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Social Phobia

The Family and the Brain

BY

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ABSTRACT

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The present thesis investigated family history and neurobiology of social phobia. Social phobia is a disabling disorder characterized by a marked fear of scrutiny in a variety of social situations. By using a validated questionnaire, study I related family history of excessive social anxiety to social phobia and avoidant personality disorder in epidemiologically identified probands in the Swedish general population. A two- to threefold increased relative risk of social anxiety was observed for both diagnostic groups. Thus, having an affected family member is associated with approximately a doubled risk for both social phobia and avoidant personality disorder.

The neurobiological studies explored situational and anticipatory elicited anxiety by means of positron emission tomography and ^{15}O-water. Study II examined the functional neuroanatomy of social anxiety provocation in social phobics and a healthy comparison group during a public speaking task. Social phobia symptomatology was associated with higher neural activity in the amygdaloid complex, i.e. “the alarm system” of the brain, and lower activity in the prefrontal cortex. Study III examined the neural correlates of anxiety elicited by the anticipation of public speaking in individuals with social phobia. Anticipatory anxiety was accompanied by enhanced regional cerebral blood flow in the dorsolateral prefrontal and inferior temporal cortices as well as in the amygdaloid-hippocampal region. Brain blood flow was lower in the temporal pole and in the cerebellum. These results suggest that social phobia has a neuroanatomical basis in a highly sensitive fear network centered in the amygdaloid-hippocampal region and encompassing the prefrontal cortex.

Key words: Anticipation, anxiety, avoidant personality disorder, family history, fear, neuroimaging, positron emission tomography, regional cerebral blood flow, social phobia, symptom provocation.

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“The brain is my second favorite organ”
Woody Allen

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ABBREVIATIONS USED IN TEXT

ANOVA	Analysis of variance
APA	American Psychiatric Association
APD	Avoidant personality disorder
BAS	the Behavioral activation system
BIS	the Behavioral inhibition system
DAT1	the Dopamine transporter gene
D4DR	the Dopamine 4 receptor gene
DIP-Q	the DSM-IV and ICD-10 Personality Disorder Questionnaire
DSM-I	the Diagnostic and Statistical Manual of Mental Disorders, 1st edition
DSM-II	the Diagnostic and Statistical Manual of Mental Disorders, 2nd edition
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
fMRI	Functional magnetic resonance imaging
5-HT	5-hydroxotryptamine (serotonin)
5-HTP	5-hydroxotryptofan
5-HTT	5-HT transporter gene
NCS	the National Comorbidity Survey
PET	Positron emission tomography
rCBF	Regional cerebral blood flow
SSRI	Selective serotonin reuptake inhibitor
STAI-S	Spielberger's State Anxiety Inventory

INTRODUCTION

The present thesis

The expression of fear and anxiety are perfectly normal reactions in the appropriate context. But what makes some individuals and not others to go beyond this level of adaptive fear and anxiety to develop pathological anxiety?

The present thesis is about social phobia, also known as social anxiety disorder, which at least in Western countries is considered to be the most common anxiety disorder (Jefferys, 1997), characterized by a marked fear of scrutiny in a variety of social situations. The thesis is based on three studies, where the first study examines family history in social phobics, that is if social phobia runs in families in a more systematic way than what could be expected by chance. The second and third studies deal with brain functioning, i.e. they investigate the neural underpinnings of situational and anticipatory elicited social anxiety. First of all, however, I will describe what social phobia is, how common it is, its etiology, and the neurobiology of the illness.

Social phobia – What is it?

Suppose that you are speaking in front of an audience, attending a party, being addressed in a group of people, or some other common situation in real life. In the beginning of these situations your heart may pound heavily, your voice may tremble or your head may go blank and so on. For most of us this state lasts only a couple of minutes and then we feel comfortable, or at least we do not experience an intense persisting anxiety. However, for individuals with social phobia one or more of those situations are either endured with intense anxiety or avoided (e.g., Bruce & Saeed, 1999; Sareen & Stein, 2000).

Phobias can be described as an intense irrational fear of specific objects, situations, or activities (Öhman, 1994). The fourth edition of the Diagnostic and Statistical Manual of Mental Disorders – DSM-IV (APA, 1994) describes social phobia as a disabling disorder characterized by a marked fear of humiliation or scrutiny in certain performance and/or interactional situations. Public speaking is the most prevalent fear and between 15 and 30 percent of the normal population experience significant fears in this performance situation (Furmark, Tillfors, Everz, Marteinsdottir, Gefvert, & Fredrikson, 1999; Kessler, Stein, & Berglund, 1998; Stein, Torgrud, & Walker, 2000). Other common types of fears associated with social phobia are mentioned below (See Table 1).

Table 1. Common fears in social phobia

Performance situations	**Interaction situations**
Public speaking	Interacting with others
Eating in front of others	Conversing on the telephone
Writing in front of others	Speaking with strangers
Speaking in a group	Dating
Drinking in front of others	Interacting with the opposite sex
Entering a room where others are seated	Attending social gatherings
Using public toilets	Dealing with authority figures

Hence, individuals with social phobia often either avoid these kinds of situations where scrutiny may occur or they endure them with intense anxiety or distress.

When exposed to feared situations individuals with social phobia become self-focused and self-critical. Most of them, further, experience some kind of somatic symptoms of anxiety such as palpitations, trembling, sweating, or blushing (e.g., Heckelman & Schneier, 1995). However, social phobics' distress is not restricted to the phobic situation only but is present also in anticipation of it (e.g., Clark, 1997). This anticipatory anxiety could be as intense and distressing as that experienced in the feared situation (e.g., Jefferys, 1997). To be diagnosed as having a phobia, the fear must significantly interfere with the person's occupational activities or social functioning (APA, 1994). According to the DSM-IV (APA, 1994) all criteria must be met in order to make a diagnosis of social phobia (See Table 2).

Table 2. Diagnostic criteria for social phobia (APA, 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 else endured with intense anxiety or distress.
E. The avoidance, anxious anticipation, or distress in the reared social or performance situation(s) interferes significantly with the person's 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 years, the 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, a 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)

As recently as 1985, a research group (Liebowitz, Gorman, Fyer, & Klein, 1985) described social phobia as "a neglected disorder". However, the past decade has witnessed a growing body of research on the syndrome, and social phobia is now considered the most common anxiety disorder (Jefferys, 1997), with lifetime prevalence rates in the range of 7 to 16 percent (e.g., Furmark et al., 1999; Kessler et al., 1994; Lang & Stein, 2001; Stein, Walker, & Forde, 1996). Previous studies have reported that the disorder is associated with high comorbidity with depression, other anxiety disorders, personality disorders and substance-related problems as well as social impairment (e.g., Magee, Eaton, Wittchen, McGonagle, & Kessler, 1996; Merikangas et al., 1998; Moutier & Stein, 1999; Stein et al., 2001). In spite of these facts, people with social phobia do not usually seek treatment (e.g., Katzelnick & Greist, 2001; Magee et al., 1996). This is a large problem, both in the light of individual suffering and of societal costs (Greenberg et al., 1999; Lipsitz & Schneier, 2000), since untreated social phobia may have a chronic course and is associated with significant morbidity (e.g., Charitier, Hazen, & Stein, 1998; Reich, Goldenberg, Vasile, Goisman, & Keller, 1994). One hypothesis is that persons with social phobia attribute the social anxiety to their personality and therefore do not believe that there is any treatment for them. However, both pharmacotherapy like selective serotonin reuptake inhibitors (SSRIs; e.g., Van Ameringen, Mancini, Oakman, & Farvolden, 1999) and cognitive behavioral therapy (e.g., Heimberg & Juster, 1995; Heimberg et al., 1998)

have shown to be efficacious for social phobia. For most, social phobia have an early onset between 11 and 19 years of age (e.g., Bruce & Saeed, 1999; Liebowitz et al., 1985), usually preceding the comorbid disorders. Thus, it is of importance to recognize and treat social phobia early in life to be able to minimize the impact of comorbidity on quality of life.

DIAGNOSTIC ISSUES

Development of DSM criteria

Historically, social anxiety, social avoidance, and shyness have been described as early as the time of Hippocrates, and the term “social phobia” (phobie des situations sociales) was first introduced by Janet in 1903 to describe patients who feared being observed, for example while speaking or writing (e.g., Heckelman & Schneier, 1995). However, interest for and discussions about social phobia before the 1950s were rare. With the advent of behavioral therapy in the 1950s and 1960s the interest in phobias increased (e.g., Fahlén, 1995) and the British psychiatrist Isaac Marks observed in the 1960s that particular phobias, including social phobia, could be distinguished from each other by age of onset (Marks & Gelder, 1966). Though, it was not until 1980 in the third edition of the DSM (APA, 1980) that social phobia got its own specific diagnosis. Before that, in the first and second editions of the DSM (DSM I and DSM-II; 1952 and 1968) all phobias were grouped together according to a psychoanalytic perspective. A descriptive, atheoretical, multiaxial, and hierarchical system for classification of mental disorders came with the third edition of the DSM (APA, 1980), and a separate Axis II was introduced for personality disorders.

In the DSM-III (APA, 1980), social phobia was described as a discrete form of performance anxiety, more akin to specific phobia. Individuals with a more pervasive social anxiety were classified as having avoidant personality disorder (APD) and the two disorders were not allowed to co-vary. However, a wealth of studies (e.g., Barlow & Liebowitz, 1995; Lépine & Lellouch, 1995; Schneier, Johnson, Hornig, Liebowitz, & Weissman, 1992) have reported that social phobia is not restricted only to a few performance situations, like public speaking or eating in front of others, but is instead a more pervasive condition than the DSM-III implied, affecting a variety of social situations. Therefore, the diagnostic criteria for social phobia were modified in the revised edition of DSM-III-R (APA, 1987). Comorbidity between social phobia and APD was allowed, a generalized type defined by fear in “most social situations“ was introduced, and “significant distress” was changed to “interference or marked distress”. Thus, this change of the diagnostic criteria not only broadened the diagnosis of social phobia but also increased the rate of comorbidity between the Axis I disorder social phobia, especially the generalized type, and the Axis II disorder APD.

In the development of DSM-IV (APA, 1994) the DSM-IV task force systematically assessed several diagnostic issues, including the relationship of social phobia to personality traits, social anxiety caused by stuttering or other conditions, and the validity of

social phobia subtypes. Yet, empirical studies clarifying the above issues were scarce and the fourth edition of the DSM (APA, 1994) was only slightly modified. For example, features specific to children were included in the DSM-IV criteria for social phobia while childhood diagnosis of avoidant disorder was deleted.

In addition, the term "social anxiety disorder" was considered because the term "social phobia" was thought to be inappropriate for the more pervasive condition (Liebowitz, Heimberg, Fresco, Travers, & Stein, 2000). Since there was no consensus on this issue, the task force decided to retain "social phobia" but also to add "social anxiety disorder" as an alternative term.

