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Social Phobia

From Epidemiology to Brain Function

BY

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ABSTRACT

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Social phobia is a disabling anxiety disorder characterized by an excessive fear of negative evaluation in social situations. The present thesis explored the epidemiology and neurobiology of the disorder. By means of a mailed questionnaire, the point prevalence of social phobia in the Swedish general population was estimated at 15.6%. However, prevalence rates varied between 1.9 and 20.4% across the different levels of distress and impairment used to define cases. Thus, although social anxiety is widespread within the community, the precise diagnostic boundaries for social phobia are difficult to determine. Social phobia was associated with female gender, low educational attainment, psychoactive medication use, and lack of social support. A cluster analysis revealed that subtypes of social phobia mainly differed dimensionally on a mild-moderate-severe continuum, with number of cases declining with increasing severity. Public speaking was the most common social fear in all groups of social phobics and in the population at large.

In the neurobiological studies, positron emission tomography was used to examine brain serotonin metabolism and changes in the regional cerebral blood flow (rCBF) response to public speaking stress following treatment with a selective serotonin reuptake inhibitor (SSRI) or cognitive-behavioral group therapy. Social phobics exhibited lowered serotonin turnover, relative to non-phobics, mainly in the medial temporal cortex including the bilateral rhinal and periamygdaloid regions. Symptom improvement with cognitive-behavioral- as well as SSRI-treatment was accompanied by a reduced rCBF-response to public speaking in the amygdala, hippocampus and adjacent temporal cortex, i.e. regions that serve important functions in anxiety. Thorough suppression of rCBF in limbic brain regions was associated with favorable long-term treatment outcome. These results provide neuroimaging evidence for a presynaptic serotonergic dysfunction in social phobia and for a common neural mechanism whereby psychological and pharmacological anti-anxiety treatments act.

Key words: Anxiety, brain, epidemiology, fear, neuroimaging, neurotransmitters, positron emission tomography, prevalence, serotonin, social phobia, subtypes, treatment.

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'What came over you?' asked Falk. 'Had you taken leave of your senses?'
'Yes, I think I had. I had worked at my speech for almost six weeks and I knew exactly what I was going to say, but when I got up there and saw all those eyes, everything went to pieces. All my carefully constructed arguments broke down like scaffolding; I felt the ground under my feet give way and my thoughts whirled. Was it very crazy?'

- from August Strindberg's "The Red Room"
(Dent: London, 1879/1967, p. 224)

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ABBREVIATIONS USED IN TEXT

ANOVA	**Analysis of variance**
APA	**American Psychiatric Association**
APD	**Avoidant personality disorder**
BA	**Brodmann area**
^{11}C	**Carbon-11 (radio isotope)**
CBGT	**Cognitive-behavioral group therapy**
CCK-4	**Cholecystokinin tetrapeptide**
CIDI	**the Composite International Diagnostic Interview**
CRF	**Corticotropin-releasing factor**
df	**Degrees of freedom**
DIS	**the Diagnostic Interview Schedule**
DIP-Q	**the DSM-IV and ICD-10 Personality Disorder Questionnaire**
DSM-III	**the Diagnostic and Statistical Manual of Mental Disorders, 3rd edition**
DSM-III-R	**the Diagnostic and Statistical Manual of Mental Disorders, 3rd edition revised**
DSM-IV	**the Diagnostic and Statistical Manual of Mental Disorders, 4th edition**
ECA	**the Epidemiologic Catchment Area research program**
GAF	**Global assessment of functioning**
$H_2{}^{15}O$	**15-oxygen radiolabeled water**
5-HIAA	**5-hydroxyindoleacetic acid**
5-HT	**5-hydroxytryptamine (serotonin)**
5-HTP	**5-hydroxytryptophan**
ICD-10	**International Classification of Diseases and Related Health Problems, 10th ed.**
LSD	**Least significant difference**
MAOIs	**Monoamine oxidase inhibitors**
MBq	**mega Becquerel**
NCS	**the National Comorbidity Survey**
OCD	**Obsessive-compulsive disorder**
PAG	**Periaqueductal gray**
PCA	**Principal component analysis**
PRCS	**the "Personal Report of Confidence as a Speaker" (questionnaire)**
PET	**Positron emission tomography**
rCBF	**Regional cerebral blood flow**
ROI	**Region of interest**
SD	**Standard deviation**
SCID	**the Structural Clinical Interview for Psychiatric Disorders**
SSRI	**Selective serotonin reuptake inhibitor**
SIAS	**the "Social Interaction Anxiety Scale"**
STAI-S	**Spielberger's State Anxiety Inventory**
SPS	**the "Social Phobia Scale"**
SPSQ	**the "Social Phobia Screening Questionnaire"**
SVC	**Secondary visual cortex**
WL	**Waiting-list control group**

1. INTRODUCTION

1.1 About this thesis

Anxiety is an unwelcome, agonizing, and disabling companion in life for 27.4 million people each year in the USA (Greenberg et al., 1999). Anxiety is however not only a hindering barrier for the individual, but also a significant problem for society at large. In 1990, the annual societal cost of anxiety disorders in the US (e.g., in terms of psychiatric service use, mortality, lost productivity, or other workplace costs) was estimated at $42.3 billion, equivalent to $63.1 billion in 1998 dollars (Greenberg et al., 1999). Hence, it is difficult to overstate the importance of research aimed at better understanding of the symptoms, causes, treatment, and prevention of anxiety disorders.

This thesis is about social phobia, which is arguably the most common of all anxiety disorders (Jefferys, 1997), discerned by a profound fear of being observed or evaluated in various social settings. The thesis is based on four empirical studies with two major themes. The first theme deals with epidemiology, i.e. the commonness of social phobia and subtypes of the disorder. The second theme concerns brain functioning with emphasis given to neurotransmitter abnormalities and treatment effects on brain activity. The outline of the empirical studies is preceded by an introductory section, which describes the diagnosis and characterizing psychopathology of social phobia, its etiology and susceptibility to psychological and pharmacological treatments.

1.2. The diagnosis of social phobia

1.2.1 Definition

In the fourth edition of *the Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV) social phobia (also listed as social anxiety disorder) is defined as a "marked and persistent fear of one or more social or performance situations in which the person is exposed to unfamiliar people or possible scrutiny by others" (American Psychiatric Association [APA], 1994, p. 416; see Appendix A). Thus, the central feature of social phobia is an excessive fear of being observed or scrutinized by unfamiliar persons. In particular, the individual finds agonizing the potential risk of performing inadequately or showing overt signs of nervousness with resultant embarrassment or humiliation. The social fears may be limited to specific settings such as formal public appearances, or extend to a wider range of situations like social gatherings and casual conversations. When exposed to phobic situations, or in anticipation thereof, the individual typically reacts with anxiety symptoms such as palpitations, sweating, blushing, and catastrophic thinking. Symptoms arise even though the person realizes that the reactions are exaggerated and unreasonable. Consequently, the distressing situations are avoided or endured under intense anxiety. In social phobia, symptoms interfere considerably with the person's daily routines, social activities, relationships, occupational/academic functioning, or alternatively there is apparent distress about having the phobia. If the individual is under age 18, the DSM-IV criteria require a minimum duration of at least six months. Moreover, other medical conditions or mental disorders must not better account for the social anxiety symptoms. DSM-IV also specifies a generalized subtype of social phobia, which is the appropriate diagnosis when the fears extend to "most social situations".

The operational criteria for social phobia in the current 10th revision of *the International Classification of Diseases and Related Health Problems* (ICD-10; World Health Organization, 1993) have a few differences in comparison to DSM-IV. ICD-10 stipulates that the fear of scrutiny involves small groups of people, rather than crowds, and gives emphasis to specific stress-related physical symptoms such as blushing, hand tremor, nausea, and urgency of micturation.

1.2.2. Historical perspectives on the diagnosis

The term "phobia" has its origins in the Greek word φόβος meaning terror or fear. In ancient times the god Phobos was believed to call forth fear and terror in the enemies of the Greek (Davey, 1997). Large numbers of fears have been named by adding "phobia" to a Latin or Greek prefix. Some examples of relevance to social anxiety are *scopophobia* (fear of being observed), *xenophobia* (fear of strangers), and *antrophophobia* (fear of people). The early concept formation of social phobia has been described by several authors (e.g., Fahlén, 1995; Heckelman & Schneier, 1995; Schneier, Johnson, Hornig, Liebowitz, & Weissman, 1992). Literary descriptions of shyness and social anxiety can be traced back to Hippocrates 400 B.C. (Heckelman & Schneier, 1995), but the first explicit reference to social phobia, or "phobie des situations sociales", was made in the early 1900's by Janet (1903). In the 1930's, Schilder used the term "social neurosis" to describe extremely shy patients (Schilder, 1938, cited by Fahlén, 1995). In the 1950's, following Joseph Wolpe's pioneering work on systematic desensitization, the interest in behavioral therapy of phobias increased sharply. Working in this tradition, the British psychiatrist Isaac Marks proposed in the 1960's that social phobias could be thought of as a distinct category (Marks, 1969; Marks & Gelder, 1966). Gradually this idea gained recognition by the American Psychiatric Association, and in 1980 social phobia was officially included as a psychiatric diagnosis in the third edition of the Diagnostic and Statistical Manual of Mental Disorders - DSM-III (APA, 1980).

Closely resembling a specific (or simple) phobia, the DSM-III described social phobia as a circumscribed fear of performance situations, with activities such as speaking, eating, or urinating in front of others causing "significant distress". This overlooked individuals exhibiting excessive anxiety in numerous social settings, including informal conversations and interactional situations, although these individuals could be diagnosed as having avoidant personality disorder - a diagnosis on the axis II. Comorbidity between these two diagnoses was not allowed. The diagnostic criteria were revised in the DSM-III-R (APA, 1987). "Significant distress" was changed to "interference or marked distress", comorbidity between social phobia and avoidant personality disorder was now allowed, and the generalized subtype of social phobia was introduced. In comparison to this substantial revision, the diagnostic criteria were only slightly modified in going from DSM-III-R to the current fourth version of the DSM (APA, 1994).

Following the introduction of social phobia in DSM-III, research activity devoted to this disorder was initially scant, which led some authorities to describe social phobia as "the neglected anxiety disorder" (Liebowitz, Gorman, Fyer, & Klein, 1985). However, this picture has changed altogether as social phobia has received massive attention in the past ten years resulting in an enormous number of studies. It is noteworthy that a number of recent studies have preferred the name "social anxiety disorder", which is the alternative label given in DSM-IV. It is foreseeable that this name will replace social phobia in future editions of the DSM because it is considered to

be better differentiated from specific phobia and may also convey the sense of pervasiveness and impairment in a better way (Liebowitz, Heimberg, Fresco, & Stein, 2000).

1.3 Characterizing psychopathology

1.3.1 Feared situations

As stated in DSM-IV, individuals with social phobia fear and avoid situations in which they risk negative evaluation, mainly by unfamiliar people. Virtually all situations in which the person is being observed by others or gets in the focus of attention can become problematic. Public speaking, however, is the most prevalent social fear (Kessler, Stein, & Berglund, 1998; Pollard & Henderson, 1988; Stein, Walker, & Forde, 1994; Turner, Beidel, & Townsley, 1992). In the social phobia literature, performance circumstances are commonly distinguished from interactional situations. Public speaking involves a performance in front of other people, as do eating, drinking, writing, acting, playing an instrument, and urinating in front of others. Fear arising in such situations may thus be classified as performance fears (Hazen & Stein, 1995). Interactional fears, on the other hand, may occur in settings such as parties, social gatherings, meetings, and face-to-face conversations with strangers or authorities. Such fears may also arise in situations that involve ambiguous or novel roles.

1.3.2 Symptomatology

Three separate response systems are often used to analyze emotional behavior: the cognitive-verbal, the behavioral-expressive, and the bodily-expressive system (Lang, 1985). Thus, it might be fruitful to distinguish between cognitive, behavioral, and physiologic aspects of social phobia. It should be noted that the characteristic symptoms of social phobia may be present in the phobic situation, before the situation, and also after leaving it (Wells & Clark, 1997).

Cognitive aspects

Virtually all cognitive models of social phobia (Beck, Emery, & Greenberg, 1985; Clark & Wells, 1995; Rapee & Heimberg, 1997) emphasize that social phobics are overly concerned with how they are being perceived and evaluated by others. In the cognitive perspective, social anxiety may emerge from an excess of negative thoughts, perceived personal shortcomings, excessively high standards for one's own performance, and/or unrealistic beliefs about the standards people ordinarily use to evaluate others. According to the self-presentation theory, social anxiety occurs when the individual is motivated to make particular impressions on others but distrusts his or her own ability to successfully do so (Leary & Kowalski, 1995).

Prior to a problematic social situation, social phobics frequently review in detail what they think might happen and how they can deal with the various difficulties arising. These ruminations may sensitize the individual so that he or she enters the situation in a pre-activated self-focused processing mode (Wells & Clark, 1997). During stressful situations, socially anxious individuals typically report more negative and fewer positive thoughts than non-clinical or low anxious subjects (Rapee, 1995; Stopa & Clark, 1993). The negative thoughts do not always stop immediately on leaving a social situation. Rather, the negative ruminations tend to go on as the phobic individual afterwards mentally reviews in detail what happened. Wells and Clark (1997) use the term "post-mortem processing" to describe retrospective thinking about the phobic

situations. Post-mortem processing may be traced to a strongly felt need to repair self-esteem and plan more effective strategies to deal with the situation in the future.

In the anxiety disorders, considerable research effort has been devoted to the issue of information-processing biases toward threat-relevant cues, e.g. with regard to attention, interpretation, and memory. Such biases have been reported in individuals with social phobia (Lampe, 2000; Musa & Lépine, 2000). For instance, empirical studies using the Stroop paradigm, dot probe test, and lexical decision tasks, generally support that social phobics show greater vigilance to socially threatening information relative to physically threatening or neutral information (Musa & Lépine, 2000). On the other hand, Wells and Clark (1997) review evidence in support of their notion that hypervigilance to interoceptive threat cues lead social phobics to avoid or direct attention away from external threat information in the social environment. Hence, they argue that socially anxious individuals are cognitively characterized by self-focused attention and poor encoding of environmental cues (Wells & Clark, 1997).

There is also support of an interpretation bias in social phobics. For instance, socially anxious individuals have a tendency to rate their own performance far worse than do independent judges (Rapee, 1995). Furthermore, it has been demonstrated that social phobics tend to interpret ambiguous events as negative and overestimate the probability of negative social outcomes (Musa & Lépine, 2000). Socially anxious individuals also exaggerate the extent to which observers can notice that they feel distressed (Leary & Kowalski, 1995). Wells and Clark (1997) argue that the socially phobic individual typically constructs a negative image of him/herself from an "observer perspective", i.e. the person often sees him/herself as if outside the body looking back at the self.

Cognitive studies have also explored whether social phobics show enhanced memory retrieval of threat relevant information. The empirical support of such a memory bias has been mixed and positive results may be contingent upon specific encoding conditions (Musa & Lépine, 2000). However, some studies do suggest that socially anxious individuals tend to remember more negative data about themselves than do less distressed people (Breck & Smith, 1983; O'Banion & Arkowitz, 1977).

Behavioral aspects

According to the principles of operant conditioning (Skinner, 1974), phobias are thought to be maintained by escape and avoidance behaviors. For example, when a spider phobic runs away from the basement after seeing a spider crawling on the floor, the escape behavior is negatively reinforced because it terminates aversive exposure. Future avoidance of entering the basement similarly prevents potential aversive exposure. However, while these strategies reduce anxiety in the short perspective, the phobic individual never gets a chance to learn more adequate and nondistressing ways to deal with the phobic object. That is why exposure to feared events is an essential feature in behavioral treatments of phobias. Escape and avoidance are prominent also in social phobia, even though social situations are perhaps more difficult to avoid completely, and to flee from, compared with phobogenic situations in specific phobia and agoraphobia. Running out of the classroom when talking in class, going home early from a party, or hanging up the telephone before the other party has been able to answer, are some examples of escape behaviors in social phobia. Avoidance may be manifested in countless ways. Example cases here would be when a talented student refrains from entering university because of fear of talking in class or when a skillful employee turns down a promotion because the new position lays greater emphasis on social contacts.

Wells and Clark (1997) argue that social phobia is maintained by subtle avoidance maneuvers or "safety behaviors", practiced by socially anxious individuals when phobic situations are endured. Avoiding eye contact when talking in class, wearing cool clothes to avoid sweating, and holding arms rigid to avoid shaking are some examples of such safety behaviors. These are intended to reduce the risk of social failure, but in the process they prevent disconfirmation of negative beliefs and preserve self-focused attention.

The issue of social skills should also be mentioned among the behavioral aspects of social phobia. It could be suspected that social phobics lack the proper skills (verbal or non-verbal) necessary to master social interactions or performance situations. However, research on this topic has been inconsistent (Rapee, 1995). Even though social phobics appear to have inadequate abilities in some studies, this might reflect inhibition rather than actual lack of skills. It is also possible that such social abilities are inhibited only during states of high anxiety in phobic situations (Rapee, 1995).

Physiological aspects

Social phobics exhibit basically the same somatic symptoms during (or in anticipation of) anxiogenic exposure as observed in other anxiety disorders (Rapee, 1995), i.e. palpitations, sweating, tremors, hot flushes, etc. These arousal symptoms stem from exaggerated activity in the sympathetic division of the autonomic nervous system, and are characteristic features of the "fight-or-flight" response (Cannon, 1927). Autonomic arousal is also accompanied by increased blood pressure and increased secretion of stress hormones initiated by the hypothalamus-pituitary gland-adrenocortical axis. However, facial blushing and somatic symptoms of embarrassment, which are common in social phobia, might not be simply mediated by increased sympathetic activity (Stein & Bouwer, 1997). For instance, blushing has sometimes been associated with lowered heart rate and blood pressure and may stem from vasodilatation due to relaxation of sympathetic tone, active cholinergic stimulation, or sympathetic arousal of beta-adrenergic receptors (Stein & Bouwer, 1997). While the DSM-IV does not emphasize specific physical symptoms beyond the appearance of a psychophysiological anxiety reaction, blushing, hand tremor, nausea, and urgency of micturation are listed in the ICD-10 criteria for social phobia.

