well known that comorbidity of anxiety disorder and mood disorders is common, and social phobia is no exception. Given the high degree of impairment associated with social phobia, especially in the area of interpersonal relationships, it is not surprising that many patients with social phobia develop secondary depressive symptoms. Therefore studies show that persons with social phobia have a significantly increased risk of having other anxiety disorders, affective disorders as well as substance use disorders (den Boer, 2000; J. P. Lepine & Pelissolo, 1996), as shown in figure 2.

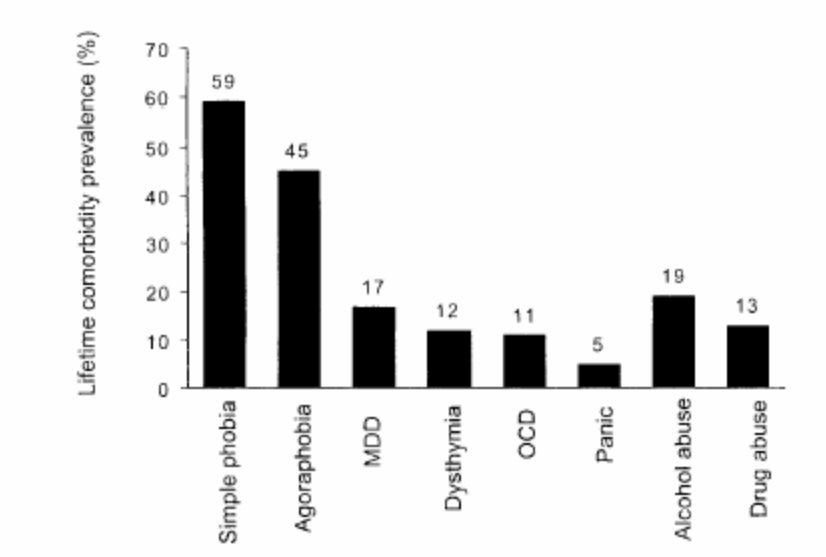

Figure 2: Lifetime comorbidity prevalence in social anxiety disorder. MDD, major depressive disorder; OCD, obsessive-compulsive disorder (den Boer, 2000)

The Epidemiological Catchment Area (ECA) study found that 69% of social phobic persons in the community had comorbid lifetime mental illness, and the onset of social phobia occurred first in 77% (F. R. Schneier et al., 1992). In the National Comorbidity Survey (NCS), 81% of the patients meeting criteria for social phobia also met criteria for another disorder (Magee, Eaton, Wittchen, McGonagle, & Kessler, 1996). Looking at the prevalence and association between current DSM-IV axis I and axis II disorders, the 2001-2002 National Epidemiologic Survey on alcohol and related conditions (NESARC) showed, that among individuals with a current mood or anxiety disorder, nearly half had at least one personality disorder (Grant et al., 2004). Avoidant (61.4%) and dependent (20.4%) personality disorder as well as obsessive-compulsive (46.8%), paranoid (44.9%) and schizoid (34.1%) personality disorder were strongly related to social phobia (Grant et al., 2004).