Prevalence and caseness

The first wave of international epidemiological studies estimated lifetime prevalence of social phobia to about 1 to 4 percent (e.g., Bourdon et al., 1988; Schneier et al., 1992; Wells, Bushnell, Hornblow, Joyce, & Oakley-Browne 1989). However, recent studies based on more current diagnostic criteria, consistent with the DSM-III-R and DSM-IV (APA, 1987; 1994), and using a broader range of social situations, have reported lifetime prevalence rates in the 7 to 16 percent range (see e.g., Lipsitz & Schneier, 2000 and Sareen & Stein, 2000 for a review). For example, a large community study in the US, the National Comorbidity Study (NCS), reported a lifetime prevalence of 13.3 percent, hence making social phobia the most common anxiety disorder in the USA, and the third most common mental disorder behind alcohol abuse and major depressive disorder (Kessler et al., 1994; Magee et al., 1996). Another community study in Switzerland reported even higher lifetime estimates of social phobia than the NCS did – 16 percent (Wacker, Müllejans, Klein, & Battegay, 1992). In Sweden, Furmark and colleagues (1999) further supported that social phobia is among the most common mental disorders when they in a community survey noted a point prevalence of 15.6 percent. Thus, caseness of social phobia seems to vary with number of feared situations used as well as the required level of social impairment and distress. However, several explanations underlying the large between-study variability observed, including differences in assessment approaches and cross-cultural differences, have been discussed in the literature (see e.g. Chapman, Mannuzza, & Fyer, 1995; Furmark et al., 1999, and Lang & Stein, 2001 for a review).

Sociodemographic findings

A number of recent epidemiological studies (e.g., Davidson, Hughes, George, & Blazer, 1993; Furmark et al., 1999; Magee et al., 1996) have reported that social phobia usually appears to be more common among females (the male to female ratio in community samples is approximately 1:1.5), young people, unmarried individuals, and in those with lower education. However, males are more likely to seek treatment (e.g., Weinstock, 1999). One explanation may be that it is less accepted among men to show social anxiety symptoms in Western society than it is among women, and therefore men view themselves as more impaired.

Subtypes of social phobia

The generalized subtype was first introduced in the DSM-III-R (APA, 1987) and is currently defined as a fear of most social situations. Though, not explicitly defined in the DSM system, the literature refers to another social phobia subtype described as "discrete", "circumscribed", "limited", "performance", or "nongeneralized" (e.g., Heckelman & Schneier, 1995; Heimberg, Holt, Schneier, Spitzer, & Liebowitz, 1993). The latter subtype is typically used to classify individuals fearing only one or two distinct situations (e.g., Heimberg et al., 1993).

Briefly, there has been considerable criticism of the DSM-III-R subgroups including issues such as unclear definition of "most common situations" and lack of conclusive evidence for a qualitative distinction between subtypes, as opposed to a continuum of severity. The DSM-IV task force tried to address these concerns by considering a tripartite subtyping scheme, in addition to the implicit two-part organization used in the DSM-III-R, but the empirical data was insufficient to support an adoption of it (see e.g., Heckelman & Schneier, 1995 for a review). Recent studies (e.g., Eng, Heimberg, Coles, Schneier, & Liebowitz, 2000; Furmark et al., 2000) have used more data driven methods such as cluster analytic procedures to identify empirically defined subgroups of patients with social phobia in comparison to earlier theoretical classification systems based for instance on number of feared situations (e.g., Heimberg et al., 1993). For example, Furmark and coworkers (2000) in a community study found support for three homogenous subtypes distributed along a continuum of severity. Another recent community study (Stein et al., 2000) also implied that social anxiety seemed to exist on a continuum of severity. Further, Kessler, Stein, and Berglund (1998) used latent class analysis to distinguish between social phobia subtypes in the general population. They found that social fears could be disaggregated into two broad classes, where the first is characterized largely by speaking fears and the second by a broader range of fears.

The subtypes of social phobia usually differ in level of severity and social impairment, demographic characteristics, physiological response to behavioral challenges (see e.g., Heimberg et al., 1993 for a review), comorbidity (e.g., Lang & Stein, 2001), personality traits like neuroticism and extroversion (Stemberger et al., 1995), and level of impairment after treatment (e.g., Brown, Heimberg, & Juster, 1995; Hope, Herbert, & White, 1995). Moreover, Mannuzza and colleagues (1995) reported that familial social phobia was more common among patients with generalized social phobia than among those with nongeneralized social phobia and nonphobics, whereas no difference was observed between the latter two. Similarly, in a clinical study Stein and colleagues (1998) revealed a tenfold risk increase for generalized social phobia and APD among relatives of probands with the generalized subtype compared to relatives to comparison probands. These data indicate that generalized social phobia may have a stronger familial component than other subtypes and that specificity could exist. In contrast, Furmark et al. (2000) reported that the empirically derived social phobia subgroups did not differ regarding family history of excessive social anxiety.

To conclude, in the conceptual debate, irrespective of which classification system is used, there seems to be consensus in that persons with generalized social phobia differ from the other subtypes primarily in severity of their social phobia. This suggests that the subtypes may reflect arbitrary cutoffs along a continuum of social anxiety rather than distinctive subtypes.

Comorbidity with avoidant personality disorder

Features central to the concept of personality disorders are their early onset, pervasiveness, interpersonal focus, impairment, and persistence over many years. APD is characterized by social inhibition, feelings of inadequacy, and hypersensitivity to criticism and negative evaluation (APA, 1994). In the DSM system social phobia and APD are diagnosed as separate entities. The theoretical basis for placing social phobia and APD on different axis in DSM is that APD is described as social withdrawal without performance problems, and social phobia as performance problems but not self-esteem difficulties (Reich, 2000). Because the criteria have changed somewhat with each revision these differences have more or less been retained. Yet, at least four items for diagnosing APD (1, 2, 3, and 7) in the DSM-IV (APA, 1994) overlap with the social phobia criteria. In addition, the untreated form of social phobia, especially the generalized subtype, has many features in common with a personality disorder (e.g., Barlow & Liebowitz, 1995; Johnson & Lydiard, 1995). However, this does not automatically mean that generalized social phobia is a personality disorder.

A major nosological theme in research on social anxiety is whether the Axis I disorder social phobia and the Axis II disorder APD representing distinct clinical categories or not. In contrast to the DSM-III (APA, 1980) the revised DSM-III-R (APA, 1987) allowed comorbidity between social phobia and APD. The DSM-III-R (APA, 1987) also refined the criteria for social phobia and included a generalized type. Since social phobia and APD share several diagnostic as well as experiential characteristics, one of the consequences is that a high rate of comorbidity has been reported, especially between generalized social phobia and APD (20-89%; e.g., Fahlén, 1995; Holt, Heimberg & Hope, 1992; Schneier et al., 1992; Schneier, Spitzer, Gibbon, Fyer & Liebowitz, 1991). Thus, it seems clear that generalized social phobia to a great extent, if not completely, overlaps with APD.

Generalized social phobics with as compared to those without comorbid APD have, in various studies, been observed to display increased anxiety and depression assessed with self reports, to be more impaired in daily life, and to meet the criteria for another Axis I or II diagnosis more often (e.g. Herbert, Hope, & Bellack, 1992; Turner, Beidel, & Townsley, 1992; Brown et al., 1995). This is consistent with other studies in which an association between low social functioning and the presence of personality pathology have been observed (e.g., Alpert et al., 1997; Reich et al., 1994; Van Velzen, Emmelkamp & Scholing, 2000). Nonetheless, several researchers (e.g., Boone et al., 1999; Moutier & Stein, 1999; Wideger, 1992) have concluded that most previous investigations agree in that none of the differences

observed between social phobia and APD point to qualitative distinctions but instead reflect differences in degree of social anxiety and function. Some studies indicate, however, that there are qualitative differences between social phobia and APD (e.g., Hofmann, Newman, Ehlers, & Roth, 1995; Tran & Chambless, 1995). In addition, some treatment studies (see e.g., Reich, 2000 for a review) do not distinguish between social phobia and APD.

Thus, it seems as though findings reflect the blurred border between phobic symptomatology and personality traits as defined in DSM-IV (APA, 1994) rather than true differences. Social phobia and APD may instead reflect a spectrum of social anxiety with no clear demarcation line. However, even though the pattern of results might cast doubt on the usefulness of discriminating social phobia from APD in terms of social anxiety, they may support the clinical diagnostic validity in terms of functional impairment. One possible way to further try to validate the distinction between social phobia and APD could be through family and genetic studies.

Shyness

Many individuals with social phobia describe themselves as shy and both shy individuals and social phobics share a similar antecedent of fear of negative evaluation. Prevalence rates for shyness have been estimated to range from 20 to 40 percent among college students and tend to overlap extensively with social phobia (e.g., Cheek, Carpentieri, Smith, Rierdan, & Koff, 1986). Yet, since there are no broadly adopted definition of shyness it is not clear where shyness ends and social phobia begins. Taken together, social anxiety most likely reflects a continuum where shyness describes the low to middle range, social phobia describes the middle to upper end and finally social phobia comorbid with APD describes the upper to extreme end.

ETIOLOGY

Despite a dramatic increase of research on social phobia during the past decade, the etiology of the illness is still to an essential degree unknown. However, it has been postulated that both genetic and environmental factors determine an individual's vulnerability to acquire social phobia (e.g., Herbert, 1995; Stemberger et al., 1995). Variables to be considered in relation to the development of social anxiety include genetics and family aggregation, behavioral inhibition, personality traits, family environment, various forms of the associative learning account, cognitive factors, and neurobiological influences.

Genetics and family aggregation

Available data suggest that there is a heritable contribution to social phobia (see e.g., Hudson & Rapee, 2000 for a review). Several family and twin studies have explored genetic factors in social phobia (e.g., Fyer, Mannuzza, Chapman, Liebowitz, & Klein, 1993; Kendler, Myers, Prescott, & Neale, 2001). Family studies assess whether a disorder tends to aggregate in

families in a more systematic way than what could be expected by chance, but do not separate genetic from environmental factors to a given trait or state. Discriminating among these requires twin or adoption studies.

A number of studies in clinical populations have consistently found higher rates of social phobia in relatives of social phobia probands (approximately a two- to threefold increased risk) in comparison to relatives of control probands (Fyer et al., 1993; Fyer, Mannuzza, Chapman, Martin, & Klein, 1995; Mannuzza, Schneier, Chapman, Liebowitz, Klein, & Fyer, 1995; Reich & Yates, 1988; Stein et al., 1998; Stemberger et al., 1995). In addition, two studies (Mannuzza et al., 1995; Stein et al., 1998) suggest that the generalized subtype of social phobia have a stronger familial component than the nongeneralized one.