1.3.3 Age of onset and natural course

According to several retrospective studies, social phobia typically begins between early and late adolescence (Amies, Gelder, & Shaw, 1983; Liebowitz et al., 1985; Mannuzza, Fyer, Liebowitz, & Klein, 1990; Turner, Beidel, Dancu, & Keys, 1986). However, some reports suggest an even earlier age of onset, and social phobia is not uncommon in anxiety-disorder clinics for children (Last, Strauss, & Francis, 1987). From a developmental perspective it has been argued that concerns about negative evaluation from other people or self-consciousness typically emerge around 8 years of age. Consequently, social phobia should be rare in younger children (Hudson & Rapee, 2000).

There is some empirical research suggesting that social phobia (Chartier, Hazen, & Stein, 1998; Reich, Goldenberg, Vasile, Goisman, & Keller, 1994; Solyom, Ledwidge, & Solyom, 1986) and shyness (Caspi, Elder, & Bem, 1988) remains fairly stable across the lifespan. However, some epidemiological studies report a markedly higher prevalence using lifetime- as compared to one-month estimates of prevalence (c.f. Kessler et al., 1994; Magee, Eaton, Wittchen, McGonagle, & Kessler, 1996). This may argue against a chronic course, considering

that most phobics do not seek treatment (Magee et al., 1996; Weiller, Bisserbe, Boyer, Lepine, & Lecrubier, 1996).

1.3.4 Other associated features

Gender distribution

In the general population it has consistently been observed that women are more likely to have social phobia - the women to men ratio being approximately 3:2 (Chapman, Mannuzza, & Fyer, 1995; Moutier & Stein, 1999). However, men seem to be somewhat more likely to seek treatment, possibly because social phobic symptoms have more handicapping consequences for men than for women (Weinstock, 1999).

Marital status

Several epidemiological studies have reported that social phobia is over-represented among unmarried individuals (Davidson, Hughes, George, & Blazer, 1993; Magee et al., 1996; Schneier et al., 1992). In clinical samples it has also been observed that individuals with social phobia are less likely to be married than individuals with other anxiety disorders (Sanderson, DiNardo, Rapee, & Barlow, 1990). Similarly, studies of shyness have reported that shy males married and had their first child at least 3 years later than the nonshy males (Caspi et al., 1988).

Age at assessment

Large-scale epidemiological studies have noted significant age-differences, such that the highest lifetime prevalence rates of social phobia have been observed among the youngest individuals and the lowest rates among the oldest individuals (Magee et al., 1996; Schneier et al., 1992). Although this could reflect recall failure or poor reporting accuracy among the older subjects, or greater exclusion from the sample of the more aged phobics, it is possible that social phobia is on the rise in younger cohorts (Heimberg, Stein, Hiripi, & Kessler, 2000; see also 2.1.1).

Career factors and quality of life

Turner and colleagues (1986) found that the overwhelming majority of their studied group of social phobics reported that their social anxiety led to significant occupational or academic interference. Schneier et al. (1992) observed that social phobia was associated with lower levels of educational attainment and income level. Social phobia is also associated with substantial reductions in work productivity (Wittchen, Fuetsch, Sonntag, Müller, & Liebowitz, 2000). Moreover, it has been noted that shy people are less likely than the nonshy to engage in career promoting behaviors (Phillips & Bruch, 1988). Collectively, these data suggest that excessive social anxiety may hamper career advancement. In addition, social phobia is associated with a substantial decrease in the quality of life, impairing vital areas such as family functioning and social and romantic relationships (Wittchen et al., 2000). Wittchen and colleagues (2000) also observed considerable subjective suffering and negative life impact in subthreshold social phobia, i.e. among individuals who met the all diagnostic criteria except the impairment/distress criterion according to the diagnostic interview.

1.3.5 Diagnostic and conceptual issues

Subtypes of social phobia

As mentioned previously, the DSM-III-R introduced a generalized subtype of social phobia (when the fear includes "most social situations"). Other forms of social phobia have often been referred to as "nongeneralized", but some authors have proposed more fine-grained subtyping schemes. The issue of subtypes is further discussed elsewhere (see 2.1.2).

Comorbidity

Social phobia is commonly accompanied by other psychiatric disorders. In the US National Comorbidity Survey, other anxiety disorders such as simple phobia, agoraphobia, panic disorder, and generalized anxiety showed the highest degree of comorbidity with social phobia (57%), followed by affective disorders (41%) and substance abuse disorders (40%) (Magee et al., 1996). Other studies suggest that the lifetime comorbidity rates are greater than 10% for specific phobia, agoraphobia, major depressive disorder, obsessive-compulsive disorder, alcohol abuse, and drug abuse (Moutier & Stein, 1999). Rates of comorbidity are highest in patients with the generalized subtype (Moutier & Stein, 1999) and in most cases social phobia precedes the onset of comorbid disorders (Schneier et al., 1992). The association between social phobia and alcohol abuse has been noted by several investigators, suggesting that social phobics frequently self-medicate to relieve their anxiety (Merikangas et al., 1998). It has also been reported that comorbid conditions are associated with an increased risk of attempting suicide (Schneier et al., 1992). Even though comorbid patients probably are the most impaired, empirical data suggest that "pure" and even subthreshold social phobia can be very disabling (Wittchen et al., 2000).

Avoidant personality disorder

Several investigators have reported that social phobics show a high degree of comorbidity with the axis II diagnosis avoidant personality disorder (APD), ranging from 25 to 89% (median 57.6%) for the generalized subtype and from 0-44% (median 17.5%) for the nongeneralized type of social phobia (Heimberg, 1996; Herbert, Hope, & Bellack, 1992; Holt, Heimberg, & Hope, 1992; Schneier, Spitzer, Gibbon, Fyer, & Liebowitz, 1991; Turner et al., 1992). Because of the substantial overlap, the discriminant validity of APD relative to social phobia has been much debated. Given the considerable difficulties in distinguishing between APD and generalized social phobia, it might be argued that having two diagnoses is redundant because in reality they both define one and the same disorder. The DSM-IV task force recognized this problem but eventually decided that both diagnoses should be retained awaiting further research (Heckelman & Schneier, 1995). According to a dimensional view, both APD and social phobia, including its subtypes, represent arbitrary cutoffs along a continuum of severity. APD has often been thought of as a particularly severe form of social phobia (Holt et al., 1992). However, Heimberg (1996) argued that the concept of APD does not serve a needed function alongside the more informative diagnosis of social phobia, and other authors have also speculated that APD might be dropped in future revisions of the DSM (Hazen & Stein, 1995).

Differential diagnosis

Individuals with social phobia are usually well recognized by the content of their fears, but the diagnostic distinction can sometimes be tricky. For example, panic disordered patients may

experience panic attacks in social or performance settings, individuals with generalized anxiety disorder may worry about social situations, and depressed patients may exhibit social withdrawal (Heckelman & Schneier, 1995).

Shyness

Superficially, there are many similarities between social phobia and shyness. Individuals with social phobia typically describe themselves as being shy, and the fear of negative evaluation from others is central to both concepts. Unlike social phobia however, shyness is not a psychiatric diagnosis with specific criteria - rather it is often defined by subjects' self-attributions as being either shy or nonshy (Heckelman & Schneier, 1995). Furthermore, the prevalence rates of shyness in college students have been up to 40% in some studies (Cheek, Carpentieri, Smith, Rierdan, & Koff, 1986) which are higher than for social phobia. Thus, while shyness and social phobia often overlap, shyness is probably a broader and more heterogeneous category (Heckelman & Schneier, 1995). In a similar vein, socially anxious individuals could be described using a number of other concepts that also lack specific criteria in a diagnostic sense, such as being introvert, neurotic, inhibited, reserved, withdrawn, or isolated.

1.4 Etiology: Some factors related to the origins of social phobia

1.4.1 Genetic factors

A two- to three-fold increased risk of having social phobia has typically been observed among first-degree relatives of social phobics in clinical samples (Bruch & Heimberg, 1994; Fyer, Mannuzza, Chapman, Liebowitz, & Klein, 1993; Fyer, Mannuzza, Chapman, Martin, & Klein, 1995; Mannuza et al., 1995; Reich & Yates, 1988; Stemberger, Turner, Beidel, & Calhoun, 1995). Stein et al. (1998) noted that it is the relative risk for the generalized subtype that is uniquely higher (approximately 10-fold in their study) among relatives of probands with generalized social phobia. Moreover, a positive family history of excessive social anxiety has been observed in social phobics in the general population (Lieb et al., 2000; Tillfors, Furmark, Ekselius, & Fredrikson, in press) and community studies also suggest that the rate of social phobia is raised among mothers of shy children (Cooper & Eke, 1999). Because social phobia and other anxiety disorders tend to cluster in families, a genetic cause might be suspected. However, in the etiologic perspective family studies cannot properly distinguish genetic from environmental influences.

To disentangle the genetic contributions Kendler, Neale, Kessler, Heath, and Eaves (1992) studied the concordance for social phobia in monozygotic and dizygotic twin-pairs, and observed a significantly higher concordance rate in the former group. The heritability index was estimated at approximately 30% suggesting that genetic factors explained one-third and nonshared environmental factors two-thirds of the variability in familial transmission of social phobia (Kendler et al., 1992). Genetic influences have also been noted on social fears defined in a broader sense (Torgersen, 1983; Phillips, Fulker, & Rose, 1987) and on other variables of relevance to social phobia such as behavioral inhibition (Kagan, Reznick, & Snidman, 1988; see below), neuroticism, and introversion (Henderson, 1982). Taken together these data suggest that genetic factors play at least a moderate role in the etiology of social phobia.

1.4.2. Temperamental factors

Temperament refers to inborn biases towards certain moods and emotional reaction styles (Mussen, Conger, Kagan, & Huston, 1990). Jerome Kagan and coworkers have depicted two temperamental styles of children called inhibited and uninhibited. Inhibited children are characterized by withdrawal and increased autonomic arousal in situations of uncertainty, in contrast to uninhibited children who tend to react with spontaneity and approach in these situations (c.f. Kagan et al., 1988). About 10-15% of American (Caucasian) children belongs to each category. Longitudinal studies suggest that children with a stable pattern of behavioral inhibition have an increased risk for developing phobic disorders, particularly social phobia. An increased risk of social phobia has also been observed in the parents of inhibited children (Rosenbaum et al., 1991). Thus, it is possible that behavioral inhibition is a childhood precursor to social phobia in adults. However, it is unclear whether behavioral inhibition is a risk factor for later social phobia specifically or an anxiety proneness in general (Rosenbaum et al., 1991).

1.4.3. Conditioning and ethological factors

Classical conditioning models suggest that social phobia may emerge from aversive social experiences through processes of associative learning (Mineka & Zinbarg, 1995). Making a mistake or an unfavorable impression in social situations, e.g. when talking in class (becoming the conditioned stimuli), might result in the individual being ridiculed, laughed at, or exposed to hostility from others (the unconditioned stimuli). Thereby a social situation acquires the potential to elicit fear or anxiety reactions (a conditioned response) in the future. There is evidence that social phobics frequently attribute the onset of their phobia to such conditioning experiences. For instance, Öst (1985) noted that conditioning was a likely etiologic pathway in 56.3% of the social phobia patient sample whereas Stemberger et al. (1995) reported that 44% of their patient sample had a history of traumatic conditioning. Hofmann and colleagues observed, however, that although traumatic speaking events in the past were common among speech phobics, only 15% reported such events at the same time as their phobia started and none of them reported traumatic speaking events before their phobia onset (Hofmann, Ehlers, & Roth, 1995). Other authors have noted that social phobia onset is gradual rather than abrupt (e.g., Fahlén, 1995). This could mean that conditioning to contexts are more important than conditioning to specific fear cues. In the brain, cue conditioning is thought to be served by the amygdala whereas contextual fear conditioning requires longer times to be consolidated and is dependent on the hippocampus (Kim, Rison, & Fanselow, 1993).

It is conceivable that social phobics acquire fear reactions with more ease and/or show a higher resistance to extinction of learned fear compared with non-phobics. A related issue is the notion of *preparedness* (Seligman, 1971). According to the preparedness theory, humans have an evolutionarily formed predisposition to easily learn fear reactions to objects or situations that were threatening to our early ancestors. In a series of studies on fear conditioning, Arne Öhman and colleagues (Öhman, 1986) have demonstrated that angry faces belong to the class of evolutionary fear-relevant stimuli, capable of eliciting conditioned fear reactions even when presented below the threshold of conscious awareness. In the context of dominance hierarchies, which have been evolutionarily important in the regulation of social life in animals and humans, the angry face might signify an increased risk of dominance conflict and potentially harmful assault. Social phobia in turn might be related to fearful and submissive behavior typically seen in defeated animals taking a lower position in the hierarchy. Blushing and other symptoms of

embarrassment may constitute evolutionarily shaped appeasement displays that reduce the likelihood that a dominant conspecific will attack (Stein & Bouwer, 1997).

1.4.4. Family factors

If parents themselves are socially anxious their children might acquire social fears and avoidance through processes of modeling (Bandura, 1977). Öst (1985) reported that 15.6% of a studied sample of social phobics attributed the acquisition of their phobia to modeling factors. Also, families that are high in anxiety probably socialize less with other people, thereby restricting the child's exposure to social situations. Under such circumstances, an anxious child has less opportunities to develop social skills and to learn that social situations are harmless (Hudson & Rapee, 2000). Moreover, patients with social phobia tend to describe their parents as overprotective (Bruch & Heimberg, 1994; Rapee & Melville, 1997). A controlling or overprotecting parenting style may be associated with fearful and socially withdrawn behavior in children, although this might be true not only for social phobics but for anxious individuals in general (Hudson & Rapee, 2000).

1.4.5. Birth order

Sibling position might have an impact on social phobia because some studies have reported increased rates of social anxiety or shyness among firstborn or only children relative to those born later (Hudson & Rapee, 2000). Social anxiety may occur because of an increased pressure placed on firstborn children to succeed or because these children lack the benefits of having older siblings as social role models. However, other investigators have reported that first born children show less trait anxiety than later-born siblings (Gates, Lineberger, Crockett, & Hubbard, 1988) and that increasing adult fearfulness correlates with increasing birth order in the sibship (Croake, Myers, & Singh, 1987). Thus, to date, reports on birth-order are inconclusive.

1.4.6. Peer-rejection and social isolation

Childhood experiences of peer-rejection and subsequent social isolation are not uncommon among individuals with social phobia. Rapee and Melville (1997) noted that social phobics retrospectively reported having fewer friends during middle childhood. Hudson and Rapee (2000) review evidence supporting that "love shy" men often retrospectively report peer-rejection experiences such as bullying, being picked last for sport teams, or never having close friends to play with. It is possible that negative life experiences early in life sensitize the individual, e.g. so that aversive stimuli of milder intensity may become capable of exciting fear circuits in the brain. Thus, the likelihood increases that the person will react with anxiety when exposed to psychosocial stressors in the future. In this case, social fears are acquired by non-associative learning. Also, peer-rejection or neglect could lead to social isolation, which in turn might hamper the development of social skills. Lack of social skills, in turn, probably further augment social isolation (Hudson & Rapee, 2000).

1.4.7. A multifactorial approach

It is unlikely that any single factor underlies the etiology of social phobia. In a stress-diathesis model both environmental and genetic factors are recognized as important. For instance, even though various forms of environmental influences or learning can be significant, it is also possible that socially anxious individuals learn fear reactions more easily than do non-anxious

persons due to genetic reasons. Thus, an inherited vulnerability might interact with environmental stressors leading to the acquisition of a social fear. As mentioned previously, social phobia, whether it is learned or innate, is likely to be maintained by avoidance/escape behaviors and cognitive biases. Also, excessive social anxiety is probably mediated by overly reactive fear circuits or dysfunctional neurotransmitter/receptor systems in the brain. This issue is further discussed elsewhere in this thesis (2.2.1).

1.5 Treatment: Major Research findings

Following the huge increase in empirical studies on social phobia in the 1990's, the effects of various treatments also started to be evaluated extensively. To date, there is evidence for the effectiveness of both pharmacological and psychological (i.e. cognitive-behavioral) treatments.

1.5.1 Pharmacological treatments

Selective serotonin reuptake inhibitors

Selective serotonin reuptake inhibitors (SSRIs) were originally developed for the treatment of depression, but clinicians soon observed that these agents also have anti-anxiety effects. Fluoxetine appears to be the first SSRI used in social phobia, as reported by Sterbach (1990). Since then, numerous open trials or naturalistic studies have demonstrated the effectiveness of sertraline, paroxetine, and citalopram (c.f. Van Ameringen, Mancini, Oakman, & Farvolden, 1999). The beneficial effects of SSRIs in the treatment of social phobia have now also been confirmed in several randomized placebo-controlled trials, e.g., on fluvoxamine (Stein, Fyer, Davidson, Pollack, & Wiita, 1999b; Van Vliet, Den Boer, & Westenberg, 1994), sertraline (Katzelnick et al., 1995), and paroxetine (Allgulander, 1999; Baldwin, Bobes, Stein, Scharwachter, & Faure, 1999; Stein et al., 1998b; Stein et al., 1999a). Although other agents have been equally beneficial in controlled studies, much of the current pharmacological research on social phobia concerns the SSRIs. When issues such as safety, tolerability, drug dependency, and effect on comorbid conditions are considered, the SSRIs have many advantages. In a recent review, Van Ameringen et al. (1999) argued that the SSRIs are very likely to become the new gold standard for the pharmacological treatment of social phobia.

Other drugs

Before the introduction of SSRIs, the monoamine oxidase inhibitors (MAOIs) were considered to be the pharmacological treatment of choice in social phobia. Phenelzine in particular has been proven effective in double-blind, placebo-controlled studies (Gelernter et al., 1991; Liebowitz et al., 1992; Versiani et al., 1992; Heimberg et al., 1998). However, clinicians are somewhat reluctant to use the classical MAOIs because of the potential risk for life-threatening hypertonic reactions. Consequently, safe treatment requires strict dietary restrictions. Promising results have been obtained with reversible inhibitors of monoamine-oxidase-A, such as brofaromine (Fahlén, Nilsson, Borg, Humble, & Pauli, 1995; Lott et al., 1997; Van Vliet, Den Boer, & Westenberg, 1992) and moclobemide (the International Multicenter Clinical Trial Group on Moclobemide in Social phobia, 1997; Noyes et al., 1997; Versiani et al., 1992; but poor outcome was reported by Schneier et al., 1998).