In research on specific links between social phobia in parents and offspring, a community study by Lieb and colleagues (2000) showed an association between parental social phobia and social phobia among offspring corresponding to an odds ratio of 4.7. Moreover, two studies of anxiety and social phobia (Mancini, Van Ameringen, Szatmari, Fugere, & Boyle, 1996; Merikangas, Avenevoli, Dierker, & Grillon, 1999) also observed increased rates of social phobia in offspring of anxious parents in clinical populations. In a study on shyness, a related concept which significantly overlaps with the symptomatology of social phobia, Cooper & Eke (1999) revealed that the rate of social phobia was enhanced among mothers of shy children. In addition, Skre, Onstad, Edvardsen, Torgersen, and Kringlen (1994) observed in a clinical population that more female than male relatives of persons with anxiety syndromes suffered from anxiety disorders themselves.

Some studies (Fyer et al., 1995; Reich & Yates, 1988) suggest that a specific familial transmission for social phobia exists, and hence that the disorder “breeds true”. For example, Fyer and coworkers (1995) found an increased relative risk for social phobia but not for specific phobia and agoraphobia in relatives of the probands with social phobia. Thus, preliminary evidence suggests a familial loading for social phobia that is etiologically specific.

The strongest evidence of a heritable contribution to social phobia comes from two epidemiologically based twin studies (Kendler et al., 2001; Kendler, Neale, Kessler, Heath, & Eaves, 1992). Kendler and colleagues (1992) reported that familial transmission of social phobia in female twins seems to be determined by a combination of genetic and individual-specific environmental factors, explaining about 1/3 and 2/3 of the variance, respectively. The source of variance in the liability for genetic factors specific for social phobia was 21 percent, and a further 10 percent was due to genetic factors shared by all phobias. In male twins the familial aggregation of social phobia susceptibility, including associated irrational fears, was due both to genetic (1/4) and individual-specific environmental (3/4) factors (Kendler et al., 2001). In addition, Kendler and coworkers (2001) also found evidence of shared environmental factors in men but not in women that had an impact on social phobia. Furthermore, the pattern of results from the study of phobias in male twins (Kendler et al.,

2001) suggests that fears are a milder form of the same liability dimension that produces pathological conditions.

Genetic studies examining related constructs such as shyness (e.g., Buss, Plomin, & Willerman, 1973) and social fears (e.g., Skre, Onstad, Torgersen, Lygren, & Kringlen, 2000) have demonstrated higher concordance for monozygotic (i.e., identical) than for dizygotic (i.e., nonidentical) twins, which further support a genetic contribution to social phobia. Additionally, in an adoption study of shyness Daniels and Plomin (1985) observed that shyness in infants was associated with shyness in biological mothers at 24 months but not with shyness in mothers of the adopted children at either 12 or 24 months, probably reflecting genetic influence on infant shyness. Moreover, genetic influences have been evident also in other variables thought to have relevance for the development of social phobia including behavioral inhibition (e.g., Robinson, Kagan, Reznick, & Corley, 1992), neuroticism, and introversion (e.g., Henderson, 1982). Taken together, these data suggest a genetic contribution to social phobia and other related concepts.

However, most twin studies on anxiety disorders have not succeeded in finding evidence for a specific genetic heritability of anxiety disorders and thereby rather provide evidence for a genetic predisposition towards general anxiousness (e.g., Andrews, Stewart, Allen, & Hendersen, 1990; Andrews, Stewart, Morris-Yates, Holt, & Henderson, 1990; Torgensen, 1983). Though, there is, as in the twin study of Kendler and coworkers (1992) for instance, some evidence for an involvement of specific genetic factors in the etiology of social phobia. Thus, whereas family studies suggest that there is a specific familial transmission for social phobia, a number of genetic studies instead provide evidence for a general predisposition toward anxiousness. In a review Hudson and Rapee (2000) hypothesized that the family environment rather than genetic factors are the key to this specific transmission pattern found in the family studies of social phobia, since family history studies measure both genetic and environmental factors, and twin studies primarily measures genetic ones.

Discussing what might be transmitted between generations, Stein, Chartier, Lizak, and Jang in a recent study (2001), stressed the importance of a broader phenotype specification such as a temperamental or personality construct as an underlying vulnerability factor in social phobia. Supporting the above position they found that relatives of generalized social phobia probands scored significantly higher than relatives of control probands on measures of trait anxiety, social anxiety, and on the temperament harm avoidance.

Behavioral inhibition

The term temperament refers to “early dispositional differences that are associated with emotional reactivity” (Davidson & Ekman, 1994, p. 95). It is suggested, to at least partly, have a genetic basis. Temperament research has in the past decade focused on the temperamental construct behavioral inhibition, which is characterized largely by withdrawal, wariness, avoidance, and shyness as well as heightened physiological arousal in novel situations (e.g.,

Kagan, Reznick, & Snidman, 1988; Reznick et al., 1986). Cloniger (e.g., 1986) has described a similar temperamental construct, harm avoidance, characterized by passive avoidant behaviors such as fear of uncertainty and shyness of strangers. Physiological correlates of behavioral inhibition include evidence of sympathetic hyperactivity (e.g., Kagan et al., 1988), interpreted as being associated with a lower threshold of excitability in the amygdala (Kagan, Snidman, & Arcus, 1993). Features of behavioral inhibition have been found also in other species such as dogs and primates suggesting that it is an evolutionarily conserved temperamental phenotype (e.g., Smoller & Tsuang, 1998). Further, the behavioral inhibition pattern has been observed cross-culturally (e.g., Turner, Beidel, & Wolff, 1996).

Behavioral inhibition, observed in approximately 15 percent of white American children, has an early onset, about 4 months of age, and has at the extreme level been found to persist until at least age 7 (e.g., Kagan et al., 1993). Important to note is that only a relatively small percentage of the above 15 percent behaviorally inhibited children remain so over several years. Another 25 to 30 percent exhibit an “uninhibited” temperament style described by outgoing sociability and affective spontaneity. The inhibited children have been described as more irritable as infants, more fearful, and more in the periphery in social groups than their friends throughout kindergarten, and finally more introverted and cautious in school (e.g., Turner et al., 1996). The behaviorally inhibited temperamental style has functionally been related to negative affect including fear and anxiety as well as the personality trait introversion (see e.g., Turner et al., 1996 for a review).

Twin studies (DiLalla, Kagan, & Reznick, 1994; Matheny, 1989; Robinson et al., 1992) indicate that there is a genetic contribution to behavioral inhibition, especially in those children with extreme manifestation of the syndrome. Since the syndrome contains many behaviors related to anxiety disorders in general and particularly social phobia, questions concerning possible relationships have been raised. More recent studies have found increased rates of current social phobia and a past history of childhood anxiety disorders in parents of behaviorally inhibited children, in comparison with parents without behaviorally inhibited children and controls (Rosenbaum et al., 1991; 1992). Significantly higher rates of anxiety disorders, including for instance overanxious disorders, avoidant disorders and phobic disorders, have been found in the stable behaviorally inhibited children compared to uninhibited children and controls (e.g., Biederman et al., 1993). In a review of the syndrome however, Turner et al (1996) concluded that behavioral inhibition might reflect one but not the only factor related to the development of anxiety disorders, since also uninhibited children develop pathological anxiety.

To conclude, data indicate that behavioral inhibition reflects an enhanced anxiety proneness of familial origin. The syndrome may be a precursor to either anxiety disorders in general or social phobia in particular later in life. However, the exact nature of this relationship has yet to be elucidated, and evidence so far suggests a limited association between behavioral inhibition and anxiety disorders.

Personality traits

Studies of personality and individual differences have suggested that the mechanisms underlying individual variance of normal behavior could be due to combinations of a small number of dimensions, for example the five-factor model of the personality dimensions of neuroticism, extraversion, openness to experience, agreeableness, and conscientiousness (Costa & McCrae, 1985), whereas psychopathology represents extremes of the dimensions (e.g., Smoller & Tsuang, 1998). For instance, in a recent study Stemberger and coworkers (1995) reported that individuals with the generalized subtype of social phobia scored higher on neuroticism and lower on extraversion (i.e. more introverted) compared to a nongeneralized subgroup and controls. The function of the behavioral inhibition system, which may be a precursor to anxiety disorders in adulthood, is also associated with high levels of neuroticism and introversion (Mineka & Zinbarg, 1995). Genetic studies (e.g., Andrews et al., 1990; Young, Fentom, & Lader, 1971) have revealed that the personality trait neuroticism has a heritability of approximately 50 percent, and that the inheritance of this trait contributes to the transmission of pathological anxiety on a genetic basis. To summarize, genetic factors underlying anxiety disorders appear to be of a general nature, which could imply that it is inheritance of a general trait such as neuroticism that predisposes to pathological anxiety.

Family environment

As previously outlined, whereas some family studies have suggested that the familial component in social phobia may be etiologically specific (e.g., Fyer et al., 1995), several genetic studies (see e.g., Hudson & Rapee, 2000 for a review) have rather indicated that the genetic component is common to all of the anxiety disorders. Combining these sources of information it is likely that the family environment, or other environmental and learning factors, are of importance for channeling this general genetic anxiety proneness toward specific anxiety disorders. The literature is tapping three major areas, including childrearing styles, modeling, and restricted exposure, as candidates in the family's contribution to develop a particular anxiety disorder.

A wealth of retrospective studies (e.g., Arrindell, Emmelkamp, Monsma, & Brilman, 1983; Arrindell et al., 1989; Lieb et al., 2000) have indicated that social phobics as compared to healthy individuals perceive their parents as having been more overprotecting (or controlling) and rejecting. Further, some studies (e.g., Arrindell et al., 1983; 1989) reveal preliminary evidence that perceived parental overprotection by the probands could differentiate social phobia from other anxiety disorder such as agoraphobia and panic disorder. At least the relationship seems more consistent in social phobia. Studies (e.g., Rapee, 1997) which directly observe parent-child interactions support the data obtained in the retrospective studies and indicate that parents of anxious persons are more overprotective than parents of nonanxious persons, i.e. suggesting that the relationship may be more than a perceived one. A possible

mechanism by which overprotection from parents may be associated with increased anxiety levels in the child is the information provided to the child that the world is a dangerous place, and further that the child does not necessarily have the ability to protect him- or herself.

Modeling and restricted social exposure have gained some support concerning involvement in the development of social phobia (see e.g., Hudson & Rapee, 2000 for a review). For example Rapee and Melville (1997) reported that social phobics as compared to healthy controls, in agreement with their mothers, recalled their parents as low in socialization. Moreover, Bruch and Heimberg (1994) found that persons with social phobia, as compared to agoraphobics and a nonclinical control group, retrospectively perceived their parents as overemphasizing the opinions of others and wanting to isolate them. Parents who are themselves socially anxious may teach their child, through modeling of social concerns and restricted exposure to social situations, that social situations are harmful and the best way of handling them is avoidance.

Aside from the family environment there are other environmental factors implicated to be of relevance for the origin of social phobia, including childhood illness, social isolation, being bullied by peers, or birth order (see e.g., Hudson & Rapee, 2000 for a review). For example, some studies (e.g., Greenberg & Stravinsky, 1985) have observed that social anxiety may be related to individuals who are firstborn or the only child, albeit others (e.g., Furmark et al., 1999; Rapee & Melville, 1997) have failed to find such relation. However, since research to date is limited and at best suggestive it is too early to draw strong conclusions about the role of these factors in the development of social phobia.