High potency benzodiazepines such as clonazepam (Davidson et al., 1993c) and to a lesser extent alprazolam (Gelernter et al., 1991) are also effective in social phobia, but the potential risk of dependence and high comorbidity with substance abuse have dampened the

enthusiasm for these drugs. Other controlled trials in social phobia include the serotonin 5-HT_{1A} receptor agonist buspirone (Clark & Agras, 1991; Van Vliet, Den Boer, Westenberg, & Pian, 1997) and the serotonin 5-HT_3 receptor antagonist ondansertron (c.f. Van Ameringen et al., 1999), both of which appear to be only moderately effective. Controlled studies have failed to demonstrate superior efficacy for β-blockers relative to placebo in generalized social phobia (Liebowitz et al., 1992; Turner, Beidel, & Jacob, 1994). While β-blockers might mitigate autonomic arousal on specific occasions, these drugs are probably ineffective in achieving stable anxiolytic effects in the long-term.

1.5.2 Psychological treatments

Cognitive-behavioral group therapy

With regard to psychological treatments of social phobia, cognitive-behavioral group therapy (CBGT) following principles developed by Heimberg and coworkers (c.f. Hope & Heimberg, 1993) is perhaps the most empirically validated method. Briefly, CBGT is a structured form of psychotherapy, which incorporates simulated exposures to feared situations, cognitive restructuring, and homework assignments for in vivo exposure. It is held in a group format, ideally with 6-8 patients and two therapists. The standard treatment period runs for 12 weekly sessions, each about three hours long. The effectiveness of CBGT has been demonstrated in several controlled studies (c.f. Heimberg & Juster, 1995; Heimberg et al., 1998) and follow-up assessments have shown that the beneficial effects are still evident five years after treatment termination (Heimberg, Salzman, Holt, & Blendell, 1993b).

Based on their cognitive model of social phobia, Clark and Wells (1995) have also developed a renowned treatment package that has many similarities with Heimberg's CBGT, although a greater emphasis is put on the identification and correction of safety behaviors (described earlier) and the use of audio and video-feedback to correct distorted self-processing (Wells & Clark, 1997). It is possible that these components add additional beneficial effects to therapy (Morgan & Raffle, 1999).

Other methods

Since the 1980's four main types of psychological treatments for social phobia have been evaluated: (1) social skills training, (2) exposure to feared events, (3) anxiety management (e.g., relaxation, distraction, brief cognitive procedures), and (4) cognitive therapy. As pointed out by Butler and Wells (1995), all these methods have been effective, at least to some extent, although their relative value is difficult to determine because of differences in study designs, outcome measures, patient selection, comparisons made etc. Moreover, the basic treatment components are frequently combined. In a meta-analysis of 42 cognitive-behavioral treatment studies on social phobia, Taylor (1996) noted that all interventions reviewed, including placebo, had larger effect-sizes than that of waiting-list controls, but only exposure in combination with cognitive restructuring significantly surpassed placebo. Psychodynamic treatment has not been evaluated in controlled studies. It should also be mentioned that although group treatment has many advantages in social phobia, individual treatment has not been shown to be less effective.

1.5.3 Psychological treatments compared and combined with pharmacotherapy

Data on the relative effectiveness of psychotherapy and pharmacotherapy are very limited. However, the effects of CBGT compare well to phenelzine (Gelernter et al., 1991) but might be

slightly less effective in the shorter perspective after 6 weeks and immediately after 12 weeks of treatment (Heimberg et al., 1998). In a study of musicians with social phobia, cognitive-behavior therapy was more effective than buspirone (Clark & Agras, 1991). In a meta-analysis Gould, Buckminster, Pollack, Otto, and Yap (1997) noted that both cognitive-behavioral and pharmacological treatments were significantly effective in social phobia, having effect sizes of .74 and .62 respectively, but did not differ between themselves. Exposure based interventions, either alone or combined with cognitive restructuring, were the most effective cognitive-behavioral treatments, whereas the SSRIs and benzodiazepines yielded the highest effect sizes for pharmacotherapy. CBGT was the most cost-effective intervention (Gould et al., 1997). Psychological treatments might be more advantageous than pharmacotherapy in terms of number of dropouts and long-term outcome, i.e. patients might relapse when medication is discontinued (Stravinsky & Greenberg, 1998).

Studies examining the combination of psychological treatment and medication are scarce, but on the whole such combinations have been disappointing as they have not exceeded the effects of the treatment methods in isolation (Clark & Agras, 1991; Falloon, Lloyd, & Harpin, 1981; Gelernter et al., 1991; Turner et al., 1994). However, combinations of the most potent psychological and pharmacological treatments have not yet been evaluated. This is an important topic for future research, especially since recent studies have reported intriguing results from combined treatments for panic disorder (Barlow, Gorman, Shear, & Woods, 2000) and depression (Keller et al., 2000).

1.5.4 How effective are "effective" treatments?

Even though both psychological and pharmacological treatments may be very useful, it is also apparent that a substantial number of patients with social phobia do not achieve a sufficiently good treatment outcome. The proportion of responders in the most promising psychological and pharmacological treatments are typically in the range of 70-80% (Heimberg et al., 1990a; 1998; Van Ameringen et al., 1999). However, as Stravinsky and Greenberg (1998) point out, the treatment results are often fairly modest and the number of patients who achieve full resolution of social phobia is considerably lower than the above figures. In treatment studies, outcome is typically reported in terms of statistically significant anxiety reduction. However, it is often unclear whether patients truly change in a meaningful way, e.g. with regard to reduced avoidance and improvements in family life, intimate relationships, activity rates, occupational and academic functioning, etc. Thus, much work remains to be done before we can speak with confidence about effective treatment for social phobia incorporating its consequences for general well-being. Also, although most patients may benefit from treatment, outcome is generally poorer in more severe forms of the disorder (e.g., in generalized as compared to nongeneralized social phobia), in the presence of comorbid conditions (e.g., avoidant personality disorder and depression), and possibly also in patients with earlier onset of the disorder (Lampe, 2000). Future treatment studies should pay attention to these issues.

2. BACKGROUND TO THE EMPIRICAL STUDIES

2.1 Background to study I and II

2.1.1 The epidemiology of social phobia:

As presented in Table 1, numerous epidemiological studies have examined the prevalence of social phobia in the general population since its official introduction in the DSM-III. Striking between-study variability in prevalence rates can be noted. According to the first wave of studies, e.g. the Epidemiologic Catchment Area (ECA) research project, DSM-III-defined social phobia was a relatively rare disorder with an estimated lifetime prevalence of about 2-3% in the United States (Bourdon et al., 1988; Davidson, Hughes, George, & Blazer, 1993; Eaton, Dryman, & Weissman, 1991; Schneier et al., 1992). Roughly similar numbers were reported in New Zealand (Wells, Bushnell, Hornblow, Joyce, & Oakley-Browne, 1989) and Europe (e.g., Lindal & Stefanson, 1993; Wittchen, Ahmoi Essau, von Zerssen, Krieg, & Zaudig, 1992) whereas lower counts (about 0.5%) were obtained in Korea (Lee et al.,1990a; 1990b) and Taiwan (Hwu, Yeh, & Chang, 1989). However, it has been argued that these initial studies vastly underestimated the true prevalence of social phobia (Walker & Stein, 1995) as later reports noted considerably higher figures. For instance, a lifetime prevalence rate of 13.3% was observed in the National Comorbidity Survey (NCS), making social phobia the third most common psychiatric disorder in the United States, surpassed only by alcohol dependence and major depressive disorder (Kessler et al., 1994).

It is likely that the higher prevalence rates of social phobia in more recent studies at least partly reflect the difference in diagnostic criteria between DSM-III and DSM-III-R. Recall that in DSM-III, social phobia was conceptualized primarily as a fear of circumscribed performance-situations such as speaking or eating in front of others. Individuals with a broader range of fears, including those with interactional anxiety, were excluded but could be diagnosed as having avoidant personality disorder. The diagnostic criteria were broadened in the DSM-III-R, which opened the door for individuals with interactional fears, as well as those with APD, to be diagnosed as having social phobia. Sharp increases in prevalence rates in going from DSM-III to more modern diagnostic criteria have been noted not only in the NCS but also in several other studies. For instance, in Canada the point prevalence of DSM-IV social phobia was estimated at roughly 10% by Stein, Walker, and Forde (1996), which can be compared to 2.9% reported by Costello (1982) using DSM-III criteria. Similar trends have been noted, e.g. in New Zealand and Switzerland (see Table 1).

There might also be other methodological explanations underlying the increases in prevalence rates of later studies. Several limitations of the Diagnostic Interview Schedule (DIS) (Robins, Helzer, Croughan, & Ratcliff, 1981), i.e. the assessment instrument used in the early ECA-studies, have been noted. For instance, only three phobic situations were assessed by the DIS (Chapman et al., 1995). The NCS (Kessler et al., 1994) used a somewhat more comprehensive assessment tool, a modified version of the Composite International Diagnostic Interview (CIDI; Robins et al., 1988), which asked about six social situations. This could have increased the likelihood of identifying individuals with social phobia because assessment of many situations is important to avoid missing cases (Heckelman & Schneier, 1995).

Another possibility is that the early ECA/DIS-studies focused only on severe cases of social phobia by requiring a high level of psychosocial impairment (Stein et al., 1994). It has been

demonstrated that small modifications of the required level of distress and impairment used to define cases can influence prevalence estimates dramatically. For example, Pollard and Henderson (1988) noted that the point prevalence rates of social phobia varied between 2.0 and 22.6% when different levels of significant distress were applied. Stein and colleagues (1994) reported that the rate of social anxiety syndrome in a Canadian community sample varied from 1.9 to 18.7% as the required level of psychosocial interference was altered. In another epidemiological report, Stein et al. (1996) noted that about 10% of the respondents fulfilled the DSM-IV criteria for social phobia, but this rate increased to 16% by adjusting the threshold for inclusion from 6 to 5 on a seven-point impairment scale. Also, in a recent postal survey, 26.9% of a large French sample admitted at least one strong fear in social situations with resultant fear/avoidance most or some of the time, but successively narrowing the definition of social phobia resulted in a one-month prevalence of 0.9% at the most stringent cut-off level (Pélissolo, André, Moutard-Martin, Wittchen, & Lépine, 2000). Thus, it is likely that arbitrariness in the choice of diagnostic threshold partly underlies the between-study variability in prevalence.

Yet another methodological concern is the choice of prevalence period. Rather small variations between the lifetime, one-year, and one-month prevalence have been noted in many studies, e.g. the ECA-reports, whereas other studies have reported striking differences. For instance, while the lifetime prevalence of social phobia was 13.3% in the National Comorbidity Survey, only 7.9% of the respondents fulfilled the criteria during the preceding 12-month period (Kessler et al., 1994), and only 4.5% did so during the last thirty days (Magee et al., 1996). Judging from these findings, a considerable proportion of individuals seems to recover from social phobia, presumably either through treatment or "spontaneous remission". However, this interpretation is inconsistent with many reports describing social phobia as an undertreated disorder (Magee et al., 1996; Weiller et al., 1996) that follows a rather chronic course (Chartier et al., 1998; Reich et al., 1994; Solyom, et al., 1986). Alternatively, the variability across prevalence-periods could be attributed to methodological flaws, such as unreliable assessment instruments, or reporting biases. For instance, reporting biases associated with recall over longer time periods is a well-recognized problem (e.g., Parker, 1987). However, the epidemiological data suggest that the reporting bias among older subjects, if it exists, is manifested as an exaggeration of social phobia early in life. This, in turn, implies that the higher lifetime prevalence observed in younger as compared to older individuals (Magee et al., 1996; Schneier et al., 1992) reflects a true cohort effect rather than a failure among older phobics to recall their remitted social phobia.

Furthermore, cross-cultural studies that at least superficially use an identical methodology also report significant differences in prevalence rates (Table 1). One extreme example is the use of the CIDI in Udmurtia, Russia which for social phobia yielded a DSM-III-R lifetime prevalence of 52.7% (Pakriev, Vasar, Aluoja, & Shlik, 2000) as compared to 13.3% in the US (Kessler et al., 1994) and 7.8% in the Netherlands (Bijl, Ravelli, & Van Zessen, 1998). Although this could reflect true cultural variations, other explanations exist. It is possible that there are differences across countries and research groups in the way the diagnostic instruments are administered and translated. There might also be differences among cultures in attitudes about revealing information to interviewers, and variations in the cultural relevance of the questions asked (Chapman et al., 1995). Random sampling errors are also possible, but perhaps not likely given the large samples used (Chapman et al., 1995).

To recapitulate, epidemiological studies on social phobia have reported highly varying prevalence estimates (range 0-52.7% in Table 1). Among the numerous methodological explanations that might underlie this variability, it should be mentioned that different studies have used different diagnostic criteria, assessment methods, prevalence periods, and required levels of severity/impairment to define cases. Future epidemiological research should be planned with these issues in mind. Using ICD-criteria might yield a lower prevalence compared with DSM-definitions (Pakriev et al., 2000; Wacker et al., 1992). Also, only a small number of studies reports on the prevalence of isolated social fears. Nonetheless, judging from existing data it is likely that public speaking is the most frequently endorsed situational fear in the general community (Kessler et al., 1998; Pollard & Henderson, 1988; Stein et al., 1994).

Table 1. The prevalence of social phobia in adult non-clinical samples (ECA=Epidemiologic Catchment Area program, NCS=National Comorbidity Survey; DIS=Diagnostic Interview Schedule, CIDI=Composite International Diagnostic Interview, PSE=Present State Examination).

Country/study	Prevalence (%)			Prevalence period	Diagnostic criteria	Assessment	*N*	Reference
	Male	Female	Total					
United States								
ECA, weighted	1.06	1.64		One-month	DSM-III	DIS	18572	Bourdon et al. (1988)
	1.24	1.95		Six-months				
	1.39	2.15		One-year				
	2.3	3.2		Lifetime	DSM-III	DIS	18571	Boyd et al. (1990)
			1.3	One-month				
			2.7	Lifetime	DSM-III	DIS	14436	Eaton et al. (1991)
ECA, Baltimore	1.7	2.6	2.2	Six-months	DSM-III	DIS	3481	Myers et al. (1984)
St Louis	0.9	1.5	1.2				3004	
ECA, Duke			3.1[a]	Six-months	DSM-III	DIS	3648	George et al. (1986)
			2.2[b]					
			2.7	Six-months	DSM-III	DIS	3801	Davidson et al. (1993)
			3.8	Lifetime				
ECA, four sites:	2.0	3.1	2.4	Lifetime	DSM-III	DIS	13537	Schneier et al. (1992)
Baltimore			3.1				3481	
Durham			3.2				3921	
Los Angeles			1.8				3131	
St Louis			1.9				3004	
St Louis			2.0	Point	DSM-III	Structured interview	500	Pollard & Henderson (1988)
National Twin Registry		11.5		Lifetime	DSM-III	Structured interview	2163[c]	Kendler et al. (1992)
NCS - multistage	3.8	5.2	4.5	One-month	DSM-III-R	CIDI	8098	Magee et al. (1996)
area (48 states)	6.6	9.1	7.9	One-year				Kessler et al. (1994)
	11.1	15.5	13.3	Lifetime				
Fresno County	6.7[a]	9.6[a]	7.8[a]	Lifetime	DSM-III-R	CIDI	3012[d]	Vega et al. (1998)
	6.6[b]	9.0[b]	6.8[b]					
Puerto Rico	1.1	1.1	1.1	Six-months	DSM-III	DIS	1513	Canino et al. (1987)
	1.5	1.6	1.6	Lifetime				
			1.8[a]					
			1.1[b]					
Canada								
Calgary		2.91		Point	DSM-III	PSE	449	Costello (1982)
Edmonton	1.1	1.4	1.2	Six-months	DSM-III	DIS	3258	Dick et al. (1994)
	1.4	2.0	1.7	Lifetime				Bland et al. (1988)
Ontario	5.4	7.9	6.7	One-year	DSM-III-R	CIDI	9953	Offord et al. (1996)
Winnipeg			7.1	Point	DSM-III-R	Telephone survey	526	Stein et al. (1994)
Winnipeg			9.8	Point	DSM-IV	Telephone survey	499	Stein et al. (1996)
Korea								
Seoul	0	1.0	0.5	Lifetime	DSM-III	DIS	3134	Lee et al. (1990a)
rural	0.2	1.1	0.6				1966	Lee et al. (1990b)
Taiwan								
Taipei	0.2	1.0	0.6	Lifetime	DSM-III	DIS	5005	Hwu et al. (1989)
small towns	0.6	0.5	0.5				3004	
rural villages	0.4	0.5	0.4				2995	
New Zealand								
Christchurch	4.3	3.5	3.9	Lifetime	DSM-III	DIS	1498	Wells et al. (1989)
Dunedin	7.6	14.8	11.1	One-year	DSM-III-R	DIS v.III-R	930[e]	Feehan et al. (1994)

Table 1. *(continued)*

Country/study	Prevalence (%) Male	Female	Total	Prevalence period	Diagnostic criteria	Assessment	*N*	Reference
Switzerland								
Zurich	3.1[f]	4.4[f]	3.8[f]	1979-1988	DSM-III	Structured	591	Degonda & Angst (1993)
	0.4[g]	2.7[g]	1.6[g]			interview		
Basel			16.0	Lifetime	DSM-III-R	CIDI	470	Wacker et al. (1992)
			9.6		ICD-10			
Spain		8.9		Lifetime		DIS	237	Arillo et al. (1998)[h]
Formentera island			0.9	Point	ICD-10	PSE	242	Roca et al. (1999)
France								
Paris	1.2	2.9		One-year	DSM-III-R	Structured	1787	Lépine & Lellouch (1995)
	2.1	5.4	4.1	Lifetime		interview		
French			2.3[i]	One-month	DSM-IV	Postal survey	12873	Pélissolo & Lepine (2000)
population			7.3[j]	Lifetime				
Italy								
Florence			0.45	Point	DSM-III	Structured	1110	Faravelli et al. (1989)
			1.0	Lifetime		interview		
Florence			4.0	Lifetime	DSM-III-R	CIDI	2355	Faravelli et al. (2000)
Sardinia			3.1	Lifetime		CIDI	1100	Carta & Rudas (1998)[h]
The Netherlands	2.8	4.7	3.7	One-month	DSM-III-R	CIDI	7076	Bijl et al. (1998)
	3.5	6.1	4.8	One-year				
	5.9	9.7	7.8	Lifetime				
Germany								
Munich	5.47[k]	10.35[k]	4.06[k]	Six-months	DSM-III	DIS	483	Wittchen et al. (1992)
			8.01[k]	Lifetime				
Russia								
Udmurtia			44.2	One-month	ICD-10	CIDI	855	Pakriev et al. (2000)
	35.6	50.7	44.2	One-year				
	37.5	51.8	45.6[l]	Lifetime				
Iceland	2.5	4.5	3.5	Lifetime	DSM-III	DIS	862	Lindal & Stefanson (1993)
	2.5	5.0	4.0	Six months		Postal survey	775	Arnarson et al. (1998)
Sweden								
Stockholm	10.0	17.6	14.2	Point	DSM-IV	Postal survey	621	Study I
Gotland	14.6	19.4	17.2				581	
total sample	12.2	18.5	15.6				1202	

[a]urban; [b]rural [c]female-female twin pairs [d]Mexican Americans [e]18-year-olds only [f]pure social phobia [g]social phobia with agoraphobia [h]cited in Lecrubier et al. (2000) [i]0.9% with a more narrow definition [j]1.9% with a more narrow definition [k]undivided simple and social phobia [l]52.7% with DSM-III-R criteria

2.1.2 The issue of social phobia subtypes

With emphasis given to performance-oriented fears, the DSM-III definition of social phobia overlooked individuals exhibiting excessive anxiety in numerous social settings, including face-to-face conversations and interactional situations. As previously outlined, the diagnostic criteria were revised in DSM-III-R and a generalized subtype, described as fear of "most social situations", was then introduced. Although not formally listed in the DSM-nomenclature, the remainder of social phobia has by exclusion often been referred to as "nongeneralized" (Hazen & Stein, 1995; Heimberg, Holt, Schneier, Spitzer, & Liebowitz, 1993a).

However, the subtype organization in DSM-III-R has been subject to substantial criticism. First, the phrase "most social situations" was not fully operationalized. Second, using the quantity rather than the quality of social situations for a categorical distinction (generalized vs.

nongeneralized social phobia) might have questionable face validity (Heckelman & Schneier, 1995). Third, the implicit two-part subtype structure in DSM-III-R may be reorganized into a more fine-grained tripartite system. Heimberg and coworkers (Heimberg et al., 1993a; Herbert et al., 1992; Holt et al., 1992) have proposed that, while the term generalized social phobia can be used as a description of severely affected phobics, those who fear only one or two distinct situations form a separate subgroup referred to as "discrete" (or circumscribed) social phobia. Arguably, an intermediate category of social phobics are constituted of individuals who fear a number of social situations even though they are functioning quite well in broad social contexts. The term "nongeneralized" has also been utilized specifically for this group of social phobics (Heimberg et al., 1993a; Herbert et al., 1992; Holt et al., 1992). Fourth, underscoring qualitative features some investigators have suggested that the type of social fear, i.e. the distinction between performance and interactional fears, could be used to distinguish subtypes (e.g., Mannuzza et al., 1995; Turner et al., 1992). Hence, in the social phobia literature "performance" and "limited interactional" subtypes have been discussed (Heimberg et al., 1993a). On the other hand, the relevance of categorical subtypes has been challenged because individuals with social phobia may differ mainly in degree of severity rather than in a qualitative sense (Hazen & Stein, 1995; Heckelman & Schneier, 1995).

Given the conceptual problems, social phobia subtyping still remains matter of dispute. In the absence of empirical evidence, the social phobia task force refrained from including other subtypes than generalized social phobia in the development of the fourth edition of the DSM (Hazen & Stein, 1995). Thus, the DSM-III-R system was kept intact in DSM-IV. As a consequence of the diagnostic difficulties, little is known about the prevalence of social phobia subtypes in the general population. By applying latent-class analysis on the National Comorbidity Survey data, Kessler and colleagues (1998) identified two broad classes of social phobics, those with speaking fears and those who endorsed at least one other social fear, superficially resembling the nongeneralized and generalized subtypes. US lifetime prevalence estimates were 4.8% and 8.5%, respectively. Recently, Wittchen, Stein, and Kessler (1999) observed that the lifetime prevalence of DSM-IV social phobia in German adolescents was 9.5% in females and 4.9% in men and about one-third was classified as having generalized social phobia. However, more epidemiological research is clearly needed, and future research efforts should give careful attention to the definition of social phobia subtypes. To obtain empirically derived and fine-grained subtypes, future research could benefit from abandoning *a priori* definitions that are based on theoretical speculation, and instead adopt data-driven classification methods such as cluster analysis.

Further research on social phobia subtypes is also motivated because preliminary evidence suggests that subtypes may differ with regard to a number of variables that could have implications both for preventive strategies and the choice of treatment, such as age of onset (Brown, Heimberg, & Juster, 1995; Mannuzza et al., 1995), history of traumatic conditioning experiences (Stemberger et al., 1995), social skills (Tran & Chambless, 1995), psychophysiological stress responses (Heimberg et al., 1990b; Levin et al., 1993), and level of impairment after therapy (Hope, Herbert & White, 1995; Brown, Heimberg, & Juster, 1995).

2.2 Background to study III and IV

2.2.1 Neurobiological correlates to anxiety

In the 1930's, following previous pioneering work by William James (1884/1969) and Walter Cannon (1927), the American anatomist James Papez proposed an early model of the neuroanatomical circuitry underlying emotions (Papez, 1937). Although it was principally based on theoretical speculation, the model outlined by Papez became very influential. Since then, there have been great advances in our knowledge of the emotional brain (see review by LeDoux, 1996), particularly in the field of fear and anxiety. Our understanding of the neural circuitry underlying anxiety mainly stems from several decades of experimental research in animals utilizing lesion, electrical stimulation, pharmacological, and single cell recording techniques. During more recent years, functional neuroimaging methods have been applied to study emotions in humans. Together, these streams of research have been of profound importance in the development of *affective neuroscience* as a scientific discipline in its own right (Davidson & Sutton, 1995). We may now, enlightened by extensive empirical research (in contrast to Papez), delineate a model of the neuroanatomy of fear and anxiety.

Neuroanatomy of anxiety: An integrated model

In an attempt to unify animal and human research findings on anxiety into an integrated neuroanatomical model (see Figure 1), Charney and colleagues (Charney & Deutch, 1996; Charney, Grillon, & Bremner, 1998) firstly suggested that such a model should distinguish between afferent and efferent systems as well as an intermediate stimulus processing chain. Fear or anxiety (concepts that are often used synonymously although distinctions can be made) can be thought of as the organism's response to exteroceptive or interoceptive stimuli that signify threat. The afferent arm of the anxiety circuit includes the sensory systems (visual, auditory, somatosensory), which pass on the information in the anxiety-inducing stimulus from peripheral receptor cells to the dorsal thalamus. The thalamus in turn relays sensory information to primary sensory areas in the cortex and the stimulus is further processed in neighboring cortical association regions. The association areas then project to widespread parts of the brain including the amygdala, rhinal, cingulate, and orbitofrontal cortices. The amygdala, which also receives crude sensory information directly from the thalamus, is the most widely studied and probably the most crucial structure for the interpretation and expression of fear/anxiety. It has been called "the hub in the wheel of fear" (LeDoux, 1996). The amygdala is interconnected with the hippocampus, which in turn participates in contextual analyses, as well as the consolidation and retrieval of fearful memories. The hippocampus receives inputs from all sensory systems via transition areas consisting of the entorhinal, perirhinal, and parahippocampal cortices. The amygdala projects to the efferent fear system, e.g., the locus coeruleus, periaqueductal gray, hypothalamus, and striatum, subserving many executive aspects of anxiety including autonomic, endocrine, and skeletal-motor responses (Charney & Deutch, 1996; Charney et al., 1998).

It is beyond the scope of the present thesis to give a detailed review of each structure in the neuroanatomical anxiety model (Figure 1), and other regions not included may be considered important as well. However, because of the enormous interest devoted to the amygdala and hippocampus in affective and cognitive neuroscience, a more thorough description of the functional role of these subcortical structures in anxiety is presented below.

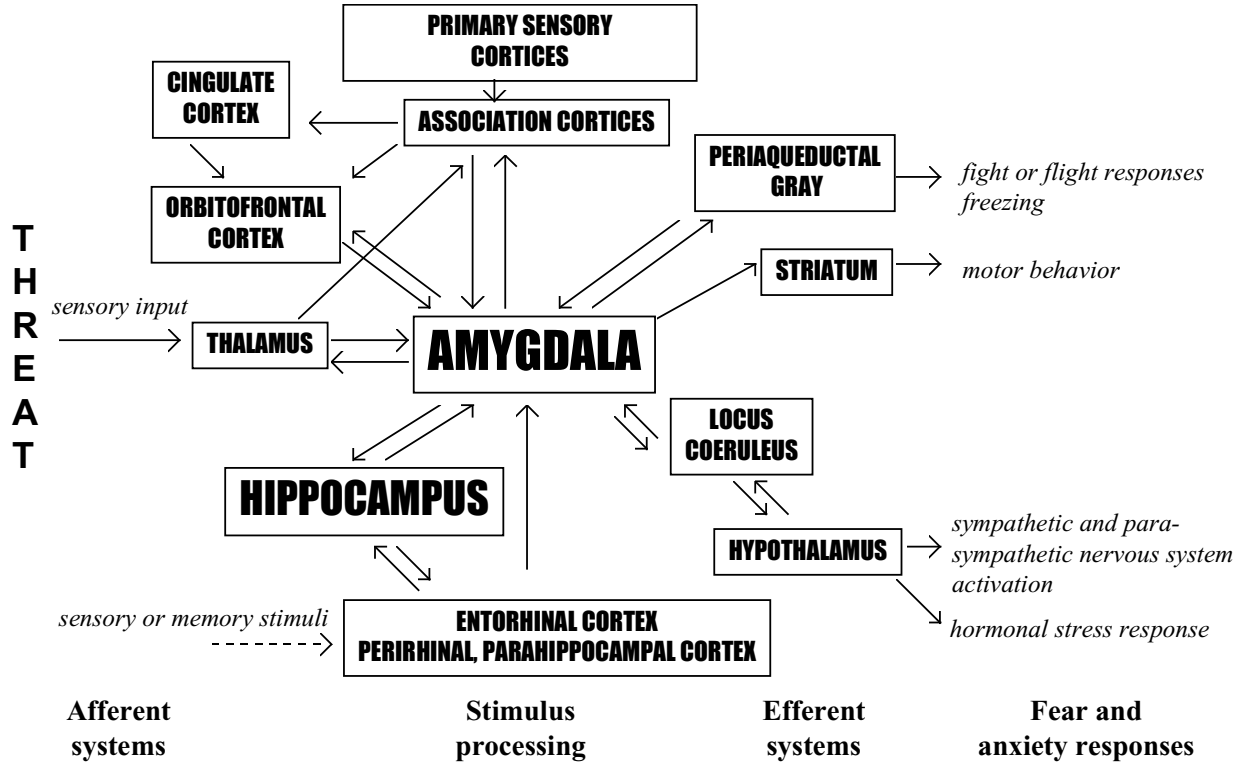

Figure 1. Brain regions mediating fear and anxiety. The figure is a modified version of a model previously presented by Charney and Deutch (1996).

The amygdala

With regard to animal studies, Heinrich Klüver and Paul Bucy reported in 1937 that lesions to the temporal lobe in rhesus monkeys yielded sedative effects such as exaggerated tameness and willingness to approach normally fear provoking stimuli (Klüver & Bucy, 1937). It was later demonstrated that the change in emotional behavior following such lesions could be attributed specifically to the defective amygdala (Weiskrantz, 1956). Several other lines of evidence also support that the amygdala plays a crucial role in fear and anxiety in animals. For instance, electrical stimulation of the amygdala can evoke fearful or defensive behavior as well as rage attacks (Kling & Brothers, 1992). Single-cell recordings indicate that neurons in the amygdala are sensitive to frightening and emotionally salient stimuli (Jacobs & McGinty, 1972; O'Keefe & Bouma, 1969). Moreover, fear conditioning paradigms have frequently been used to study the neural basis of emotional information processing. It is well documented that the amygdala is an important site for the mechanisms underlying increased startle reflex in the presence of a cue previously paired with an electric shock or aversive stimuli (Davis, 1992). Neuronal firing in the amygdala can also be altered when a neutral stimulus is paired with aversive stimulation (Applegate, Frysinger, Kapp, & Gallagher, 1982; Pascoe & Kapp, 1985; Umemoto & Olds, 1975) and studies have shown that injections of anxiolytic drugs into the amygdala affect behavioral correlates of conditioned anxiety (Scheel-Krüger & Petersen, 1982; Shibata, Kataoka, Gomita, & Ueki, 1982; Shibata, Yamashita, Yamamoto, Ozaki, & Ueki, 1989). LeDoux and coworkers (LeDoux, Romanski, & Xagoraris, 1989; LeDoux, Ruggiero, & Reis, 1985) have demonstrated that auditory and visual fear conditioning occurs in rats with lesions to the auditory and visual cortex, respectively. It has been suggested that the emotional learning process is mediated by

direct projections from the thalamus to the amygdala, bypassing cortical circuits. Interruption of the thalamo-amygdala connection as well as lesions of the amygdala itself have been reported to interfere with fear conditioning (Kim & Davis, 1993; LeDoux, 1996).

Also in humans there are many sources of evidence supporting that the amygdala is involved in fear or anxiety. In human patients with damage to the amygdaloid complex, impairments have been noted with regard to: fear conditioning (Bechara et al., 1995; LaBar, LeDoux, Spencer, & Phelps, 1995), startle reflex potentiation by aversive emotive stimuli (Angrilli et al., 1996); declarative memory for emotional material (Adolphs, Cahill, Schul, & Babinsky, 1997; Cahill, Babinsky, Markowitsch, & McGaugh, 1995; Markowitsch et al., 1994) as well as the recognition of fear in facial expressions (Adolphs, Tranel, Damasio, & Damasio, 1994; 1995; Adolphs et al., 1999; Broks et al., 1998; Calder et al., 1996; Sprengelmeyer et al., 1999; Young et al., 1995), verbatim material (Scott et al., 1997; Sprengelmeyer et al. 1999), and body postures (Sprengelmeyer et al., 1999). Evidence from sedative psychosurgery suggests that damage to the amygdaloid complex results in at least some loss or change of negative affect (Aggleton, 1992). Electrical stimulation of the amygdaloid complex in man has been reported to elicit symptoms of fear (Halgren, 1982). Similarly, fear seems to be the most common affect produced by temporal lobe epileptic discharge, which is associated with abnormal electrical activity in the amygdala (Gloor, 1992).

Neuroimaging is another source of evidence for amygdalar participation in fear. In the initial wave of brain mapping studies, amygdalar involvement was generally not observed during symptom provocation in patients with anxiety disorders (see reviews by Dager et al., 1996; Rauch & Shin, 1997). A number of recent studies, however, have noted amygdalar activation, e.g., in patients with posttraumatic stress disorder scanned during conditions that involved trauma reminders (Rauch et al., 1996; Shin et al., 1997) or perception of threat-related stimuli (Rauch et al., 2000). Provocative stimulation has also been reported to activate the amygdala in patients with obsessive-compulsive disorder (Breiter et al., 1996b). Furthermore, in brain mapping studies of healthy volunteers, amygdalar activation has been noted during anxiety induced by drugs such as cholecystokinin tetrapeptide [CCK-4] (Benkelfat et al., 1995) and procaine (Ketter et al., 1996; Servan-Schreiber, Perlstein, Cohen, & Mintun, 1998). Other emotionally relevant neuroimaging studies have shown that the amygdala is engaged in the perceptual processing of fearful facial expressions (Breiter et al., 1996a; Morris et al., 1996; 1998; Phillips et al. 1997; Whalen et al., 1998b), linguistic threat cues (Isenberg et al., 1999), aversive pictures (Irwin et al., 1996; Lane et al., 1997; Paradiso et al., 1999), aversive odor (Birbaumer et al., 1998; Zald & Pardo, 1997), and aversive gustatory (Zald, Lee, Fluegel, & Pardo, 1998) stimulation. Finally, consistent with the vast animal literature, a number of recent imaging studies suggest that the amygdala is involved in fear conditioning processes also in humans (Büchel, Dolan, Armony, & Friston, 1999; Büchel, Morris, Dolan & Friston, 1998; Furmark, Fischer, Wik, Larsson, & Fredrikson, 1997; LaBar, Gatenby, Gore, LeDoux & Phelps, 1998; Morris, Öhman, & Dolan, 1998; Schneider et al., 1999).

In summary, substantial evidence supports that the amygdala is fundamentally involved in fear and anxiety, both in animals and in humans. However, despite the huge body of research there is still some uncertainty about wether the amygdaloid complex truly is necessary for the production of negative emotions, as some lesion studies suggest that patients with amygdala damage exhibit normal reactions to affectively provocative stimulation and several neuroimaging studies report that emotionally alerting stimuli fail to activate the amygdala (Cahill, 1999). Recently, it has been argued that the amygdala is involved in threat detection, but mainly in

ambiguous situations (Whalen, 1998). Also, the exact role of the amygdala and its subnuclei in aversive memory formation is not clear. The amygdala may serve only time-limited modulatory functions in memory storage and may not be necessary for all types of fear acquisition (Cahill, 1999). Moreover, amygdalar functioning is probably not limited to the domain of emotions or to negative emotions only (Hamann, Ely, Grafton, & Kilts, 1999; Rolls, 1999).