In addition, developmental periods have also been discussed as being important in the origin of social phobia (e.g., Hudson & Rapee, 2000). The research suggest that the onset of adolescence coincides with the onset of enhanced self-consciousness, which in turn, according to some studies, corresponds to the onset of social phobia. Still others theorize (e.g., Öhman, 1986) that the onset of social phobia in early adulthood is due to this period being the time when an individual tries to find a place within the social system.

Cognitive factors

Since it is not clear if cognitive factors are antecedents or consequences of social phobia recent cognitive theories of social phobia have largely focused on information processing suggested to, at least, play a role in the maintenance of social anxiety (Musa & Lépine, 2000). A possible scenario may be that once social phobia has developed, it is maintained by cognitive biases. A selective bias for threat is thought to be an important factor in anxious states, affecting information processing in attention to, interpretation of, and memory of threatful events (Musa & Lépine, 2000). A number of cognitive theories trying to explain social anxiety have been developed (e.g., Beck & Emery, 1985; Leary & Kowalski, 1995; Clark & Wells, 1995).

Research using experimental paradigms such as the Stroop test supports that social phobics are hypervigilant to social threats (see e.g., Musa & Lepine, 2000 for a review).

For instance, Mattia, Heimberg, and Hope (1993), in a revised version of the Stroop test, reported increased response latencies to socially threatening words in persons with social phobia compared to a control group, indicating a bias towards threatening stimuli. Furthermore, the existence of a memory bias, that is, better retrieval of threat relevant stimuli, for individuals with social phobia, has mixed support. For example, Lundh and Öst (1996) found a memory bias for critical faces in social phobics as compared to healthy individuals, while others have failed to find memory biases for threatening stimuli in individuals with social phobia (e.g., Rapee, McCullum, Melville, Ravenscroft, & Rodney, 1994). There is also support for an interpretation bias in social phobics involving tendencies to underestimate the efficacy of their own behavior (e.g., Stopa & Clark, 1993), interpret ambiguous stimuli as negative (e.g., Amir, Foa, & Coles, 1998), and to overestimate the probability of danger in social situations (e.g., Foa, Franklin, Perry, & Herbert, 1996).

Associative learning accounts

Theories of the origin and maintenance of phobias also include the various forms of the associative learning account, according to which fear of social situations are held to be learned from pairings with aversive stimuli, i.e. classical conditioning, such as particularly embarrassing or humiliating life events (Mineka & Zinbarg, 1995). Although the classical conditioning model can explain why phobics react with subjective and physiological fear when they are exposed to the phobic object or situation, it fails to account for the persistent avoidance behavior that phobics display. A solution to the latter is the two-stage theory of Mowrer (1960, cited in Merckelbach, de Jong, Muris, & van den Hout, 1996). Briefly, Mowrer claimed that the initial acquisition of a phobia is due to classical conditioning. Then the phobia is maintained by instrumental learning, which means that the individual learns that avoiding the phobic stimulus can reduce fear. This in turn reinforces the avoidance behavior and makes it an integral part of the phobia. Though, the classical conditioning model of phobias and its extension have been subject to an extensive criticism. For instance, the model fails to explain why specific fears are nonrandomly distributed and why not all phobias can be traced back to a confrontation with a traumatic or aversive event (see e.g., Merckelbach et al., 1996 for a review). Öst and Hugdahl (1981) however reported that 58 percent of their social phobic sample could identify a specific traumatic event prior to the onset of their disorder. Moreover, Stemberger and coworkers (1995) found that 56 percent of persons with specific and 40 percent of persons with generalized social phobia recalled an aversive event that marked the onset. On the other hand, a lot of people can not trace back their phobia to a specific event but instead retrospectively describe always having been anxious (e.g., Menzies & Clarke, 1995).

An evolutionarily oriented revision of the classical conditioning approach is the preparedness theory (Seligman, 1971), which implies that there is an evolution-based predisposition to acquire fears of for example angry or rejecting faces. This theory predicts genetic influences, in line with the moderate genetic contribution reported in social phobia,

which will optimize evolutionary fitness (Kendler et al., 1992). In experiments done by Öhman and colleagues (see e.g., Öhman, 1986 for a review) they observed that people conditioned to angry faces showed significant resistance to extinction compared to those exposed to happy and neutral faces. Furthermore, these experiments elucidated that individuals acquired conditioned autonomic responses more readily to evolutionarily relevant cues such as angry faces than happy and neutral faces. Taken together, the data seem to support the central tenet of preparedness theory. Conditioning could be demonstrated even when the conditioned stimuli (the angry faces) were presented below the threshold of consciousness (Öhman, 1986). Lastely, according to Öhman and Dimberg (e.g., 1978) social fears have evolved as a by-product to dominance hierarchies involving highly ritualized displays, which in turn have strong facial components.

Neurobiological influences

Despite an accumulation of neurobiological studies on social phobia in the past decade, the specific biological features of the illness remain poorly understood. The major neurotransmitter systems implicated in the regulation of social anxiety are the serotonergic and dopaminergic (e.g., Bell, Malizia, & Nutt, 1999; Potts, Book, & Davidson, 1996; Tancer, 1993). Below I will briefly discuss the support for the contribution of each of the two systems to the symptomatology of social phobia. I am aware, however, that it is unlikely that a dysfunction in a single neurotransmitter system is solely responsible for the pathophysiology of social phobia. Instead it is more likely that these systems act in an integrated way, and also interact with other transmitting agents.

Serotonin

Serotonin, or 5-hydroxotryptamine (5-HT), is involved in a range of functions including emotional states such as mood and anxiety (e.g., Lesch et al., 1996). Yet, there is no consensus on whether 5-HT enhances or attenuates anxiety (e.g., Graeff, Guimaraes, De Andrade, & Deakin, 1996). Early animal data indicate that elevated 5-HT function is accompanied by an increase in aversive and avoidant behavior, whereas more recent developed animal models of anxiety do not always fit the above hypothesis (Graeff, Viana, & Mora, 1997; Handley, 1995). Further, also clinical studies are in disagreement (e.g., Graeff et al., 1997). However, clinical studies on SSRIs, a group of drugs that enhance 5-HT function, have shown to be effective in anxiety disorders including social phobia (e.g., Stein & Stahl, 2000).

Based on the clinical effectiveness of SSRIs in the treatment of social phobia (e.g., Van Ameringen et al., 1999), and challenge studies using fenfluramin (a 5-HT releasing agent), and metacholrophenylpiperazine (a 5-HT receptor agonist), serotonergic involvement in social anxiety is supported (e.g., Nutt, Bell, & Malizia, 1998; Potts et al., 1996; Stein, 1998). The challenge studies indicate that 5-HT_2 receptors are hypersensitive in individuals with social phobia and associated with enhanced anxiety reactions. At the same time, the paradox of on the

one hand increased anxiety in response to serotonergic agents, and on the other hand that SSRIs have an anxiolytic effect through elevated serotonergic neurotransmission, illustrates the complexity surrounding the role of 5-HT in anxiety, and highlights the need to clarify its specific functions in social phobia.

One possible solution of the contradiction comes from a proposal by Deakin and Graeff (1991) suggesting that at least two independent serotonergic pathways are involved in anxiety. An ascending pathway from the dorsal raphe nucleus to the amygdala and frontal cortex is believed to facilitate conditioned fear, while a descending pathway to the periaqueductal grey region is supposed to inhibit unconditioned fear. A further explanation could be the distinction between short and more long lasting effects of enhanced 5-HT concentrations in the brain. Partial support for the latter could be that clinical data do indicate that early in treatment with SSRIs, there can be an increase in anxiety symptoms before the more long lasting anxiolytic effect is established (Stein & Stahl, 2000).

Preliminary evidence indicates that SSRIs also may have a role in the treatment of selective mutism, an illness thought to be a childhood variant of social phobia (Nickell & Uhde, 1995). A recent study (Knutson et al., 1998) has indicated that SSRIs may enhance sociability even in healthy individuals. In addition, in adult male vervet monkeys, drugs that enhance 5-HT concentrations in the brain, advance the acquisition of social dominance (e.g., Raleigh, McGuire, Brammer, Pollack, & Yuwiler, 1991).

Variance in traits related to anxiety such as neuroticism and harm avoidance are thought to be generated by a complex interaction of environmental and genetic factors involving distinct brain systems such as the midbrain raphe 5-HT system (e.g., Lesch et al., 1996). Although heritability ranges from 40 to 60 percent for neuroticism and harm avoidance (e.g., Herbst, Zonderman, McCrae, & Costa, 2000), research in molecular genetics has just began to try to identify the genes underlying anxiety symptoms. Lesch and coworkers (1996) found that both neuroticism and harm avoidance were associated with a polymorphism in the 5-HT transporter (5-HTT) gene regulatory region. Low transcriptional activity, leading to less available 5-HT in the brain, is related to anxiety. However, this association accounted only for 7 to 9 percent of the variance for the observed traits. Both replications (Katsugari et al., 1999; Ricketts et al., 1998) of the latter study, but also numerous failures to replicate (Ebstein et al., 1997a; Gelernter, Kranzler, Coccaro, Siever, & New, 1998; Herbst et al., 2000; Kumakiri et al., 1999; Mazzanti et al., 1998) have been reported. Further, two studies (Heils et al., 1996; Mazzanti et al., 1998) revealed an association between the 5-HTT gene regulatory region and two subdimensions of harm avoidance, anticipatory worry and fear of uncertainty. Since neuroticism and harm avoidance are suggested to play a role in the predisposition toward anxiety disorders in general and particularly social phobia, Stein, Chartier, Kozak, King, and Kennedy (1998) conducted a study to determine if the generalized subtype of social phobia was genetically linked either to the 5-HTT gene or to the 5-HT_{2A} receptor gene. They found no evidence of linkage between generalized social phobia and the two above genes. Additionally,

Chatterjee, Sunitha, Velayudhan, and Khanna (1997) explored platelet 5-HT_2 receptor density in social phobics and healthy controls. They revealed no difference between the two groups. Thus, this inconsistency among the above molecular genetic studies raises questions of construct validity which could be low for the concepts used and if the wrong combination of genes was targeted.

Dopamine

Monoamine oxidase inhibitors have shown to have an anxiolytic effect on social phobia, which lends some support to the theory that the dopamine system is involved in the regulation of social anxiety (e.g., Potts et al., 1996; Stein, 1998). However, monoamine oxidase inhibitors act on serotonin as well as dopamine, which makes it difficult to disentangle these two systems from each other. Further, two studies (Lauterbach & Duvoisin, 1987; Stein, Heuser, Juncos, & Uhde, 1990) have found an elevated rate of social phobia in patients with Parkinson's disease, an illness characterized by low brain dopamine concentrations.