The hippocampus

At least since the 1950's, the hippocampus has been of prime interest for studies of memory and cognition following the initial observations of H.M. - a well-studied patient who became severely amnesic after surgical removal of the hippocampal regions (Scoville & Milner, 1957). H.M. also appeared to have lost at least some capacity for anxiety (Gray & McNaughton, 1996). However, in the neuroscientific literature, cognitive functions such as episodic memory encoding and spatial analysis have generally been attributed to the hippocampus whereas emotive functions are often overlooked. Questioning the sharp distinction between cognition and emotion, Jeffrey Gray and colleagues have argued that the septo-hippocampal region is crucial for the behavioral inhibition system, which in turn mediates the condition of anxiety (Gray & McNaughton, 1996). The behavioral inhibition system is activated at times of risk assessment when the organism stops ongoing behavior and becomes attentive while bodily resources are mobilized in preparation for a quick behavioral response such as fight or flight. Anxiety may thus be thought of as excessive activity in the septo-hippocampal behavioral inhibition system. This notion receives support from animal studies suggesting that the behavioral changes caused by anxiolytic drugs are paralleled by patterns seen after lesions to this system (Gray & McNaughton, 1996).

Moreover, fear conditioning studies in animals have shown that the hippocampus (together with the rhinal cortex) participates in conditioning to fear contexts, but probably not in conditioning to specific fear cues (LeDoux, 1996). Phobic avoidance develops from learning which settings are dangerous, presumably involving contextual analyses at the hippocampal level (Gorman, Kent, Sullivan, & Coplan, 2000). Furthermore, when a fear or anxiety-inducing sensory stimulus is passed on through the thalamus into the temporal cortex, the hippocampus, and the amygdala, it is likely that appurtenant memory traces of anxious experiences are stimulated (Charney et al., 1998). Thus, the hippocampus is probably involved in the consolidation and retrieval of fearful memories, or at least certain aspects of such memories.

Also in neuroimaging studies of patients with anxiety disorders, the hippocampal and parahippocampal regions have been of fundamental interest ever since the pioneering imaging report on panic disorder by Reiman, Raichle, Butler, Herscovitch, and Robins (1984). In a recent positron emission tomography (PET) study, patients with panic disorder showed an increase in resting-state glucose metabolism in the left hippocampus and parahippocampal area, relative to healthy controls (Bisaga et al., 1998). A trait abnormality in this brain territory could be associated with vulnerability for misprocessing anxiety-provoking stimuli (Bisaga et al., 1998).

In summation, the hippocampus appears to play an important role in traumatic memory consolidation and retrieval, context-specific processing of anxiogenic information, behavioral inhibition, and the fluctuation of approach-avoidance behaviors during threat evaluation. The hippocampus projects to the amygdala and receives convergated inputs from sensory systems through projections from the "transition" cortex, i.e. the entorhinal, perirhinal, and parahippocampal cortical regions (LeDoux, 1996). It has been proposed that the hippocampal region, together with the amygdala and transition cortex, serve as an alarm center, cautioning the

individual to threatening exteroceptive stimulation (Reiman, 1997).

2.2.2 Serotonin and anxiety

In the brain, serotonin or 5-hydroxytryptamine (5-HT) is a neurotransmitter synthesized from L-tryptophan, which is an amino acid that primarily comes from the diet. The synthesis involves several steps. First, tryptophan is transformed to the serotonin precursor 5-hydroxytrypthophan (5-HTP) by means of the enzyme tryptophan hydroxylase. Another enzyme, 5-HTP-decarboxylase, then converts 5-HTP to 5-HT, i.e., to serotonin. Serotonin is eventually broken down into its synaptically inactive metabolite 5-hydroxyindoleacetic acid (5-HIAA). This process is catalyzed by yet another enzyme - monoamine oxidase. The cellbodies of serotonergic neurons are found in the brainstem raphe region, and there are two principal serotonergic pathways: (a) descending projections from the caudal raphe into the spinal cord and (b) ascending projections from the medial and dorsal raphe nuclei, which reach widespread areas of the central nervous system. Interestingly, the serotonergic innervation is particularly dense in medial temporal lobe regions including the amygdala and hippocampus (Jacobs & Azmitia, 1992). SSRIs block the reuptake of serotonin into the presynaptic nerve terminal, thereby increasing the concentration of serotonin in the synaptic cleft.

Although it is highly unlikely that complex emotional reactions like anxiety can be explained by deficiencies in just one neurotransmitter, there is substantial evidence that serotonin plays a pivotal role in the regulation of anxiety. This opinion is supported by numerous animal studies which have evaluated the effects of serotonergic drugs on various behavioral correlates to aversive emotional states (Handley, 1995). Also, initial clinical observations in human patients suggested anxiolytic effects of drugs acting upon serotonergic transmission in the brain, and this has now been demonstrated in controlled studies (c.f. Gorman & Kent, 1999). In the pharmacotherapy of anxiety disorders such as social phobia, the SSRIs have rapidly become the drug treatment of choice (Van Ameringen et al., 1999). It has also been speculated that behavioral therapy of anxiety disorders is effective due to a direct effect on the serotonergic system (Baer, 1996).

However, the specific functions of serotonin in anxiety regulation still remain to be clarified. For instance, it is not agreed whether serotonin increases or decreases anxiety. According to the classical theory, excessive 5-HT induces anxiety (while decreases are associated with impulsiveness and aggressiveness). This notion is mainly supported by earlier experimental studies in animals evaluating the effect of serotonergic drugs on punished behavior or approach/avoidance conflict situations, but these studies sometimes used anxiety models of questionable ecological validity (Graeff, Viana & Mora, 1997). While other studies conversely suggested an anxiolytic effect of 5-HT, the classic view was mainly challenged by the introduction of SSRIs, which are antidepressant and anti-anxiety medications that are widely held to enhance 5-HT neurotransmission (Graeff, Guimaraes, De Andrade, & Deakin, 1996). To reconcile the conflicting evidence regarding increases and decreases, Deakin and Graeff (1991) have suggested a dual role of 5-HT such that the ascending 5-HT pathway from the dorsal raphe to the amygdala and frontal cortex elevates conditioned fear, whereas 5-HT inhibits innate anxiety reactions in the periaqueductal gray region. Further exploration is needed to clear up this issue.

2.2.3 Brain mechanisms in anti-anxiety treatments

The neural effects of SSRIs

Given the uncertainties with regard to the way serotonin influences anxiety, the neural mechanisms underlying effective SSRI-treatment of anxiety are incompletely understood. In SSRI-treatment, there also appears to be some heterogeneity among clinical groups. For instance, SSRI-treatment of depression, panic disorder, and obsessive-compulsive disorder can vary in dose requirement, initial anxiogenic effects, response latency, and principal action on presynaptic or postsynaptic processes (Nutt et al., 1999). Gorman et al. (2000) argued that the conflicting results in research on 5-HT and anxiety could be better understood after a more refined analysis of the pathways participating in serotonergic neurotransmission. First, projections of 5-HT neurons to the locus coeruleus are inhibitory, such that increased activation of the serotonergic neurons in the raphe attenuate noradrenergic neurons in the locus coeruleus, with resultant decreases in cardiovascular or autonomic symptoms of anxiety. Second, as previously noted by Deakin and Graeff (1991), defensive or escape reactions are mitigated by inhibitory projections of the raphe neurons to the periaqueductal gray region. Third, increasing levels of serotonin may diminish the hormonal stress response by preventing the hypothalamic release of corticotropin-releasing factor (CRF). Thus, SSRIs may act by diminishing arousal at the locus coeruleus level, defense/escape behaviors at the periaqueductal gray level, and concentrations of anxiety provoking CRF at the hypothalamic level (Gorman et al., 2000). Also, some preliminary evidence suggests that increasing levels of serotonin may inhibit cortical and thalamic inputs from activating the amygdala itself (Gorman et al., 2000).

Different or common brain mechanisms in pharmacotherapy versus psychotherapy?

Because it is poorly understood how successful treatment of anxiety disorders relates to concomitant changes in brain activity in the first place, it is not known whether efficacious drug treatment and psychotherapy engage similar or different neurofunctional networks. In an early article, Gorman, Liebowitz, Fyer, and Stein (1989) hypothesized that anti-panic medications work "bottom-up" through stabilization of unstable brain stem nuclei, and that cognitive-behavioral therapy works "top-down" through modification of dysfunctional cognitions, presumably involving the prefrontal cortex. However, the rationale for behavioral treatment of anxiety is based largely on classical fear conditioning theories (Craske & Rowe, 1997). Recall that numerous animal studies indicate that fear conditioning processes are crucially dependent on subcortical structures such as the amygdala and hippocampus (LeDoux, 1996). It has also been observed in animals that anxiolytic effects can be achieved by injections of benzodiazepines directly into the amygdaloid complex (Scheel-Krüger & Petersen, 1982; Shibata et al., 1982; 1989) and that the effects of anxiolytic drug administration are paralleled by lesions to the hippocampus (c.f. Gray & McNaughton, 1996). The amygdala and hippocampus may be important targets not only for traditional anxiolytic drugs but possibly also for successful psychological treatments and second-generation (e.g., SSRI) pharmacotherapy.

Revising their early theory, Gorman and colleagues (2000) recently suggested that SSRI-medications may reduce anxiety by attenuating the activity of the amygdala, thereby disrupting its potential to stimulate projection sites downstream, e.g. in hypothalamic and brain stem regions. Psychotherapies might exert their effects upstream from the amygdala. Cognitive biases and abnormal emotional reactions may be modified by enhancing the capacity of the medial prefrontal cortex to inhibit the amygdala. Reduction of avoidance behaviors may stem from

"deconditioning" of fear originally learned at the level of the hippocampus, as suggested by studies of contextual fear conditioning in animals. (Gorman et al., 2000). Gray and McNaughton (1996) have suggested that behavior therapy is beneficial because it allows systematic habituation of the septo-hippocampal response to anxiety-provoking stimuli. Also, it can probably not be excluded that cognitive-behavior therapy has a direct action in the amygdala. Alternatively, while it is possible that anti-anxiety treatments intervene directly in abnormally functioning brain regions (e.g., the amygdala), it is equally possible that they compensate for abnormality by influencing other areas in the brain (Reiman, 1997).

Various underlying mechanisms have previously been discussed in the psychotherapy literature. For instance, cognitive theories of anxiety reduction have stressed the importance of processes such as improved self-efficacy (Bandura, 1977) or increased accuracy of fear estimations (Rachman, 1994). Presumably the cognitive mechanisms engage frontal or more wide-spread parts of the neocortex that participate in conscious awareness. Behavioral theories of anxiety reduction have, in addition, suggested that therapy may act by habituation, extinction, or other emotional processing mechanisms (Craske & Rowe, 1997), which probably rely more on subcortical structures like the amygdala. Conceivably, the different components in treatment packages, such as exposure and cognitive restructuring, could differ with regard to principal sites of action in the afferent arm, in the intermediate stimulus processing chain, or in the efferent arm of the anxiety model outlined in Figure 1.

Also, with regard SSRI-treatment it has been suggested that, in addition to the direct drug effect, SSRIs could work indirectly through "psychological" processes (Hayward & Wardle, 1997). Neurochemical changes caused by the drug might modify the individual's experience of anxiety. Exposure to anxiogenic situations is then increasingly tolerated and the individual may habituate, or alternatively, learn new approach behaviors and form success-memories that compete with fear reactions as suggested by the extinction and emotional processing theories (Hayward & Wardle, 1997). At the time of market introduction, it was proposed that the SSRIs acted by "toughening" the individual, making him/her less sensitive to stressful events (Kramer, 1993). Presumably, this corresponds to less sensitive fear circuits in the brain, which could in theory be equally achieved by psychological treatments.

Neuroimaging studies

While there are informed speculations about brain mechanisms in anti-anxiety treatments, as outlined above, modern neuroimaging techniques provide the means to put these speculations under scientific scrutiny. Not only could neuroimaging, employed before and after treatment, be very helpful in unraveling the mechanisms underlying anxiety reduction. Such studies could also identify prognostic and prescriptive factors associated with different therapies. Ultimately, imaging studies could facilitate the development of treatment components that are directly tailored to intervene with the underlying pathophysiology.

Despite their potential, brain imaging tools have quite seldom been used in psychiatric treatment studies. However, in a landmark PET-study, Baxter et al. (1992) reported that both behavior therapy and fluoxetine reduced resting glucose metabolism in the right caudate nucleus in patients with obsessive-compulsive disorder (OCD). The behavioral therapy results were later replicated by Schwartz, Stoessel, Baxter, Martin, and Phelps (1996), and treatment response could also be predicted from initial metabolism in the orbitofrontal cortex (Brody et al., 1998). Neural changes following pharmacotherapy of OCD have been investigated by several other

groups (e.g., Baxter et al., 1987; Hoehn-Saric, Perlson, Harris, Machlin, & Camargo, 1991; Molina et al., 1995; Perani et al., 1995; Rubin, Ananth, Villanueva-Meyer, Trajmar, & Mena, 1995; Rubin et al., 1995; Swedo et al., 1992). Imaging reports on treatment for other anxiety disorders are surprisingly few and methodologically heterogeneous, but include studies of benzodiazepines in generalized anxiety (Buchsbaum et al., 1987; Mathew & Wilson, 1991; Wu et al., 1991) and specific phobia (Fredrikson, Wik, Annas, Ericson, & Stone-Elander, 1995), tricyclic antidepressants in panic disorder (Nordahl et al., 1998), and eye movement desensitization in posttraumatic stress disorder (Levin, Lazrove, & van der Kolk, 1999). A consistent pattern of brain regions mediating anxiety reduction does not emerge because findings are mixed and sometimes negative. Also in depression, some studies report that treatment normalizes abnormal resting-state glucose hypometabolism, often initially seen in the prefrontal cortex, while others suggest that metabolic hypoactivity persists after successful therapy, thus constituting a trait rather than a state marker (Kumar, 1997; Trivedi & Husain, 1997). It should be noted that nearly all neuroimaging treatment studies on negative affect have evaluated changes in the resting-state only. While such studies are informative, activation studies exploring the effects of treatment on provoked anxiety conditions also need to be performed.

2.2.4 Neurobiological studies of social phobia

Serotonin and social phobia

As mentioned, social phobics respond favorably to medications that act upon serotonergic neurotransmission in the brain (Van Ameringen et al., 1999) and some data also imply that SSRIs may increase sociability in normal healthy volunteers (Knutson et al., 1998). Moreover, it has been observed that, relative to controls, social phobics have a greater cortisol response to the serotonin-releasing compound fenfluramine, possibly indicating supersensitivity of the post-synaptic 5-HT receptors (Tancer, 1993). Also, serotonin drugs may facilitate the achievement of social dominance in vervet monkeys (Raleigh, McGuire, Brammer, Pollack, & Yuwiler, 1991). Taken together, these data suggest that serotonin is somehow involved in the pathophysiology of social phobia. However, the complexity of this issue is illustrated by the fact that social phobics may respond with increasing anxiety to fenfluramine or meta-chlorophenylpiperazine challenges, which increase serotonin concentration (Nutt, Bell, & Malizia, 1998), whereas decreasing levels of public speaking anxiety following oral fenfluramine administration have been observed in healthy volunteers (Graeff et al., 1996). Thus, the exact role of the serotonin system in social phobia (and other anxiety disorders) remains to be elucidated.

Neuroimaging: Studies of social anxiety provocation

Functional neuroimaging techniques such as PET have only recently been applied to study states of social anxiety. Using ^{15}O-water PET, Reiman (1997) studied social phobics singing the alphabet song either alone or under observed conditions. Evaluative anxiety was associated with significantly increased regional cerebral blood flow (rCBF) in the thalamus, midbrain, and the lateral prefrontal, midcingulate, sensorimotor, and anterior temporal cortices. Trends for significance were observed in the amygdala, hippocampus, hypothalamus, and cerebellum as well as in the medial prefrontal and anterior cingulate cortices. In other PET-studies, social anxiety has been associated with rCBF-redistribution in the right dorsolateral prefrontal and the left parietal areas (Bell, Malizia, & Nutt, 1999) and also in the visual and medial frontal cortices (van Ameringen et al., 1998). It should be emphasized that all these studies (Reiman, 1997; Bell et al.,

1999; van Ameringen et al., 1998) report preliminary data only. In a recently completed PET-study (Tillfors et al., submitted) our group observed that the neural response (indexed by rCBF) to public speaking, relative to speaking alone, differed between social phobics and healthy controls. Relative to controls, neuronal activity was more elevated in phobics in the amygdaloid complex, while rCBF increased less in the retrosplenial, parietal, and secondary visual cortices and decreased more in the orbitofrontal, insular, and temporal pole cortical areas.

Neuroimaging: Treatment studies

Previous studies exploring treatment effects on provoked social anxiety states are lacking. However, Van der Linden et al. (2000) recently reported results from single photon emission computed tomography assessments before and after eight weeks of SSRI (citalopram) treatment. Results suggested that pharmacotherapy reduced resting-state neuronal activity in the left-sided temporal, mid frontal and cingulate cortices whereas increases were noted in occipital regions bilaterally, but the findings did not survive correction for multiple comparisons.

Neuroimaging: Other studies

To date, neuroimaging research in social phobia also encompass studies of brain structural volume (Potts, Davidson, Krishnan, & Doraiswamy, 1994), dopaminergic function (Schneier et al., 2000; Tiihonen et al., 1997), resting metabolic activity (Davidson et al., 1993b; Stein & Leslie, 1996; Tupler et al., 1997), electroencephalograms during anticipatory anxiety (Davidson, Marshall, Tomarken, & Henriques, 2000), and brain perfusion during unpleasant emotional perception (Birbaumer et al., 1998) and aversive conditioning processes (Schneider et al., 1999). This type of research has only begun and more studies are needed to delineate brain dysfunctions that are specific for social phobia.