Animal research has observed low central nervous system dopamine activity in timid mice (e.g., Bell et al., 1999). Yet, a levodopa challenge study by Tancer and coworkers (1994/1995) tried to examine the latter in humans but did not find any evidence of dopaminergic dysfunction based on this measure in individuals with social phobia compared to healthy controls.

Another avenue of research has investigated the possibility of a relationship between the dopamine 4 receptor gene (D4DR) and the temperamental trait novelty seeking, characterized by excitement in response to novel stimuli and hypothesized to be mediated at least in part by genetic variability in dopamine transmission (e.g., Ebstein et al., 1996). Novelty seeking is thought to be a central feature of behavioral inhibition, which might be a precursor to social phobia. Some studies (Benjamin et al., 1996; Ebstein et al., 1996; Ebstein, Nemanov, Klotz, Gritsenko, & Belmaker, 1997b; Noble et al., 1998; Ono et al., 1997; Strobel, Wehr, Michel, & Brocke, 1999) have demonstrated an association between the longer allele of polymorphic exon III repeat sequences of the D4DR and high levels of novelty seeking, probably reflecting a decreased receptor sensitivity, whereas others have failed to replicate the above association (Ekelund, Lichtermann, Järvelin, & Peltonen, 1999; Gelernter, Kranzler, Coccaro, Siever, New, & Mulgrew, 1997; Herbst et al., 2000; Kühn et al., 1999; Malhotra et al., 1996; Pogue-Geile, Ferrell, Deka, Debski, & Manuck, 1998; Sander et al., 1997; Sullivan et al., 1998). Further, Rowe et al. (1998) examined the relation of the dopamine transporter gene (DAT1) to symptoms of internalizing disorders, including social phobia, in children with an average age of 10 years. The DAT1 10-repeat allele was found to be associated with all of the internalizing disorders and thereby also with social phobia. The function of the DAT1 10-repeat allele remains to be elucidated, even though the gene has in one recent study (Jacobsen et al., 2000) been suggested to be related to significantly lower dopamine transport binding.

Taken together, these data at least partly support a role for both 5-HT and dopamine in the regulation of social anxiety, even though the issue needs much further exploration. Moreover, an improved understanding of the neurobiological underpinnings of social anxiety may lead to development of new drugs with specific mechanisms of action.

THEORIES OF EMOTION

In pioneering work, William James (1894, cited in e.g., James, 1994) proposed that it was feedback from bodily responses that determined feelings and not the opposite, that is "we do not tremble because we are afraid, we are afraid because we tremble" (LeDoux, 1996, pp. 44-45). Thus, according to the James-Lange theory physiology always precedes subjective feelings, and hence without this physiological component there are no emotions. Second, there are no dedicated brain centers for emotion, other than the necessary sensory and motor cortices. Cannon and Bard (e.g., Cannon, 1927) later questioned the James-Lange theory. They claimed that the solution to the riddle of emotion is found within the brain and highlighted the hypothalamus together with the thalamus to play central roles in emotion. Emotional experience and emotional expressions were evoked simultaneously according to Cannon-Bard.

Papez (1937) reanalyzed the Cannon-Bard hypothesis and elaborated the brain circuit of emotion in more detail. He theorized that the cingulate cortex, thalamus, hypothalamus, and hippocampus played crucial roles in the circuitry underlying emotion. Around the 1950s, MacLean (e.g., 1949) posited the hippocampal formation (the term also included the amygdala) to be crucial in emotional experiences. These latter two theories of emotion have had a tremendous impact of subsequent emotion research.

Modern-day neuroanatomical models of emotion focus on the central nervous system, and feedback from the periphery is suggested to contribute to emotional intensity (e.g., Davidson, Jackson, & Kalin, 2000a; LeDoux, 1996). This account stems mainly from animal, lesion, and neuroimaging research, in contrast to earlier models of the emotional brain that were largely based on animal studies and theoretical reasoning. The current view of the neural circuitry underlying fear and anxiety is presented below.

NEURONAL UNDERPINNINGS OF FEAR AND ANXIETY

Evidence accumulated from animal, lesion, and neuroimaging data converge on the amygdala, in interaction with the prefrontal cortex and the hippocampus, playing a pivotal role in a neural circuit underlying fear and anxiety (e.g., Charney & Deutch, 1996; Charney, Grillon, & Bremner, 1998; Davidson et al., 2000a; Gorman, Kent, Sullivan, & Coplan, 2000; LeDoux, 1996). In the present thesis I will use fear and anxiety interchangeably even though distinctions can be made. Although much of the previous literature has focused on the above structures as critical components in human emotion processing, other regions, including the insular, the

anterior cingulate, and the parietal cortices, as well as the striatum, have been suggested to play an important role in this circuit too.

The amygdala monitors both external and internal stimuli and mediates behaviors that facilitate survival (e.g., Charney et al., 1998; Davidson & Sutton, 1995; LeDoux, 1996) (See Figure 1). The amygdala receives inputs or afferents from a wide range of regions in the brain. Briefly, it gets information about the external environment both from the sensory thalamus and from unimodal and polymodal cortical sensory processing regions. The former direct thalamus-amygdala pathway is suggested to provide the amygdala with a crude albeit fast image of the external world, whereas the latter thalamus-cortical-amygdala pathway provides the amygdala with more detailed and accurate information, such as objects and events. In addition, the shorter pathway is thought to allow a person to respond to threatening stimuli in a preconscious way, which partly may explain why some emotional responses are introspectively difficult to understand. Visceral afferent information ascends from the brainstem and from the hypothalamus. Moreover, the reciprocal interaction with the hippocampus and its related cortically regions, including the entorhinal and perirhinal areas, allow the amygdala to incorporate information about important processes such as contextual analyses, as well as an individual's prior experience, i.e. memory. This in turn may allow emotions to be triggered by fearful memories. Finally, inputs from the ventromedial prefrontal cortex are suggested to modulate emotional reactivity via inhibitory influences on the amygdala. For example, lesions of the ventromedial prefrontal cortex have shown to delay the extinction of fears (see e.g., LeDoux, 1996 for a review).

Different outputs or efferents from the amygdala mediate autonomic, neuroendocrine and skeletal motor responses subserving different expressions of anxiety and fear. For instance, projections to the periaqueductal gray control freezing, whereas projections to the striatum control avoidance and approach behavior. Furthermore, projections to the lateral hypothalamus through the rostral ventral lateral medulla in the brainstem control sympathetic autonomic nervous system activation, and efferents to the paraventricular hypothalamus and the bed nucleus of the stria terminalis exhibit control over stress reactions involving the pituitary-adrenal axis (e.g., Charney et al., 1998).

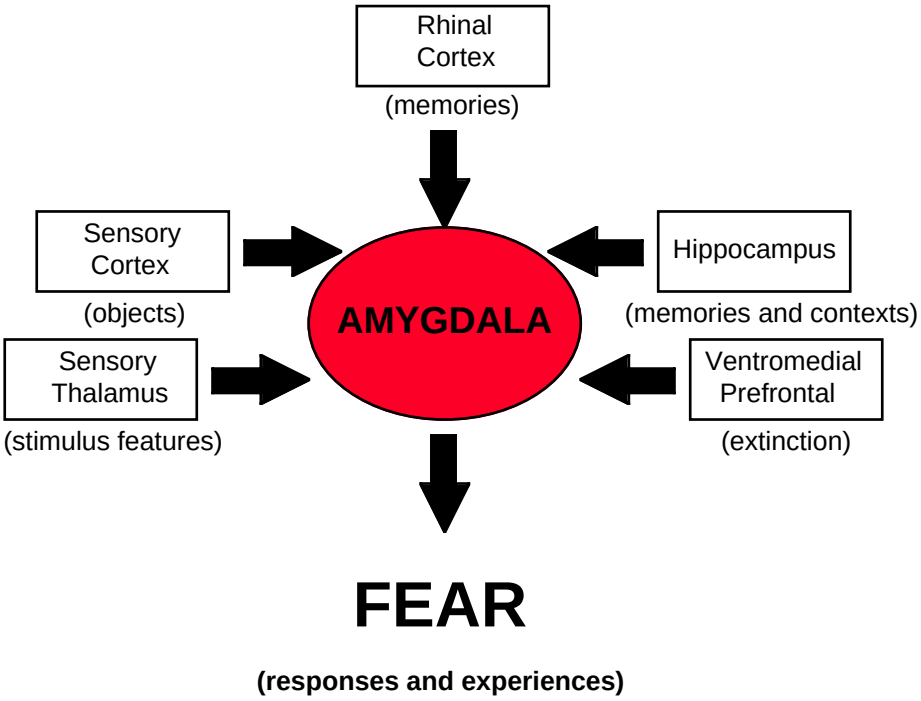

Figure 1. Brain regions mediating fear and anxiety. The figure is a modified version of a model previously presented by LeDoux (1996).

As previously outlined, most of the literature has focused on the amygdala, prefrontal cortex, and hippocampus to play a crucial role in emotional processes, and therefore I will present a more detailed description of the function of these three regions below.

Amygdala

The amygdala (Latin for almond) is located within the temporal lobes and support for its involvement in emotional processes, particularly in fear and anxiety, comes from a large body of research (e.g., see reviews by Davidson et al., 2000a; Davidson & Irwin, 1999; Davis & Whalen, 2001). Historically, Heinrich Klüver and Paul Bucy (1937) described a behavioral syndrome in rhesus monkeys with bilateral removal of the temporal lobes, which resulted in major affective disturbances expressed in behaviors such as abnormal approach, hyper-orality and sexuality, exaggerated tameness, and profound changes in social behavior. The Klüver and Bucy syndrome focused attention on the amygdala and its crucial role in regulating emotional behaviors. Further lines of evidence encompass single-cell recordings (Jacobs & McGinty, 1972; O'Keefe & Bouma, 1969), and electrical stimulation of amygdala (Kling & Brothers, 1992). For example, cells in the amygdala have been found that respond to emotionally salient stimuli such as faces (see e.g., Davis & Whalen, 2001 for a review). Moreover, there is compelling evidence that the amygdala is necessary for the acquisition of Pavlovian fear

conditioning (e.g., Davidson et al., 2000a ; LeDoux, 1996). Yet, it is not clear whether the amygdala is the place where this learned information is stored (e.g., Cahill, Weinberger, Roozendaal, & McGaugh, 1999).

A growing body of human lesion data supports the view that the amygdala is important for the perception and production of fear and anxiety as well as associative aversive learning (e.g., Davidson & Irwin, 1999; Davis & Whalen, 2001). However, the extent to which the human amygdala is involved also in positive affects it not clear. In humans, discrete lesions of the amygdala have been associated with impairment in memories for faces (e.g., Adolphs, Cahill, Schul, & Babinsky, 1997; Tranel & Hyman, 1990; Young et al., 1995), deficits in recognition of facial signs of fear (e.g., Adolphs et al., 1999; Broks et al ., 1998; Calder et al., 1996), impairment in electrodermal conditioning (e.g., Bechara et al., 1995; LaBar, LeDoux, Spencer, & Phelps, 1995), deficits in the recognition of vocal expressions of fear and anger (Scott et al., 1997; Sprengelmeyer et al., 1999), and deficits in startle potentiation in response to aversive stimuli (Angrilli et al., 1996). In addition, fear seems to be the most prevalent affect elicited by temporal lobe epileptic discharge (Gloor, 1992).