Other approaches

Outside the field of neuroimaging, neurobiologically oriented studies of social phobia include examinations of psychoactive drug effects, genetic contributions, neuroendocrine imbalances as well as psychophysiological, biochemical, and behavioral responses to various stressful challenges (see reviews by Bell et al., 1999; Miner & Davidson, 1995; Nickell & Uhde, 1995; Nutt et al., 1998; Potts, Book & Davidson, 1996; Stein, 1998). While many of the findings are intriguing, much work remains to be done before a clear and consistent picture of specific neurobiological abnormalities in social phobia emerges.

3. THE EMPIRICAL STUDIES

3.1 Empirical studies on the epidemiology and subtypes of social phobia

3.1.1 Study I

Social phobia in the general population: prevalence and sociodemographic profile

Aim and background

The first study sought to determine the point prevalence and demographic characteristics of social phobia in the Swedish general population. A mailed questionnaire assessing anxiety in multiple

performance and interactional situations was used to identify cases of social phobia, reveal demographic features, and to yield frequency estimates of social fears in the general community. The study was motivated for several reasons. Prevalence estimates of social phobia are important in the planning of mental health interventions, and Scandinavian studies on this topic are lacking. The majority of epidemiological studies have used out-dated (i.e. DSM-III) diagnostic criteria whereas studies using modern DSM-IV definitions of social phobia are rare. Also, previous studies have generally used few situational probes, which inflates the risk of missing cases. Some demographic/descriptive characteristics have shown inconsistent results across studies whereas other variables such as urbanicity, immigration, birth order, and social support are understudied. Finally, data on the distribution of social fears in the normal population are scarce.

Method

A questionnaire hereafter referred to as "the Social Phobia Screening Questionnaire" (SPSQ) was constructed by the authors in a consensus process and then mailed to a large general population sample. The SPSQ assessed the level of social distress in 14 potentially phobic situations. Each situation was rated on a 0-4 (min-max) distress scale yielding a total distress score of 0-56 for each individual. The situational questions served partly to yield prevalence estimates of social fears independent of social phobia, and partly to determine whether "marked distress" as defined in the DSM-IV criteria was a fulfilled condition. Presence of social phobia was further determined by means of diagnostic true/false questions covering criteria A-D in DSM-IV. Each question/criterion was formulated as a statement, e.g. "in the following situation(s) I always become very nervous", which was followed by the list of the 14 situations. Subjects could tick a box corresponding to a social situation or choose "none of the above situations". The question covering the E-criterion concerned impairment in three different life domains (occupational/academic, leisure time, or social activities). Thus, the level of impairment endorsed by the individual could vary between 0-3 (min-max).

The *a priori* definition used to define cases of social phobia was as follows: (a) distress rating of ≥ 3 on at least one of the 14 potentially phobic situations, (b) this situation had to be consistently endorsed in the subsequent diagnostic questions assessing criteria A-D, and (c) the subject had to admit impairment or marked distress due to social anxiety in at least one of the three life domains assessed by the E-criterion question. Prevalence of social phobia was also estimated across different cut-off levels, i.e. varying degrees of distress and impairment used in conjunction with the diagnostic questions. Point prevalence was chosen over other estimates in order to avoid reliability problems associated with recall over longer time periods. The SPSQ also included a section assessing demographic characteristics and family history of excessive social anxiety. A final section assessed avoidant personality disorder with diagnostic questions extracted, with permission, from the DSM-IV and ICD-10 Personality Disorder Questionnaire; DIP-Q (Ottosson et al., 1998).

In a preliminary psychometric evaluation, the SPSQ correctly classified all 35 cases and 19 of 20 non-cases in a reference sample interviewed with the structured clinical interview for axis I disorders (SCID; First et al., 1998). The alpha coefficient for the 14-item social distress scale was 0.90 and it correlated highly with the Social Phobia Scale ($r = 0.77$, $p<0.0001$) and the Social Interaction Anxiety Scale ($r = 0.79$, $p<0.0001$), which are established clinical measures (Mattick & Clarke, 1998). This indicated that the measures of sensitivity (100%), specificity (95%), homogeneity, and concurrent validity were satisfactory.

The SPSQ was mailed to 2000 adults (1000 male/female, aged 18-70) randomly selected from a population based registry (Enator). Subjects were selected from the greater Stockholm area or the island of Gotland in equal proportion (1000/each). These regions were chosen in order to evaluate urban-rural differences. The Gotland sample was also selected from three different urban-rural regions. Questionnaires were filled out anonymously. After reminders, interpretable questionnaires were obtained from 1202 respondents, i.e. 60.1% (541 men, 661 women; mean age= 41.8, *SD*=14.1; 621 from Stockholm and 581 from Gotland).

Table 2. The prevalence of social phobia assessed with diagnostic (DSM-IV) questions and varying levels of social distress and functional impairment. No. 4 was the a priori chosen cut-off level.

Cut-off level	Prevalence *n* (%)
1) Diagnostic questions; impairment ≥ 1 domain	245 (20.4)
2) Diagnostic questions; impairment ≥ 2 domains	91 (7.6)
3) Diagnostic questions; impairment = 3 domains	34 (2.8)
4) Diagnostic questions; distress rating ≥ 3; impairment ≥ 1 domain	*188 (15.6)*
5) Diagnostic questions; distress rating ≥ 3; impairment ≥ 2 domains	84 (7.0)
6) Diagnostic questions; distress rating ≥ 3; impairment = 3 domains	31 (2.6)
7) Diagnostic questions; distress rating = 4; impairment ≥ 1 domain	90 (7.5)
8) Diagnostic questions; distress rating = 4; impairment ≥ 2 domains	51 (4.2)
9) Diagnostic questions; distress rating = 4; impairment = 3 domains	23 (1.9)

Main results

The point prevalence of social phobia was estimated at 15.6% (95% confidence interval: 13.5-17.6%) using the *a priori* definition, but prevalence rates varied between 1.9-20.4% across the different levels of distress and impairment used to define cases (see Table 2). Eighty-eight (14.2%) individuals in the Stockholm sample and 100 (17.2%) Gotlanders met the criteria for social phobia. There were no significant differences in prevalence rates between the Stockholm and Gotland samples ($\chi^2 = 2.1$, $df = 1$, n.s.), nor between different Gotland urban/rural regions ($\chi^2 = 4.6$, $df = 2$, n.s.). Public speaking was the most common social fear both in social phobics (77.1%) and in the entire sample (24.0%) - see Table 3. In comparison with non-phobic individuals, social phobia was associated with female gender ($\chi^2 = 8.8$, $df = 1$, $p<0.005$), low educational attainment ($\chi^2 = 11.3$, $df = 2$, $p<0.005$), psychotropic medication use ($\chi^2 = 20.1$, df = 1, $p<0.0001$), lack of social support ($\chi^2 = 29.2$, $df = 1$, $p<0.0001$), and younger age ($\chi^2 = 7.7$, $df = 2$, $p<0.05$), although the latter finding did not survive Bonferroni-correction. An attrition analysis based on telephone interviews revealed that 12 of 80 (12.5%) contacted nonresponders met the impairment criterion, which was significantly fewer than among questionnaire responders ($\chi^2 = 9.1$, $df = 1$, $p<0.005$).

Conclusions

It was observed that social phobia was a highly common disorder, with an estimated point prevalence of 15.6% although this estimate was highly sensitive to variations in the diagnostic cut-off level used. The results are consistent with previous studies showing that: (a) the use of modern diagnostic criteria (DSM-III-R or DSM-IV) usually yields considerably higher prevalence rates than the older DSM-III studies, (b) prevalence rates may vary dramatically across different

diagnostic thresholds, e.g., the required level of impairment and distress, (c) public speaking is by far the most prevalent social fear, and (d) in the general population social phobia is more common in women than in men and also in those with lower educational levels, whereas urbanicity appears to have relatively little impact. It can be concluded that social anxiety is a distressing problem for a substantial proportion of the general population although the exact diagnostic boundaries for social phobia are difficult to determine.

Table 3. The prevalence of social fears, i.e. the proportion of individuals that rated the potentially phobic situation as ≥ 3 on a 0-4 social distress scale.

Situation	Prevalence *n* (%)		
	Social phobia	No phobia	Total
1. Speaking (or performing) in front of a group of people	145 (77.1)	143 (14.1)	288 (24.0)
2. Being addressed in a group of people	47 (25.0)	26 (2.6)	73 (6.1)
3. Maintaining a conversation with someone unfamiliar	44 (23.4)	43 (4.2)	87 (7.2)
4. Writing in front of others	42 (22.3)	54 (5.3)	96 (8.0)
5. Expressing opinions in front of others	41 (21.8)	27 (2.7)	68 (5.7)
6. Eating/drinking in public	36 (19.1)	22 (2.2)	58 (4.8)
7. Being alone with someone unfamiliar	30 (16.0)	20 (2.0)	50 (4.2)
8. Making a phone call to someone unfamiliar	29 (15.4)	30 (3.0)	59 (4.9)
9. Using public lavatories	28 (15.0)	106 (10.5)	134 (11.1)
10. Attending a party (or a social gathering)	27 (14.4)	13 (1.3)	40 (3.3)
11. Entering a room in which unfamiliar people are seated	25 (13.3)	17 (1.7)	42 (3.5)
12. Initiating a conversation with someone unfamiliar	24 (12.8)	17 (1.7)	41 (3.4)
13. Dealing with authority figures (e.g. a boss or a teacher)	23 (12.2)	13 (1.3)	36 (3.0)
14. Interacting with colleagues during coffee- or lunchbreaks	11 (5.9)	8 (0.8)	19 (1.6)

3.1.2 Study II

Social phobia subtypes in the general population revealed by cluster analysis

Aim and background

The aim of the second study was to explore the point prevalence and descriptive characteristics of empirically derived social phobia subgroups in the general population. A fundamental problem with earlier studies on social phobia subtypes is that these tend to use *a priori* definitions based on subjective clinical observations or theoretical speculation. Studies examining subtypes could benefit from using data-driven and exploratory classification methods, such as cluster analysis, to delineate subtype formations empirically. Empirical definitions of social phobia subtypes are needed to improve diagnostics. Moreover, partly reflecting the diagnostic uncertainties, little is known about the prevalence of social phobia subgroups in the general population. Accurate determinations of subtypes could have implications for the therapy and prevention of social phobia as subtypes may differ with regard to treatment outcome and etiology.

Method

The epidemiological method was the same as in study I. Briefly, the SPSQ was used to identify cases of social phobia in the Swedish general community. To reveal subtypes, symptomatology data were extracted from the 188 identified social phobics and entered into a hierarchical cluster

analysis. This is a multivariate data-reduction technique that groups individuals based on the characteristics they possess (Hair, Anderson, Tatham, & Black, 1995). The cluster analysis was based on Ward's method and squared Euclidean distances (Hair et al., 1995). The cluster variate consisted of the following four variables: (a) distress ratings of the 14 phobic situations (range 0-56), (b) number of phobic situations rated as ≥3 on the distress scale (range 0-14), (c) level of functional impairment, i.e. the number of impaired life domains endorsed on the E-criterion question (range 0-3), and (d) number of criteria fulfilled for avoidant personality disorder (range 0-7), assessed with questions extracted from the DIP-Q (Ottosson et al., 1998). Subtypes have previously been suggested to differ on these characteristics (c.f. Rapee, 1995). Standardization in *Z*-scores was performed prior to cluster analysis.

To establish initial clusters, the percentage change in agglomeration coefficients was evaluated for solutions of two to ten clusters and a scree plot was used to detect a point of inflection (Hair et al., 1995). To decide the optimal number of clusters, the initial results were evaluated against criteria suggested by Bergman (1998), e.g., the accepted solution must be meaningful, theoretically interpretable, and the explained error sum of squares must be satisfactory. Criterion validity was evaluated by comparing clusters on the Social Phobia Scale (SPS) and the Social Interaction Anxiety Scale (SIAS) (Mattick & Clarke, 1998). Finally, profile analyses were performed in which clusters were compared on a set of sociodemographic and descriptive variables.

Main results

Three clusters emerged, consisting of social phobics scoring either high, intermediate, or low on all variables (see Figure 2). In accordance with terminology previously used in the social phobia literature these clusters were labeled generalized, nongeneralized, and discrete social phobia. However, clusters also conformed to a severe, moderate, and mild subtype. Point prevalence rates were 2.0%, 5.9%, and 7.7% respectively. The explained error sum of squares in the three-cluster solution was 69.4%. This was above the level of 67% suggested to reflect homogenous clusters (Bergman, 1998). In addition, the hierarchical three-cluster solution was compared to an iterative, nonhierarchical cluster analysis (*k*-means clustering, Hair et al., 1995) with three clusters specified in the analysis. This yielded a kappa of 0.79 and an 87.2% agreement between the two methods, suggesting that clusters were robust. All subtypes were differentiated both on the SPS and the SIAS, indicating satisfactory criterion validity. The profile analyses revealed that generalized or severe social phobia tended to be overrepresented among individuals with low levels of educational attainment and social support. Public speaking was the most common fear in all subgroups.

Conclusions

By and large, the obtained cluster solution matched the categorical three-part subtype organization previously proposed by Heimberg and coworkers (c.f. Heimberg et al., 1993a) consisting of generalized, nongeneralized, and discrete social phobia. The discrete subtype, which was dominated by public speaking phobics, was the most prevalent (7.7%), followed by the nongeneralized (5.9%), and generalized (2.0%) social phobia. However, although categorical definitions could be used, the most parsimonious interpretation of the results is that social phobia subtypes in the general population mainly differ dimensionally along a mild-moderate-severe continuum, and that the number of cases declines with increasing severity.

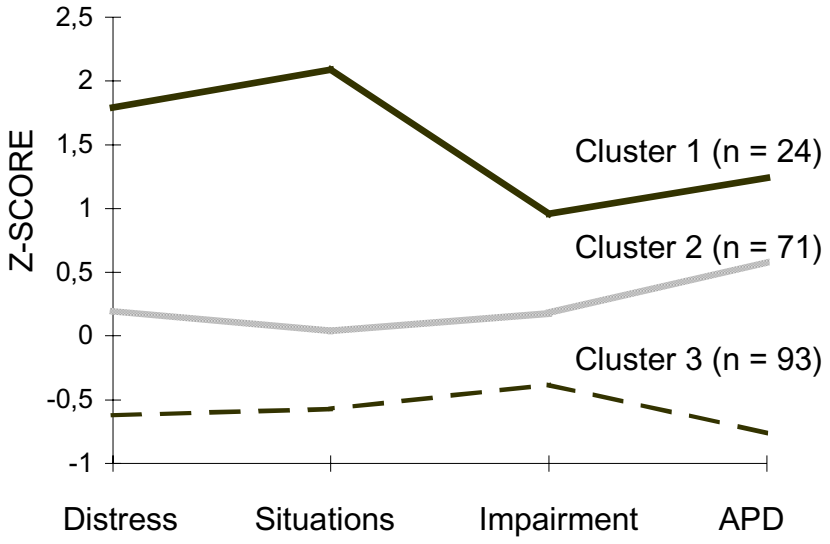

Figure 2. Cluster profiles revealed by a hierarchical cluster analysis. Three clusters , i.e. subtypes of social phobia, were obtained either with high (top line), intermediate (middle line), or low *Z*-scores (bottom line) on four variables assessed. These were: social distress ratings, number of feared situations, level of functional impairment, and number of criteria fulfilled for avoidant personality disorder (APD).

3.2 Empirical studies on brain function in social phobia

3.2.1. Study III

Presynaptic serotonin imaging in social phobia using [^{11}C]-5-hydroxy-L-tryptophan and positron emission tomography

Aim and background

Although fenfluramine challenge studies, as well as the reported efficacy of serotonin uptake blockers indicate that serotonin is involved in the regulation of social anxiety, detailed knowledge of how serotonergic imbalances contribute to the pathophysiology of social phobia and other anxiety disorders is lacking. Parallel advances in radiochemistry and neuroimaging methodologies have made it possible to study brain serotonin metabolism in human subjects. Thus, the aim of the third study was to examine cerebral radioactivity uptake derived from radiolabeled 5-hydroxytryptophan (5-HTP), i.e. the precursor to serotonin synthesis, in social phobics compared with healthy controls using PET.

Method

Eighteen (10 male/8 female, mean age = 35.2, range = 23-46 years) previously untreated patients with DSM-IV social phobia and an equal number healthy controls, similar in gender and age, were recruited by means of newspapers advertisements. Following a brief telephone interview, subsequent screening included self-report questionnaires, structured clinical (SCID) interviews

(First et al., 1998), and a public speaking test. Criteria for exclusion were: current psychiatric disorder (other than social phobia) or organic brain disorder, somatic disease, chronic use of prescribed medication, abuse of alcohol/narcotics, left-handedness, and pregnancy.

All subjects underwent PET-assessments using the radiotracer [β-^{11}C]-5-HTP. In rats, this tracer has by 75% been converted to ^{11}C-5-HIAA, the metabolite of serotonin, 40 minutes after administration (Lindner et al., 1997). Patients and controls were matched with regard to local time during scanning. All subjects refrained from tobacco, alcohol, and caffeine 12 hours, and from food (but not water) 5 hours before scanning. PET-scans were performed with a GEMS PC2048-15B eight-ring scanner with a 10 cm axial field of view and an axial/transaxial resolution of approximately 6 mm. An average [β-^{11}C]-5-HTP image, consisting of the time frames from 15-60 minutes, was made. The image from the [β-^{11}C]-5-HTP scan was automatically aligned to a $H_2{}^{15}O$ scan. This was performed in addition to the [β-^{11}C]-5-HTP scan to obtain a scan with full axial coverage of the brain to be used for stereotactical normalization. All individual [β-^{11}C]-5-HTP images were anatomically normalized in the standard Greitz brain atlas (Greitz, Bohm, Holte, & Eriksson, 1991).

PET-data were filtered with a 12 mm Gaussian filter and then analyzed using a blocked ANOVA design implemented as a multiple linear regression (Friston et al., 1995). Changes in regional normalized [β-^{11}C]-5-HTP derived uptake between patients and controls were evaluated using the spatial extent of connected clusters of voxels with a *Z*-score above 1.96 ($p<0.05$) (Friston, Worsley, Frackowiak, Mazziotta, & Evans, 1994). In addition, data on [β-^{11}C]-5-HTP derived uptake were also evaluated using principal component analysis (PCA) (c.f. Andersson et al., 1998).