Neuroimaging techniques such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) allow for study of the intact amygdala and are helping to clarify its functional role in emotional processing. Generally, early neuroimaging studies did not observe amygdalar activity during symptom provocation in different anxiety disorders using the traditional subtractive methodology (see e.g., Rauch & Shin, 1997 for a review). Results from more recent brain mapping studies in individuals with different psychiatric disorders, however, have demonstrate activation of the amygdala in posttraumatic stress disorder (Liberzon et al., 1999; Rauch et al., 1996; 2000; Semple et al., 2000; Shin et al., 1997), depression (Abercrombie et al., 1998; Drevets et al., 1992), obsessive-compulsive disorder (Breiter et al., 1996), and social phobia (Birbaumer et al., 1998; Schneider et al., 1999).

Several neuroimaging studies have observed activation of the amygdala in response to facial expressions of fear, which is in congruence with lesion data (Breiter et al., 1996; Morris et al., 1996; Phillips et al., 1997). Further, Whalen and colleagues (1998) demonstrated amygdala activity also during preconscious awareness of fearful facial expressions. Moreover, in line with both lesion and animal data, a number of brain mapping studies of classical aversive conditioning have reported amygdala activation (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). According to two fMRI studies (Büchel et al., 1998; LaBar et al., 1998) the amygdala seems to be required only in the early phases of the associative learning process. Further, other types of manipulations have been found to activate the amygdala, including unsolvable anagram tasks used to induce learned helplessness (Schneider et al., 1996), aversive odor (Zald & Pardo, 1997), aversive taste (Zald, Lee, Fluegel, & Pardo,

1998), aversive pictures (Lane et al., 1997; Paradiso et al., 1999; Reiman et al., 1997; Taylor et al., 1998), threatening words (Isenberg et al., 1999), dispositional negative affect (Abercrombie et al., 1998; Fischer, Tillfors, Furmark, & Fredrikson, 2001), and finally recall of aversive stimuli (Cahill et al., 1996; Hamann, Ely, Grafton, & Kilts, 1999).

To conclude, the above data clearly implicate the amygdala as an important site in the neural circuitry underlying anxiety and fear, both in animals and humans. A few questionmarks remain, however. For instance, does the amygdala responding to affect in general or only to negative affect in particular? Is it just in the initial stages of learning processes that amygdala activation is required? Can the amygdala, with its numerous nuclei, be treated as a functional homogeneous region? Further, Whalen has in a recent review (1998) added a complementary explanation for the amygdala activations observed in response to fear and anxiety. He considers the amygdala to be a component of a vigilance system preferentially evoked by ambiguous stimuli of biological relevance.

Prefrontal cortex

A large corpus of data support the view that the prefrontal cortex is an important part of the brain circuitry underlying emotional processing that implements both positive and negative affect (e.g., Davidson et al., 2000a; Davidson &Irwin, 1999; Davidson, Putnam, & Larson, 2000b). Prefrontal cortex is a heterogeneous region with different anatomical and functional subdivisions. Distinctions have been proposed between the ventromedial/orbitofrontal and the dorsolateral prefrontal cortices, and among the left and right hemispheres within each of these regions (e.g., Davidson et al., 2000a; Davidson &Irwin, 1999). Theories of emotion and motivation have emphasized the right hemisphere as being dominant in experiences of negative affect (the withdrawal system) and the left in positive affect (the approach system)(e.g., Davidson & Irwin, 1999; Gray, 1994; Lang, Bradley, & Cuthbert, 1990; Sutton & Davidson, 1997).

Evidence drawn from an early wave of human lesion studies that examined mood subsequent to brain damage have suggested that depressive symptoms are enhanced following left-sided anterior prefrontal damage, affecting the dorsolateral prefrontal cortex in the majority of the patients (e.g., Davidson et al., 2000a). This is in line with the idea that depression is related to deficits in positive affect. A review of Morris, Robinson, Raphael, and Hopwood, (1996), including more recent data, largely supports those early studies.

Neuroimaging studies in healthy individuals as well as in persons with anxiety disorders have reported emotion related neural alterations in the prefrontal cortex. For example, consistent with the lesion data Davidson, Ekman, Saron, Senulis, and Friesen (1990) observed that induction of positive and negative affect changed the asymmetry in electrical activity in the prefrontal cortex in a consistent manner in healthy persons. That is, film-induced disgust and fear revealed relative right-sided prefrontal and anterior temporal activation. An opposite asymmetric pattern of activation was elicited by induced positive affect. Further, Rauch,

Savage, Alpert, Fischman, and Jenike (1997), pooling data from obsessive-compulsive disorder, specific phobia, and posttraumatic disorder, found that increases in right-sided activation in the prefrontal cortex (right inferior and right medial orbital prefrontal cortex) were associated with increased negative affect. Significant decreases as well as increases in cerebral blood flow in the prefrontal cortex have been found in anxiety provocation studies on specific phobia (Fredrikson, Wik, Annas, Ericson, & Stone-Elander, 1995; Johanson et al., 1998; Wik et al., 1993) and induced panic (Fischer, Anderson, Furmark, & Fredrikson, 1998). Less support, however, is available for involvement of the prefrontal cortex in positive affect, partly because most of the research on emotion done this far has been on negative affect. However, for instance, Goel and Dolan (2001) in an fMRI study of the functional anatomy of humor reported that the ventromedial prefrontal cortex correlated with the participants' funniness ratings of the jokes. Yet, it must be noted that not all the neuroimaging data indicating asymmetries in prefrontal cortex have rigorously analyzed the interaction of condition with hemisphere, and hence, must be regarded with caution.

The ventromedial/orbitofrontal cortex, probably in interaction with the amygdala, has been implicated in choice (e.g., Baxter, Parker, Lindner, Izquierdo, & Murray, 2000; Bechara, Damasio, Damasio, & Lee, 1999; Davis & Whalen, 2001), social behaviors (e.g., Andersson, Bechara, Damasio, Tranel, & Damasio, 1999), attachment of emotional valence to significant stimuli (e.g., Rolls, 1999), and emotional regulation of negative affect including both fear/anxiety and anger (e.g., Davidson et al., 2000a; 2000b; LeDoux, 1996). This region has also been suggested to play a role in affective working memory, a process that according to Davidson and coworkers (2000a) is critical when an individual is anticipating future affective outcomes.

Phineas Gage (Harlow, 1868, cited in Damasio et al., 1994) who sustained an injury in the ventromedial/orbitofrontal prefrontal cortex, is probably the most famous case study in the literature. After the injury his personality changed dramatically, expressed in impulsive behaviors and emotional instability. Further, Bechara and coworkers (1998) reported a double dissociation between working memory and decision making whereby persons with damage to the ventromedial prefrontal cortex showed impaired decision making in anticipation of future positive and negative consequences while performing adequately on a working memory task. In contrast, individuals with lesions in the dorsolateral prefrontal cortex were impaired on the working memory task while they performed normally on the decision task.

In summary, the data reviewed provides evidence that the prefrontal cortex plays an important role in emotional processes. However, future research needs to disentangle the various subdivisions' specific role in different emotions. Further, it remains to be clarified whether the association between the prefrontal cortex and the amygdala is mostly inhibitory or excitatory as well? Similarly, do top-down or bottom-up processes mediate the neural circuitry underlying emotion?

Hippocampus

Hippocampus is largely implicated in memory and cognition, including processes such as episodic memory encoding, memory consolidation, and spatial analyses (e.g., LeDoux, 1996). To a lesser extent, though, has hippocampus been considered for a role in emotion. However, Gray and McNaughton (1996) for example argue that the septo-hippocampal formation is also a strong candidate for playing a crucial role in human anxiety conditions. They draw a distinction between two brain motivational systems: the behavioral activation system (BAS) and the behavioral inhibition system (BIS). The BAS regulates behavior in the presence of rewards whereas the BIS is activated by conflicting information regarding potential danger in the external environment, signaling to the individual the need of stopping ongoing behavior and instead become attentive. Human anxiety is thought to arise from excessive activity in the septo-hippocampal formation, which is suggested to make up the BIS. The conclusions are to a large extent based on observations that the behavior pattern elicited by anxiolytic drugs closely parallels the behavior pattern seen after damage to the BIS. Somewhat similarly, Reiman (1997) postulates that the hippocampus together with the amygdala and paralimbic areas serve as an external alarm center, which is suggested to alter an individual's attention to outside dangers.

Contextual conditioning is attributed to the hippocampus, whereas the amygdala is suggested to play a critical role in cue specific conditioning (e.g., Gorman et al., 2000; LeDoux, 1996). If the amygdala is lesioned after aversive conditioning to a tone, an animal will no longer exhibit a fear reaction to the tone, but it will react fearfully to the context where the fear conditioning took place (e.g., Gorman et al., 2000). In analogy, avoidance behaviors that social phobics display may arise from an association of excessive anxiety with the social context/situation in which the anxiety occurred. Further, the hippocampus (together with the rhinal cortex) is implicated in the formation and retrieval of fearful memories (LeDoux, 1996). It also projects extensively to the amygdala. In a phobic situation, retrieval of fearful memories of the past may allow anxiety reactions to be triggered by such memories on a hippocampal/amygdala level.

To conclude, the border between cognition and emotion does not seem so sharp, since the hippocampus appears to be involved in different aspects of emotional processes including behavior inhibition, contextual conditioning, and formation and retrieval of fearful memories.

Neuroimaging: Studies of social phobia

The use of neuroimaging to explore the neurobiological correlates of social anxiety is a relatively new technique. In previous PET-studies, social anxiety has been associated with: i) enhanced perfusion in the right dorsolateral prefrontal and the left parietal cortices (Bell et al., 1999), ii) deactivations in the visual and medial frontal cortices (Van Ameringen et al., 1998), and iii) rCBF increases in the lateral prefrontal, sensorimotor, anterior temporal, and midcingulate cortices as well as in the thalamus. Trend significances were reported for the

amygdala, hippocampus, hypothalamus, and the cerebellar vermis as well as in the anterior cingulate and medial prefrontal cortices (Reiman, 1997). Because these studies (Bell et al., 1999; Reiman, 1997; Van Ameringen et al., 1998) only reported preliminary data and since the completed studies have not yet been published, it is difficult to properly evaluate the results. Moreover, Davidson, Marshall, Tomarken, and Henriques (2000c) examined electroencephalograms in social phobics while they anticipated a public speech. A right-sided activation was observed in the anterior temporal and lateral prefrontal scalp regions. Using fMRI, Birbaumer and colleagues (1998) observed that the amygdala was activated in the processing of neutral faces in social phobics but not in non-phobics. Another fMRI study (Schneider et al., 1999) investigating aversive conditioning processes in social phobics also reported enhanced amygdaloid blood flow.

Further, other studies on social phobia encompass brain structural volume (Potts, Davidson, Krishnan, & Doraiswamy, 1994), and resting metabolic activity (Davidson et al., 1993; Stein & Leslie, 1996; Tupler et al., 1997). For example, Potts and coworkers (1994) failed to demonstrate any specific cerebral structural abnormalities in social phobics, although they did reveal a greater age related reduction in putamen volumes in persons with social phobia compared to controls. Finally, results from the latter three studies point to possible basal ganglia abnormalities in social phobia.

In addition, in a recent PET study our group (Furmark et al., submitted) explored the neural effects of SSRIs and cognitive behavioral treatments for social phobics and waiting-list controls. Symptoms improved significantly and roughly equally in both treatment groups whereas waiting-list controls did not change. Improvement was accompanied by a decreased rCBF in the amygdala, hippocampus, and neighboring cortical areas, i.e. “the alarm system” of the brain. Support for the involvement of serotonin in social phobia symptomatology comes from a recent study of presynaptic serotonin function in social phobia also performed by our group (Marteinsdottir et al., submitted) using the radiolabeled serotonin precursor, [3 -^{11}C]–5-HTP (5-HTP), and PET. We found that social phobics, as compared to healthy individuals, appear to be characterized by regionally attenuated accumulations of 5-HTP, suggesting suppressed serotonin synthesis in brain areas mediating anxiety, mainly in the periamygdaloid and rhinal cortices. Furthermore, two single photon emission computed tomography studies (Schneier et al., 2000; Tiihonen et al., 1997) indicate that social phobia may be associated with a dysfunction of the striatal dopaminergic system. In summary, these preliminary data converge in that subcortical regions, including the amygdala, hippocampus and striatum together with the prefrontal cortex seem to be involved in the regulation of social anxiety.

THE EMPIRICAL STUDIES

This thesis presents three empirical studies based on epidemiology and neuroimaging in social phobia.

Study I

Social phobia and avoidant personality disorder as related to parental history of social anxiety: A general population study

Introduction and aim

The principal aim of study I was to examine parental history of excessive social anxiety in individuals meeting the DSM-IV criteria for social phobia and/or APD in epidemiologically identified probands in the general population using a validated questionnaire. Little is still known about the etiology of social phobia, and there was no family history study of social phobia in the general population when the present study was initiated. A high comorbidity (20-89%) has been reported between the Axis I disorder social phobia and the Axis II disorder APD. By including APD it is possible to elucidate whether these two disorders represent distinct clinical categories or not. Furthermore, gender differences in the prevalence of social phobia have been well established, at least in the general population. The origins of this skewed sex distributions is not well understood, but could reflect gender dependent transmission patterns. Therefore, we also studied if a positive parental history of excessive social anxiety in mothers and fathers moderated the risk of having social phobia differentially in men and women. In addition, because anxiety severity in probands may relate to the presence of parental history, we varied the diagnostic thresholds in order to create groups differing in severity.

Method

Study I was part of a larger epidemiological investigation of social phobia and APD in the Swedish general population and the methodology has been described in detail elsewhere (Ekselius, Tillfors, Furmark, & Fredrikson, 2001; Furmark et al., 1999). Briefly, a DSM-IV compatible and validated questionnaire was mailed to 1000 women and 1000 men randomly sampled from the greater Stockholm area and the island of Gotland. Their age varied between 18 and 70. Interpretable questionnaires were returned by 1202 subjects (541 men, 661 women; mean age = 41.8, standard deviation = 14.1; 621 from Stockholm and 581 from Gotland).

The validated questionnaire (Furmark et al., 1999) consisted of four different sections. The initial section evaluated sociodemographic data. The diagnostic section was based on 14 potentially phobic situations (five performance and nine interactional situations). The third section assessed parental history of excessive social anxiety and the fourth section contained questions regarding APD taken from the DSM-IV and International Classification of

Diseases and Related Health Problems, 10th ed. Personality Disorder Questionnaire (DIP-Q; Ottosson et al., 1998).

For the aim of the present study, the third section concerning parental history of excessive social anxiety was included. We inquired whether excessive social anxiety (yes/no questions) was present in the proband's mother and father. In addition, we examined social phobia and APD using various cut-off levels to determine if the parental history pattern was consistent over various anxiety levels, because prevalence decreases with increasing severity (Furmark et al., 1999).

To be diagnosed as having social phobia an individual had to fulfill the diagnostic DSM-IV criteria assessed with the questionnaire (Furmark et al., 1999). In determining if the parental history pattern was consistent over various anxiety levels we used both an à priori definition, where 188 individuals (15.6%) met the criteria for social phobia, and a second more conservative way to define cases where the subjects with social phobia were restricted from 188 (15.6%) to 23 individuals (7.5%) in the entire sample. Moreover, to be diagnosed as having APD, the individual had to fulfill four of the seven DSM-IV criteria assessed by the DIP-Q questionnaire (Ottosson et al., 1998) and at least two of the five general criteria regarding functional impairment and distress. Since the full version of the DIP-Q questionnaire covering the general criteria required for diagnosing APD was only distributed to the Gotland sample, we restricted analyses of APD to this sample. In addition, cases of APD were also defined by evaluating the number of fulfilled DSM-IV criteria (range 4-7). When defining cases of APD in this latter way data from the total sample were used.

Approximately four months after the last reminder had been sent out, a sample of 100 non-responders, matched to mimic the original sample with respect to sex, age, and place of residence (Stockholm or Gotland), was selected to be interviewed over the telephone. Subjects were asked whether they were willing to answer a brief question from the questionnaire. Fifteen subjects refused and five subjects were unreachable by telephone. Thus, a total of 80 individuals (40 men and 40 women, mean age = 43.0, SD = 14.2, range 20-71 years) were interviewed.

Results

Different cut-off levels for social phobia and APD consistently yielded an approximately two- to threefold risk of developing social anxiety as a function of a positive parental history (See Table 3).

Table 3. Relative risks (RRs), 95% confidence intervals (CIs) and p-values based on χ^2-analyses for individuals meeting diagnostic criteria for social phobia, isolated social phobia, avoidant personality disorder (APD), isolated APD, and finally only individuals with APD comorbid with social phobia as a function of a positive and negative parental history of excessive social anxiety in the probands' relatives (PH+ and PH- denote positive and negative parental history, respectively).

		Relatives		
Disorder		**PH+**	**PH-**	
Social phobia[1]	**Yes**	46	34	
	No	79	319	χ^2 = 48.90, 1df, p = .0001
				RR = 2.9, CI = 2.21-3.80
Isolated social phobia	**Yes**	29	27	
	No	93	326	χ^2 = 22.66 1df, p = .0001
				RR = 2.3, CI = 1.71-3.18
APD[2]	**Yes**	19	10	
	No	101	331	χ^2 = 25.06, 1df, p = .0001
				RR = 2.8, CI = 2.05-3.84
Isolated APD	**Yes**	5	3	
	No	115	338	χ^2 = 5.62, 1df, p = .0177
				RR = 2.5, CI = 1.41-4.31
APD comorbid with	**Yes**	14	7	
social phobia	**No**	106	334	χ^2 = 18.87, 1df, p = .0001
				RR = 2.8, CI = 1.96-3.91

[1]includes social phobia with or without APD, [2]includes APD with or without social phobia

Further, in both sexes of the probands we observed roughly a two-to threefold increased rate of social phobia as a function both of maternal and paternal positive family history of excessive social anxiety, except among male phobics with fathers suffering from social anxiety (relative risk = 4.2). However, because of overlapping confidence intervals the difference in relative risks in the relation between fathers and sons and the other groups in the present study can probably not be regarded as statistically reliable.

A total of ten (eight subjects from Stockholm and two from Gotland) of the 80 contacted non-responders, i.e. 12.5%, met the impairment criterion as assessed by the telephone interview. Among responders, 321 individuals (26.7%) met the impairment criterion,

assessed with the questionnaire, and in this respect they differed significantly from contacted non-responders ($\chi^2 = 9.1$, df = 1, $p < .005$).

Conclusions

Having an affected family member is associated with a two- to threefold risk increase for both social phobia and APD. Because familial aggregation of social anxiety was not modulated by Axis I or II diagnosis or diagnostic cut-off levels, the data imply that social phobia and APD may represent a dimension of social anxiety rather than separate disorders. Finally, the familial mediated risk of developing social phobia was neither affected by the sex of the parents or by the sex of the probands.

Study II

Cerebral blood flow in subjects with social phobia during stressful speaking tasks: A PET-study

Introduction and aim

Because the central nervous system representation of social phobia is largely unknown the aim of study II was to examine the functional neuroanatomy of social anxiety provocation in social phobics during a public speaking task, using the same verbal task without audience as baseline. To explore the neural pattern specific for social phobia we included a healthy non-phobic comparison group.

In neuroimaging and lesion studies emphasis is placed on the amygdaloid complex, the prefrontal cortex, and the hippocampus as important neural components underlying pathological anxiety (e.g., Davidson et al., 2000a; Davidson & Irwin, 1999). But also the cingulate, secondary visual, temporal, and parietal cortices as well as the insular have previously been observed in studies on rCBF redistribution resulting from perceptually induced anxiety. These studies are reviewed in Table 4.

Therefore, we performed a hypothesis driven directed search in brain areas that have previously been reported to alter neural activity as a consequence of anxiety provocation. Briefly, we predicted an increased brain perfusion in the amygdaloid complex and lower activity in the prefrontal, orbitofrontal, insular, parietal, and temporal cortices. Finally, involvement was predicted in the anterior and posterior cingulate cortices as well as in the secondary visual cortex, but no prediction was made as to whether rCBF would increase or decrease.

Table 4. Brain imaging studies displaying functional neural correlates associated with perceptually induced anxiety in individuals with specific phobia, post traumatic stress disorder (PTSD), and social phobia.