Main results

The pixel-wise linear regression analysis revealed region specific group differences (omnibus $p<0.000001$) between social phobics and healthy controls with regard to [β-^{11}C]-5-HTP derived uptake. Patients exhibited significantly ($p<0.05$) lower uptake relative to controls bilaterally in the medial temporal cortex including the periamygdaloid, entorhinal, and perirhinal regions (Brodmann areas [BA] 34/36) as well as the left inferior temporal gyrus (BA 21). Borderline significant trends ($p=0.057$-0.068) for lowered uptake among social phobics were noted in the left anterior cingulate cortex (BA 25/33), right insula (BA 13/14), and the inferior frontal cortex (BA 47) bilaterally. Social phobics showed elevated uptake, compared to controls, in the bilateral cerebellum. In the PCA, principal components one [$F(1,34) = 7.2$; $p<0.05$] and three [$F(1,34) = 4.2$; $p<0.05$] suggested social phobia-related processes (negative loadings being associated with social phobia) which explained 18.0% and 8.0% of the variance respectively. The neural networks revealed by the PCA suggested lowered [β-^{11}C]-5-HTP derived uptake in social phobics in regions overlapping with those implicated by the subtractive analysis but also in the basal ganglia, periaqueductal gray and more widespread areas of the neocortex.

Conclusions

Social phobics, as compared to healthy individuals, were mainly characterized by attenuated [β-^{11}C]-5-HTP derived uptake in limbic/paralimbic brain regions, including the periamygdaloid and rhinal cortices, suggesting suppressed serotonergic synthesis rate in neural pathways that are

involved in the regulation of fear/anxiety. These findings are consistent with the hypothesis that serotonergic imbalances make substantial contributions to the pathophysiology of social phobia.

3.2.2 Study IV

A common neural pathway for serotonergic drug therapy and cognitive-behavioral treatment of social anxiety

Aim and background

The neurofunctional networks mediating anxiety reduction are incompletely understood, as brain mapping studies on anti-anxiety treatments are few. While a small number of resting-state studies have been performed, activation studies evaluating treatment effects on provoked anxiety conditions have been neglected in neuroimaging. Also, systematic comparisons of pharmacological and psychological treatments are lacking. Hence, it is unknown whether effective psychotherapy and pharmacotherapy of excessive anxiety engage common or different neural pathways. Also, it is not known whether changes in brain activity can predict long-term treatment outcome. The fourth study sought to address these issues by examining the effects of cognitive-behavioral therapy and SSRI-treatment on regional cerebral blood flow, measured with PET, during provoked anxiety in patients with social phobia.

Method

Eighteen (10 male/8 female, mean age = 35.2, range = 23-46 years) previously untreated DSM-IV social phobics with marked publics speaking fears were recruited by means of newspaper advertisements. Screening included self-report questionnaires, structured clinical (SCID) interviews (First et al., 1998), and a public speaking test. Informed consent was obtained. By the use of PET and ^{15}O-labeled water, rCBF was first measured at pretreatment while patients performed a 2.5 minute speech (about a travel experience or vacation) in the presence of a silently observing audience of 6-8 persons. To heighten observational anxiety the speech was recorded from a close distance with a portable videocamera. Patients were matched for severity, sex, and age in triplets, and then randomized to nine weeks of SSRI-medication, cognitive-behavioral group therapy (CBGT), or a waiting list (WL) control group with six patients in each study group. There were three generalized and three nongeneralized social phobics in each group. The SSRI-group was treated with citalopram with a 40 mg (*SD*=9.8) daily mean dosage. Patients came for check-ups at week two, four, and seven. CBGT incorporated simulated exposures to feared situations (with a focus on public speaking), cognitive restructuring, and homework assignments following principles developed by Heimberg and coworkers (c.f. Hope & Heimberg, 1993). All patients were scanned again after the nine-week treatment/waiting period. WL-subjects were thereafter treated with citalopram.

Treatment outcome was evaluated by use of public speaking state anxiety measures, i.e. the patient's subjective ratings of fear and distress on a 0-100 (min-max) scale and the Spielberger state-anxiety inventory (STAI-S) administered immediately after each scanned speech. Heart rate in beats per minute was also recorded during scans. In addition, patients completed a standard battery of social anxiety questionnaires (the SPS, SIAS, SPSQ, PRCS and GAF-scales; see study I, Bodlund, Kullgren, Ekselius, Lindström, & von Knorring, 1994; Clark et al., 1997) before, after, and one year after treatment. Patients improving ≥1 *SD* from the pretreatment mean value on 7-9 outcome variables were labeled "much improved", 4-6 variables

"moderately improved", and 0-3 variables "unimproved". Patients that were at least moderately improved were considered to be responders.

PET-data were obtained by means of previously validated methods. An eight-ring brain PET scanner (GEMS PC2048-15B) with a 10 cm axial field of view and an axial/transaxial resolution of approximately 6 mm was used. Tracer injections, 700-1300 MBq of $H_2{}^{15}O$ dissolved in 3-4 ml of water, i.e. approximately 15 MBq/kg body weight, were performed at twelve-minute intervals. PET-data were collected in fifteen 10-sec frames during 150 sec. PET-data were normalized for global flow using linear scaling. Individual rCBF-images were anatomically normalized in the standard Greitz brain atlas (Greitz et al., 1991). To improve signal-to-noise ratio patients spoke twice in front of the audience and image data were averaged across the two scans into mean images to be compatible with a random-effect model. Blocked ANOVAs, based on general linear regression (Friston et al., 1995), were used for statistical analyses. Local changes were evaluated using the spatial extent of connected clusters of voxels with a *Z*-score above 2.6 (Friston et al., 1994). Mean voxel values for each subject and condition were also extracted for ROI (region of interest) analyses, with ROIs being anatomically predefined in the computerized brain atlas (Greitz et al., 1991).

Main results

There were no significant multivariate or univariate differences between groups with regard to outcome measures before treatment. Paired *t*-tests revealed that both the SSRI and CBGT-groups improved significantly [$t(5)$ 2.2-5.9, p = 0.002-0.04] from pre to post treatment on most outcome variables whereas WL-subjects did not change on any measure [$t(5)$ = 0.1-2.0; p = 0.10-0.89]. Separate ANOVAs also indicated that treated subjects improved more than controls as significant [$F(1,16)$= 4.9-6.9, $p<0.05$] group × time interactions were noted on three social anxiety questionnaires (the SPS, PRCS, and GAF-scales), and follow-up Fisher's LSD-tests showed that the treated subjects (merged group) improved significantly ($p\leq0.01$) more than controls. In addition, borderline significant [$F(1,16)$=3.7-4.1, p = 0.06-0.07] group × time interactions were obtained on the STAI-S and distress measures and treated subjects were again more improved ($p\leq0.05$; Fisher's LSD) than waiting-list subjects on both these measures at posttreatment. There were two much improved and two moderately improved patients each (67% responder rate) in the SSRI- and CBGT-groups, suggesting that the two interventions were about equally beneficial. One WL-patient was also classified as moderately improved, possibly due to habituation effects. All nine responders confirmed symptom improvement in individual posttreatment interviews.

In CBGT- and SSRI-treated patients, symptom improvement was accompanied by a significantly reduced rCBF-response to public speaking bilaterally in the amygdala, hippocampus, and anterior/medial temporal cortex including the entorhinal, perirhinal, parahippocampal, and periamygdaloid areas. Responders (n=9), regardless of treatment approach, also decreased their neural response to public speaking in the same temporal lobe regions. Changes in rCBF were not observed in waiting-list controls. Interaction contrasts revealed that the rCBF-response to public speaking decreased significantly more in both treated groups relative to controls in the previously implicated temporal lobe regions, albeit mainly in the right hemisphere. Consistently, the rCBF-response also decreased more in responders relative to nonresponders in the right amygdala and hippocampus as well as cortically in the right rhinal/periamygdaloid areas (see Figure 3).

Altered rCBF was also noted in a few regions outside the temporal lobe. In the CBGT-group, rCBF decreased in the periaqueductal gray area while increases were noted in the right

cerebellum and secondary visual cortex (BA 19). In the SSRI-group, rCBF decreased in the left thalamus and left inferior frontal cortex (BA 10/47). Responders showed rCBF-decreases in the bilateral anterior cingulate (BA 25/32) inferior frontal (BA 47) and dorsolateral prefrontal (BA 9) cortices. In the between-group comparisons, rCBF decreased more in responders than nonresponders in the bilateral anterior cingulate (BA 24/33) and right dorsolateral prefrontal (BA 9) cortices. The SSRI- and CBGT-groups differed only with regard to perfusion in the right thalamus, which increased more with SSRI- than cognitive-behavioral treatment.

Based on the social anxiety questionnaire results, 7 of the 12 treated patients were considered to be "much improved" and 5 patients "less improved" at the one-year follow up. A stepwise discriminant analysis was performed to evaluate whether the attenuation of rCBF in the implicated subcortical regions immediately following treatment could predict level of improvement one year later. The periaqueductal gray (p=0.005), left thalamus (p=0.006), right (p=0.02), and left amygdala (p=0.06) combined to yield a significant discrimination (Wilk's Lambda=0.16, F=9.4, p<0.006) that was 100% accurate in predicting the two levels of improvement. Favorable outcome at one-year follow-up was associated with a greater initial attenuation of the subcortical rCBF-response to public speaking.

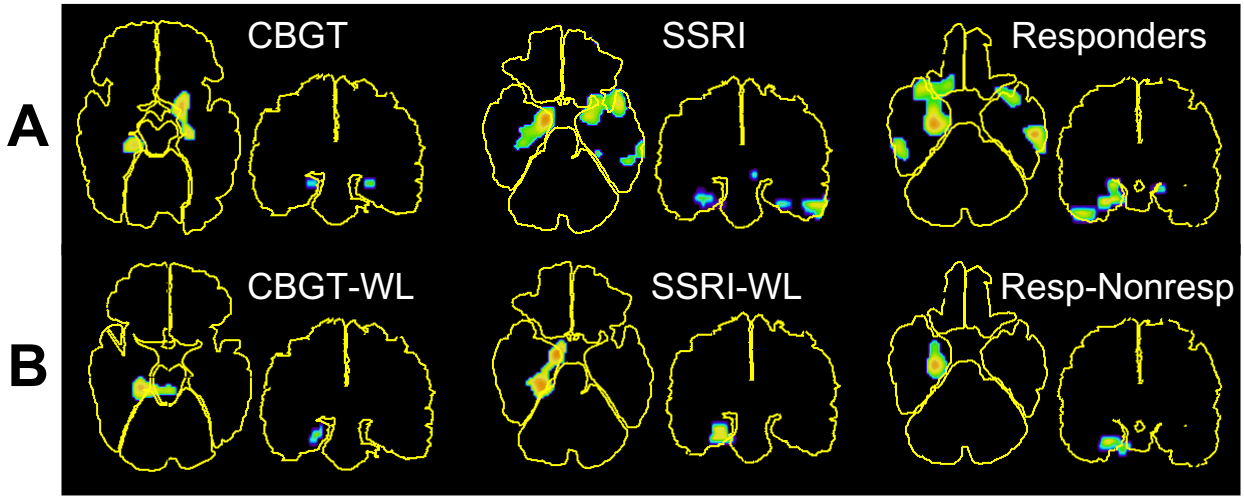

Figure 3. (A) PET-images showing significant decreases in the rCBF-response to an anxiogenic public speaking task after as compared to before treatment. Images display rCBF-decreases for social phobics treated with cognitive-behavioral group therapy (CBGT; left), a selective serotonin reuptake inhibitor (SSRI; middle), and for responders regardless of treatment approach (right). Points of neural convergence were observed in the amygdala, hippocampus, and surrounding temporal cortical regions. **(B)** Corresponding between-group differences in the amount of rCBF-change with treatment. Images show a greater reduction in the neural response to public speaking in CBGT- relative to waiting list (WL) subjects (left), SSRI- relative to WL-subjects (middle) and in responders relative to nonresponders (right).

Conclusions

Both SSRI- and cognitive-behavioral treatments were significantly and about equally effective in improving social phobia symptomatology. Neural points of convergence for the two types of treatment were observed in the amygdala, hippocampus, and neighboring cortical areas which are regions previously shown to serve important functions in anxiety. Suppression of amygdalo-hippocampal-temporal cortex neurons may thus be a common neural mechanism whereby successful anti-anxiety treatments act. The degree of response diminution to public speaking in

the amygdala, in conjunction with the PAG and left thalamus, predicted clinical status a year later. Amygdalar attenuation in particular may thus be a prerequisite for immediate and long-term anxiolytic effects.

3.3. Discussion of the individual studies

3.3.1 The epidemiological studies

Study I

At 15.6% the prevalence of social phobia appears to be higher in Sweden than in most other countries, although this figure is in the vicinity of the 13.3% lifetime prevalence noted in USA (Kessler et al., 1994) and 16% in Switzerland (Wacker, Müllejans, Klein, & Battegay, 1992). Compared with other Nordic countries the Swedish estimate is higher than the six-month prevalence rate of 4% noted in Iceland (Arnarson, Gudmundsdottir, & Boyle, 1998). Even though both studies used postal surveys, comparisons are complicated because of dissimilarities in questionnaire design. In general, it is also difficult to decide whether differences in prevalence rates, in comparison to other studies, should be attributed to a true cultural divergence or methodological factors.

The study draws attention to several methodological concerns in epidemiological studies of social phobia. Most notably, the finding that prevalence figures varied markedly (range 1.9-20.4%) across the different levels of distress and impairment used to define cases is consistent with several other reports (Pélissolo et al., 2000; Pollard & Henderson, 1988, Stein et al., 1994; 1996). The DSM-III-R and DSM-IV do not specify the required level of impairment or distress, and in the absence of a gold standard for validation, the choice of diagnostic thresholds becomes arbitrary. This, in turn, may at least partly explain why the prevalence rates across studies vary to such a large extent.

Public speaking was by far the most common social fear consistent with previous reports (Kessler et al., 1998; Pollard & Hendersson, 1998; Stein et al., 1994). Also congruent with other studies (e.g., Canino et al., 1987; George, Hughes, & Blazer, 1986; Hwu et al., 1989; Lee et al., 1990b; Magee et al., 1996; Vega et al., 1998) urbanicity did not influence the prevalence of social phobia. Morevover, the sociodemographic results are consistent with previous studies noting that social phobia is associated with female gender (c.f. Weinstock, 1999) low educational attainment (Magee et al., 1996; Schneier et al., 1992), and low social support (Magee et al., 1996). However, in the light of earlier reports (c.f. Chapman et al., 1995), the negative findings with regard to marital and occupational status and to some extent also birth-order, were unexpected. About 13% of the identified individuals with social phobia admitted that they were currently using psychoactive drugs. Nonetheless, very few of these subjects stated that social anxiety was their main problem, which fits the common description of social phobia as being an undertreated disorder (Weiller et al., 1996).

Among the limitations of the study the concerns associated with different diagnostic cut-off levels have already been mentioned. Furthermore, it was not possible to determine the extent to which comorbid psychiatric conditions affected the prevalence figures. Moreover, one interpretation of the attrition analysis is that social phobia was more common among responders than nonresponders, which could have exaggerated the prevalence estimates. However, other investigators have noted that the prevalence of a disorder is higher among nonresponders (Allgulander, 1989; Kessler et al., 1994). The generalizability of the study might be limited to the

geographical areas selected, i.e. Stockholm and Gotland, although there is no apparent reason to suspect that the samples differ systematically from the Swedish general population. It could also be argued that the postal survey methodology has drawbacks, particularly in comparison to structured diagnostic interviews. However, several limitations of the most common interviews used in epidemiological research have been discussed in the social phobia literature (c.f. Stein et al. 1994). Also, the psychometric evaluation suggested that the SPSQ was a satisfactory assessment tool. To the extent that the prevalence of 15.6% included subsyndromal cases, it is plausible that this primarily reflects the lack of stringency in the diagnostic (DSM-IV) criteria and general difficulties associated with making a precise demarcation of the disorder.

To summarize, study I suggests that, while there are considerable obstacles in setting the accurate diagnostic boundaries for social phobia, it is evident that social anxiety is a distressing problem for a remarkably large number of individuals in the general community.

Study II

By the use of cluster analysis three homogenous groups of social phobics were identified which, by and large, matched the categorical tripartite subtype system previously proposed by Heimberg and coworkers (Heimberg et al. 1993a; Herbert et al. 1992; Holt et al. 1992), consisting of generalized, nongeneralized, and discrete social phobia. In contrast to clinical samples where the generalized subtype dominates (c.f. Turner et al., 1986) discrete social phobia was the most common in the general population (point prevalence 7.7%), followed by the nongeneralized (5.9%) and generalized (2.0%) subtypes. None of the prevalence rates differed as a function of urbanicity. Compared with the other subtypes, generalized social phobia tended to be over-represented among those who were poorly educated and lacked social support. Public speaking was the most common fear in all groups, acknowledged by nearly 80% of all social phobics. The discrete type was dominated by public speaking fear and 3.2% of the respondents in the entire sample fulfilled the criteria for social phobia with public speaking as their only fear. This is consistent with other studies in which about 3-5% of the general population has reported public speaking phobia in isolation (Stein et al. 1994; 1996).

In general, results are difficult to compare with other studies on social phobia subtypes because exploratory classification techniques have been neglected. However, as mentioned previously, Kessler et al. (1998) estimated the prevalence of empirically derived subtypes by the use of latent-class analysis, noting a US lifetime prevalence of 4.8% for phobics with speaking fears (one of two classes identified) and 8.5% for those who endorsed at least one other fear (the second main class). However, the subtype classification in the Kessler et al. (1998) study was restricted because only six situations were assessed and only one of these concerned interactional fear.

Other epidemiological data on subtypes are scarce. Wittchen et al. (1999) noted that about one third of the social phobics in a German adolescent sample were of the generalized subtype, i.e. roughly 3% of the women and 1.5% of the men. In the Epidemiological Catchment Area project, Schneier et al. (1992) observed that the majority (79.5%) of subjects with social phobia feared only one of three assessed categories of fear whereas 17.2% feared two categories and 3.3% feared all three categories. In a Canadian telephone survey Stein et al. (1994) observed that 68.6% of those reporting social anxiety acknowledged difficulty with more than one social situation, 39.7% with more than two, and 8.7% with more than four of seven situations. These

findings suggest that the generalized (or severe) subtype is in minority relative to other forms of social phobia in the general community.

Although the three subtypes in study II may be described categorically as generalized, nongeneralized, and discrete types, they mainly conformed to a severe, moderate, and milder form of social phobia. The DSM-IV encourages the use of mild-moderate-severe diagnostic specifiers, and this dimensional terminology might be the most appropriate for social phobia. The use of negations, as in "nongeneralized", is awkward because this subtype can also be described, e.g. as "nondiscrete". Also, the meaning of "nongeneralized" has varied across studies. Many other subtype labels have been discussed in the literature, such as "specific", "circumscribed", "performance", and "limited interactional", but a sensible and empirically sound rationale for categorical subtype designations remains to be established. In comparison, the severe-moderate-mild terminology appears conceptually clear and empirically supported.

Several limitations apply to study II. General concerns associated with the survey method, attrition, and difficulties in setting diagnostic thresholds have been discussed in conjunction with study I. Self-report measures as opposed to clinical interviews were relied upon to identify cases of social phobia. Also, cluster analysis does not estimate the variate empirically. Instead it is specified by the researcher, which makes the definition of the variate crucially important. The choice of variables to define clusters was motivated by previous research. Social phobia subtypes should by definition differ in number of feared situations, and they have previously been reported to differ in distress ratings, level of functional impairment, and comorbidity with avoidant personality disorder (Heimberg et al. 1990b; Herbert et al. 1992; Holt et al. 1992; Hope et al. 1995; Schneier et al. 1991; Turner et al. 1992). Lastly it should be noted that with social phobia lying on a continuum, any subtyping scheme is arbitrary, and that cluster formations along a severity continuum were not unexpected since the variables used to define clusters correlated highly.

To conclude, in the Swedish general population three homogenous groups of social phobia were identified by cluster analysis. Although these roughly matched the categorical generalized, nongeneralized, and discrete subtypes described by Heimberg and colleagues (Heimberg et al., 1993a), the three empirically derived subtypes could most parsimoniously be described dimensionally as a severe, moderate, and milder form of social phobia with number of cases decreasing with increasing severity.

3.3.2 The neurobiological studies

Study III

Results showed that patients with social phobia were characterized by lower [β-^{11}C]-5-HTP derived uptake relative to controls, suggesting suppressed serotonin synthesis rate, mainly in the temporal periamygdaloid, entorhinal, and perirhinal cortices bilaterally, but also in the left anterior cingulate, the right insula, and the inferior frontal cortex in both hemispheres. Results from the principal component analysis generally supported the obtained pattern of lowered regional [β-^{11}C]-5-HTP derived uptake in social phobia as compared to healthy individuals. Two functional networks related to social phobia were revealed by the first and third principal components. The first component was composed of the same brain territories as implicated in the subtraction analysis, but also included the basal ganglia, periaqueductal gray, and more widely distributed areas of the neocortex. The third principal component revealed a second network encompassing the mid cingulate and temporal cortices, including the perirhinal region, both of

which are commonly noted in studies of negative emotion (Charney & Deutch, 1996). The results are consistent with Handley's (1995) hypothesis of low cerebral serotonin concentration contributing to anxiety. This notion is supported by reports on the anxiolytic effects of SSRIs suggesting that anxiety relief can be attributed to serotonin enhancement.

The implicated regions with altered uptake may reflect serotonergic neural networks that are compromised in social phobia. The temporo-limbic cortex, including the periamygdaloid/rhinal regions, probably participates in the chain of events when exteroceptive stimulation is modulated by emotional significance (LeDoux, 1996). These cortical areas are probably functionally integrated with the deeper amygdalo-hippocampal structures, which in turn subserve anxiety responses or bodily defense reactions to threatening stimulation (Gray & McNaughton, 1996; Reiman, 1997). The anterior cingulate cortex could be engaged in the attentional and behavioral response to threatening stimulation and/or in the conscious experience of anxiety (Reiman, 1997). Lowered uptake was noted in the "affective division" of the cingulate, i.e. the rostral-ventral proportion including the subgenual cortex, which has been consistently implicated in neuroimaging reports on emotional manipulation (Whalen et al., 1998a). The inferior frontal gyrus might participate in affective working memory and emotional perception (Kosslyn et al., 1996; Sprengelmeyer, Rausch, Eysel, & Przuntek, 1998) and presumably facilitates behavioral integration of emotionally relevant exteroceptive information. The anterior insula has been suggested to form an interoceptive alarm system evaluating cognitions, interoceptive sensory stimuli, and body sensations that signals potential internal danger (Reiman, 1997).

Social phobia was characterized by significantly elevated uptake in the cerebellum only. The cerebellum is functionally involved in motor behavior but also in attention (Allen, Buxton, Wong & Courchesne, 1997) and other sensory/cognitive processes (Barinaga, 1996) which could be influenced by excessive social anxiety. The dorsal bounds of the cerebellar cluster extended into the superior temporal regions of the right hemisphere but because of the large axial distance from the maximum voxel in the lower regions, this finding is probably too uncertain for further neurofunctional interpretation. A trend for elevated uptake in social phobics was also observed in a pons area that was anatomically consistent with the midbrain raphe nuclei, although these structures were not delineated explicitly by the brain atlas used (Greitz et al., 1991). The functional relevance of this finding remains to be determined.

The use of the radiotracer [β-^{11}C]5-HTP is in its infancy, and this tracer needs to be further validated before unequivocal conclusions can drawn from studies using it. Thus the present findings should be regarded as preliminary. Further studies are necessary to determine whether the presynaptic serotonergic dysfunction observed truly is a reproducible feature of the patophysiology of social phobia. Future studies could also investigate whether the SSRIs and other serotonin agents enhance serotonergic neurotransmission in the brain areas implicated in this study.

Study IV

The outcome analyses showed that patients with social phobia improved significantly and about equally with nine weeks of CBGT- or SSRI-treatment whereas waiting-list controls did not change. In both treatment methods the anxiolytic effects were associated with a decreased cerebral blood flow response to anxiety provocation (public speaking) in the amygdala, hippocampus, and the adjacent entorhinal, perirhinal, parahippocampal, and periamygdaloid

cortices. This effect was very robust. In the within-group contrasts both the SSRI- and CBGT-groups showed this pattern of neural change from pre- to posttreatment, whereas the unimproved waiting-list control group did not. Additionally, responders regardless of treatment modality also exhibited an analogous change in rCBF. Moreover, between-group contrasts showed that the rCBF-response decreased significantly more in the above regions in both the SSRI- and CBGT-groups relative to waiting-list controls. Finally, the neural response to public speaking also decreased significantly more in responders as compared to nonresponders in the same temporal lobe regions. Because both CBGT- and SSRI-treated subjects improved while waiting-list controls did not, it is unlikely that the beneficial effects can be attributed to repeated testing, subject maturation, statistical regression, or other potentially confounding factors. Integration of the results with previous imaging studies on anti-anxiety treatments is difficult because these are methodologically heterogeneous and have generally assessed resting states only (e.g., Baxter et al., 1992; Schwartz et al., 1996; Van der Linden et al., 2000), used anxiolytics of the older generation (e.g., Mathew & Wilson, 1991), or reported negative findings (Fredrikson et al., 1995).

The discriminant analysis revealed that initial response decrement in the amygdala, in conjunction with the periaqueductal gray and left thalamus, could accurately discriminate much from less improved patients a year later. Thus, significant response diminution in temporo-limbic territories could be imperative both for immediate and long-term anxiety reduction. In social phobics, the amygdala and hippocampus have previously been implicated in the processing of conditioned aversive stimuli, as well as facial and unpleasant odor stimulation (Birbaumer et al., 1998; Schneider et al., 1999). Preliminary neuroimaging evidence also suggests that neuronal activity in these regions may mediate the untreated social anxiety reaction (Reiman, 1997; Tillfors et al., submitted). The amygdaloid-hippocampal region has been suggested to constitute an alarm system alerting the individual when activated by threatening stimulation (Reiman, 1997). Conceivably, the rhinal, parahippocampal, and periamygdaloid cortices transit sensory and/or memory information into this system (LeDoux, 1996). Anxiety disordered patients probably suffer from easily triggered alarm reactions, and suppression of amygdalo-hippocampal neurons could thus be a common neural mechanism whereby both pharmacological and psychological therapies exert their anxiolytic effect.

The amygdala and hippocampus have previously been demonstrated to have a role in neural habituation to emotionally salient stimuli (Fischer, Furmark, Wik, & Fredrikson, 2000; Fischer et al., 2000). Thus, as proposed by Gray and colleagues (Gray & McNaughton, 1996) it is possible that cognitive-behavior therapy works by permitting systematic habituation of neuronal activity directly in these brain structures. Although some of the rCBF-changes are compatible with cognitive mechanisms of treatment, these may be more prominent in anticipation of rather than during phobic exposure. Thus, cognitive influences on anxiety could be of general importance albeit not prominent during the scanned time frame. SSRIs may yield comparable neural effects to those of behavior therapy, e.g. by correcting for a medial raphe nucleus malfunction with resultant decreased firing of cortical and amygdaloid-hippocampal neurons (Grove, Coplan, & Hollander, 1997). An increase of serotonin may inhibit thalamic and cortical inputs from activating the amygdala (Gorman et al., 2000).

Altered perfusion with treatment was seen only in a few regions outside the temporal lobe. Decreased flow in the periaqueductal gray region (CBGT-group) probably reflects attenuated defensive reactions as this region is involved in fight-flight and freezing reactions (Behbehani, 1995). Neuronal response decrement in the left thalamus (SSRI-group), occipitotemporal junction

(CBGT/SSRI-groups), and the inferior frontal and anterior cingulate cortices (responders) could correspond to a downgraded evaluative function, e.g. a lessened assignment of affective value to exteroceptive or facial stimuli following treatment. Prefrontal rCBF-diminution (responders) may influence the experiential component of anxiety, signifying a less intense conscious experience of emotion (Reiman, 1997) or a reduction of catastrophic cognitions (Grove et al., 1997). All these rCBF-decreases might be secondary to the inhibition of the amygdala (LeDoux, 1996). Increased flow in the secondary visual cortex (SVC) in CBGT-subjects could be associated with restored external attention and lessened self-focus (Wells & Clark, 1997). Similarly, the cerebellar activation (GBGT-group) may support external attention (Allen et al., 1997), or it could reflect altered motor, sensory or cognitive activity (Barinaga, 1996). CBGT and SSRI-treatments were only distinguished by perfusion in the right thalamus, which increased less with psychotherapy than citalopram. Speculatively, thalamic activation may relate to an active inhibition of later stages in the sensory stimulus processing chain (Fischer et al., 2000).

The between-group comparisons suggested that the rCBF-response diminution was more pronounced in the right hemisphere, consistent with theories of right-hemispheric domination in negative emotion (Davidson, 1995). However, evaluation of the *Z*-score maps indicted that the left amygdalo-hippocampal regions were also significantly involved, although the left deactivations did not survive Bonferroni-correction. Because statistical power is lost in the between-group contrasts, the absence of significant left-sided temporal deactivations, when corrected for multiple comparisons, may reflect type-II errors (false negatives) rather than true lateralization effects. Among the limitations it should thus be noted that the sample size was rather small, contributing to restricted statistical power and enhanced risk of type-II errors, particularly in the between-group analyses. Also, even though the inclusion of a waiting-list control group was a methodological improvement compared with most other imaging studies on anti-anxiety treatments, other relevant comparison-groups are lacking. For instance, to evaluate the specific components of the psychological and pharmacological treatments, it would have been ideal to compare the treated groups to attentional (e.g., educational-supportive) psychotherapy and pill placebo. Furthermore, the direct physiological effects of the SSRI could have been studied by administering citalopram to a group of healthy volunteers. However, Bonne et al. (1999) recently showed that long-term administration of the SSRI fluoxetine did not change rCBF, or global flow, in healthy volunteers. Finally, it would have been interesting to examine whether the combination of CBGT and citalopram enhances the therapeutic effect on brain function. This is a topic for future research.

3.4 Overall discussion

Taken together, study I and II suggest that social anxiety can be thought of as a normally distributed variable where people are arranged from low levels of anxiety at one end of the distribution to increasingly higher levels of normal social anxiety (the majority), passing through a gray zone (e.g., shyness, introversion), then somewhere crossing the border to pathological conditions (social phobia) which then in turn could be subdivided into mild, moderate, and more severe forms of social anxiety pathology at the other end of the distribution. Thus, the more stringent diagnostic cut-off levels in study I, using higher levels of distress and impairment to define cases, may identify moderate- and severe forms of the disorder (nongeneralized and generalized subtypes) but neglect the milder (or discrete) subtype. Similarly, the most liberal cut-off level, resulting in a point-prevalence of 20.4%, probably includes not only the milder forms of

social phobia but also subsyndromal cases. However, it is possible that this dimensional view is too simplified because clinical observations suggest that some individuals may describe themselves as outgoing and nonshy even though they experience marked distress in circumscribed settings such as public speaking situations. This would suggest that social phobia and shyness (and possibly introversion, neuroticism etc.) are multivariate conditions that do not necessarily lie on the same continuum. Also, isolated public speaking phobia shows close resemblance to a specific phobia. These diagnostic topics are complex and related to the several ongoing debates in psychiatry, such as the validity and practical utility of categories versus dimensions in psychiatric diagnostics, and the relation between psychopathology and underlying personality or temperamental factors.

The neurobiological studies in this thesis also leave several intriguing questions unanswered. For instance, does the serotonin synthesis rate change as a function of treatment with SSRIs and/or CBGT? To answer this question [β-^{11}C]-5-HTP images obtained before and after therapy need to be compared, which is underway in our laboratory. Meanwhile, areas that showed both reduced pretreatment [β-^{11}C]-5-HTP derived uptake (suppressed serotonin synthesis) and changes in brain perfusion as a function of treatment were observed mainly in the medial temporal lobe (the rhinal/periamygdaloid cortices). It is possible that the reduced blood flow here following therapy corresponds to a serotonergically mediated inhibition of these areas because treatment has increased the levels of synthesized serotonin. In a similar vein, enhanced pretreatment serotonin turnover and increased posttreatment flow in cerebellar regions (noted in CBGT-patients) could mean that therapy produces disinhibition of the cerebellum, possibly resulting in less inhibited bodily expressions.

There are also other unanswered questions. Could measures of serotonin metabolism be used to predict short- and long-term treatment outcome? Are there sex differences with regard to brain perfusion and presynaptic serotonin function? Do subtypes of social phobia that are classified on the basis of other pathology variables differ in brain perfusion and/or serotonergic function? Alternatively, could neural measures such as rCBF and cerebral serotonin metabolism be used to delineate subtypes of social phobics that differ meaningfully with regard to other descriptive characteristics? These important topics are currently being investigated, or should I say scrutinized, in our laboratory.

4. CONCLUSIONS

The tentative conclusions of this thesis can be summarized as follows:

- While social anxieties, particularly in public speaking circumstances, are remarkably widespread within the Swedish general community, the exact diagnostic boundaries for social phobia are difficult to set. This is illustrated by the point prevalence of social phobia, which was estimated at 15.6%, but varied between 1.9 and 20.4% across the different levels of distress and impairment used to define cases.

- Subtypes of social phobia can most parsimoniously be described dimensionally, i.e. as representing different levels on a mild-moderate-severe continuum, with number of cases decreasing with increasing severity.

- Social phobia is characterized by a presynaptic serotonergic dysfunction, i.e. a suppressed serotonin synthesis rate indexed by a lowered uptake derived from [β-^{11}C]-5-HTP, mainly in the periamygdaloid/rhinal cortices of the temporal lobe, but also in the inferior frontal, insular, and anterior cingulate cortical regions.

- Serotonergic (SSRI) drug therapy and cognitive-behavioral treatment of social phobia exert their anxiolytic effects by attenuating activity in a common neural pathway encompassing the amygdala, hippocampus, and adjacent temporal cortex - i.e. the "alarm system" of the brain. Satisfactory long-term treatment outcome may require therapies that thoroughly suppress amygdalar/limbic activation during socially stressful events.

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APPENDIX A

The DSM-IV criteria for social phobia (American Psychiatric Association, 1994, p. 416):

A. A marked and persistent fear of one or more social or 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. Note: In children, there must be evidence of the capacity for age-appropriate social relationships with familiar people and the anxiety must occur in peer settings, not just in interactions with adults.

B. Exposure to the feared social situation almost invariably provokes anxiety, which may take the form of a situationally bound or situationally predisposed panic attack. Note: In children, the anxiety may be expressed by crying, tantrums, freezing, or shrinking from social situations with unfamiliar people.

C. The person recognizes that the fear is excessive or unreasonable: Note: In children, this feature may be absent.

D. The feared social or performance situations are avoided or are endured with intense anxiety or distress.

E. The avoidance, anxious anticipation, or distress in the feared social or performance situation(s) interferes significantly with the persons normal routine, occupational (academic) functioning, or social activities or relationships, or there is marked distress about having the phobia.

F. In individuals under age 18, duration is at least 6 months.

G. The fear or avoidance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, medication) or a general medical condition, and is not better accounted for by another mental disorder (e.g., panic disorder with or without agoraphobia, separation anxiety disorder, body dysmorphic disorder, a pervasive developmental disorder, or schizoid personality disorder).

H. If a general medical condition or another mental disorder is present, the fear in criterion A is unrelated to it: e.g., the fear is not of stuttering, trembling in Parkinson's disease, or exhibiting abnormal eating behavior in anorexia nervosa or bulimia nervosa.

Specify if **Generalized**: if the fears include most social situations (also consider the additional diagnosis of avoidant personality disorder).