First author	Symptom provocation	CG	Front	Temp	Pariet	Occip	SC/CB
Specific phobia							
Mountz 1989[pet]	Confronted by the phobic object						
Fredrikson 1993[pet]	A videotape of snakes					+**B** sec	
Wik 1993[pet]	A videotape of snakes	-**B** post	-**B** orb -**B** pre	-**B** ant		+**B** sec	-**B** hipp
O'Carrol 1993[spect]	Description of a phobic exposure	-**L** ant		-**R** post		-**B** occip	
Fredrikson 1995[pet]	A videotape of spiders	-**B** post	-**B** orb -**B** pre	-**B** ant		+**B** sec	-**B** hipp
Johanson 1998[xenon]	A videotape of spiders		-**R** front +**R** front				
PTSD							
Shin 1997[pet]	Combat pictures[c]	+**R** post -**L** ant	-**R** med -**L** bro				+**R** amy
Bremner 1999[pet]	Combat pictures and sounds[c]	+**R** post	+**L** pre -**R** pre	-**L** med	+**L** inf -**R** pariet	+**R** sec	+**R** cb -**L** thal
Liberzon 1999 [spect]	Combat sounds[c]	+**R** ant -**R** post	+**R** pre				+**L** amy
Rauch 2000[fMRI]	Masked presentations of fearful faces[c]						+**R** amy
Social phobia							
Reiman 1997[pet]	Singing in the presence of an audience	+post +ant[t]	+semo +pre	+ant			+thal +amy[t] +hipp[t] +hypo[t] +vermis[t]
Van Ameringen 1998[pet]	A videotaped interview with the patient		-med			-sec	

Abbreviations: + = more neural activity in the target task than in a reference, - = less neural activity in the target task than in a reference, amy = amygdala, ant = anterior, **B** = bilateral, bro = Brocas' area, [c] = control group included, cb = cerebellum, CG = cingulate gyrus, Front = frontal cortex, [fMRI] = Functional MRI- methodology, hipp = hippocampus, hypo = hypothalamus, inf = inferior, **L** = left, med = medial, Occip = occipital cortex, orb = orbitofrontal cortex, Pariet = parietal cortex, [pet] = PET-methodology, post = posterior, pre = prefrontal cortex, **R** = right, [spect] = SPECT- methodology, SC/CB = subcortical structures and cerebellum, sec = secondary, semo = secondary motor cortex, [t] = trend towards significance, thal = thalamus, Temp = temporal cortex

Method

Eighteen right-handed individuals (10 men and 8 women) with DSM-IV defined social phobia (mean age = 35.2 years, ± SD = 7.34, range 23-46) and six (3 men and 3 women) right-handed healthy non-phobic subjects (mean age = 22.5 years, ± SD = 1.19, range 21-26) were recruited. The number of individuals with social phobia was higher and the anxiety provocation session was repeated after treatment with cognitive-behavioral therapy and citalopram as well as for a waiting list comparison group (reported in a separate paper) creating four groups of equal sample sizes. Criteria for exclusion were: previous or current organic brain disorders and somatic diseases, current comorbid Axis I disorders, menopause, and pregnancy. Screening included psychiatric (First, Gibbon, Spitzer, & Williams, 1998) and medical histories. Informed consent was obtained.

PET and ^{15}O-water was used to measure rCBF while the participants were speaking in the presence of a surrounding audience (6-8 silently observing individuals) and alone during 2.5 min. Heart rate and subjective anxiety were also recorded. About 20 min before the initial scan, subjects were instructed to prepare a 2.5 min speech about a travel experience or a vacation. Each task was repeated and scanned twice with the order counterbalanced between subjects. During the provocation but not during the control condition participants were videotaped from a close distance to enhance social anxiety.

PET data were obtained using previously validated methods. Investigations were performed on a GEMS PC2048-15B scanner with a 10 cm axial field of view (Holte, Eriksson, & Dahlbom, 1989), producing 15 slices with a 6.5 mm slice spacing and a 6 mm axial/transaxial resolution. Before each speaking task 700-1300 Mbq of ^{15}O-water in 3-4 ml of water (approximately 15 Mbq/kg body weight) was injected with 12-min intervals. The subjects were told to start speaking immediately following injections and data were collected in fifteen 10-sec frames. Each subject had a total of four emission scans during two conditions. Data from the first 70 sec after arrival of the bolus to the brain were summed. Normalization of all individual CBF images into a standard brain shape (Greitz, Bohm, Holte, & Eriksson, 1991) was performed automatically.

Subjective and physiological measures of fear and anxiety were averaged over the repetitions for each condition separately and analyzed with repeated measures analyses of variance (ANOVAs) as well as unpaired and paired t-tests performed in Statview 4.5 for Macintosh. An alpha level of 0.05 was applied.

A group by condition blocked ANOVA (Friston et al., 1995) with one between groups factor (phobics vs comparison subjects) and one within groups factor (public vs private speaking) was used**.** The two normalized rCBF images during each task were averaged into mean images to increase signal to noise ratio and to account for between subject variance, compatible with a random effects model (Petersson, Nichols, Poline, & Holmes, 1999). In order to compare rCBF activity from the 18 social phobics with rCBF activity from the six comparisons we used a balanced contrast vector (Friston et al., 1995). Global flow was

estimated using a predefined mask outlining the brain, but excluding all voxels which changed as a consequence of study conditions using F-map masking (Andersson, 1997). PET-data were normalized for global flow using linear scaling (Andersson, 1997). A threshold z-score of 2.6 ($p < .005$) uncorrected for multiple comparisons (Kosslyn et al., 1996) was used to examine areas of activation within hypothesized brain areas.

Results

Four repeated ANOVAs (Group by Condition), using heart rate, Spielberger's State Anxiety Inventory (STAI-S; 20-80; Spielberger, Gorsuch, & Lushene, 1983), fear, and distress as dependent variables revealed significant main and interaction effects for all the variables except for the heart rate interaction (See Figure 2).

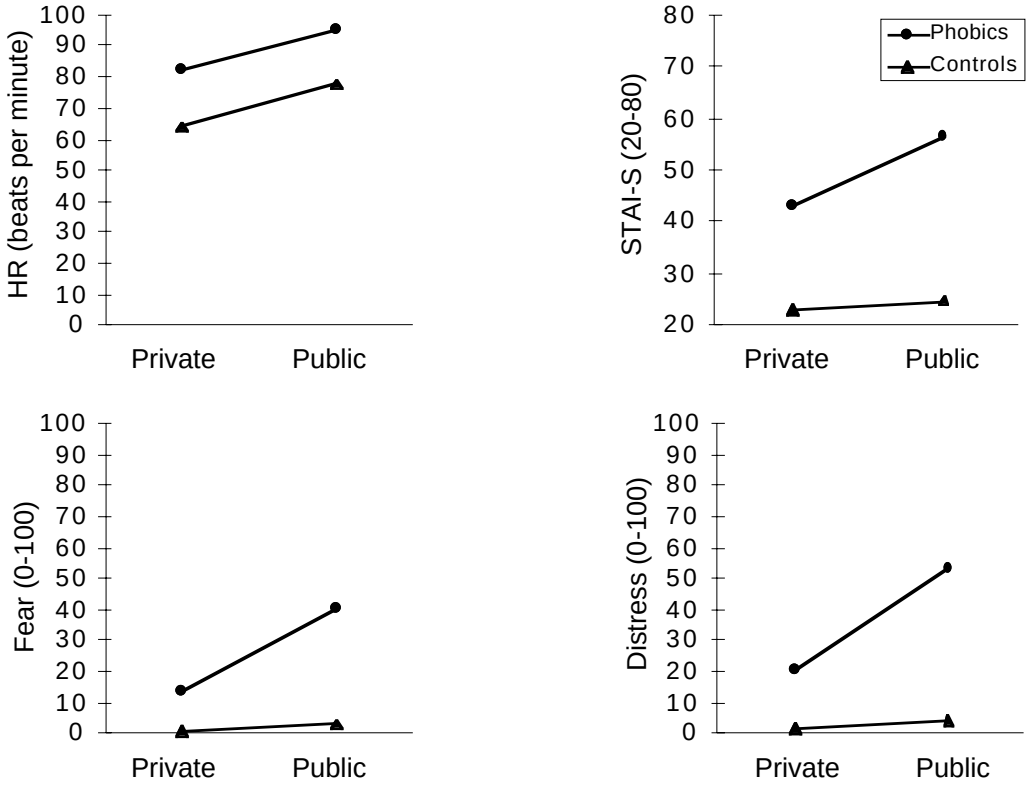

Figure 2. Interaction plots showing mean values for heart rate and subjective measures of negative affect during private and public speaking for 18 social phobics and six comparison subjects.

Increased anxiety was accompanied by enhanced rCBF in the amygdaloid complex (the amygdala and the periamygdaloid cortex corresponding to Brodmann area 34) extending into the hippocampus in social phobics relative to comparison subjects (See Table 5 and Figure 3). In addition, in social phobics rCBF-increases in the right amygdala from public to private speaking were positively correlated with the corresponding change scores in self-reported fear (r_{xy} = .52, df = 16, $p < .05$).

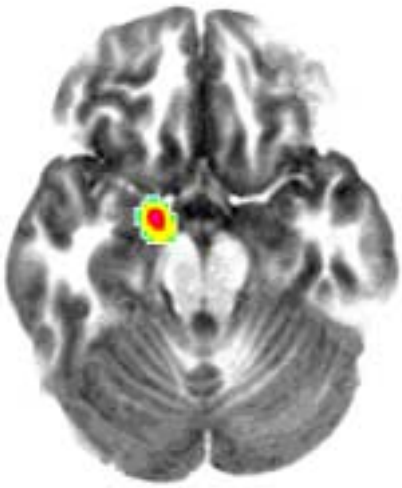

Figure 3. Increased normalized relative rCBF in the amygdaloid complex in 18 social phobics as compared to six comparison subjects during public minus private speaking.

Cortically, brain blood flow decreased in social phobics and increased in comparison subjects more during public than private speaking bilaterally in the insular cortex as well as in the right temporal pole, and increased less in the social phobia group compared to the comparison group in the right parietal and secondary visual cortices. Further, rCBF increased in the comparison group but not in social phobics bilaterally in the perirhinal and retrosplenial cortices (See Table 5). In addition, rCBF in the orbitofrontal cortex (BA 12) tended to decrease more in social phobics than in comparison subjects (maximum z-value = 2.30, n = 24; x = 3, y = 58, z = -9).

Table 5. Relative rCBF differences between social phobics and non-phobic healthy individuals during public vs private speaking. Brain areas and Talairach coordinates for maximum voxel z-value above 2.6 for relative rCBF increases and decreases (n = 24).

Brain areas	x	y	z	Maximum voxel z-value
Regions with higher rCBF in phobics				
R Amygdaloid complex	12	-8	-17	2.85
Regions with lower rCBF in phobics				
R + L Insular cortex (13, 14[a])	-38	-7	3	2.64
R + L Retrosplenial cortex (29, 30[a])	1	-45	18	3.18
R Parietal cortex (39[a])	47	-63	4	3.70
R Secondary visual cortex (19[a])	43	-66	4	3.89
R + L Perirhinal cortex (36[a])	-37	-39	-22	2.85
R Temporal pole (38[a])	41	10	-11	3.12

R = Right hemisphere, L = Left hemisphere, _ = Where the maximum voxel value is located when activation is bilateral. The coordinates in millimeters correspond to the stereotactic atlas of Talairach & Tournoux (1988). [a]Corresponding Brodmann area.

Conclusions

Situationally elicited anxiety in social phobics was associated with increased subcortical activity encompassing the amygdaloid complex. In contrast, an rCBF pattern with relatively increased cortical rather than subcortical perfusion was observed in non-phobics, indicating that cortical evaluative processes were taxed by public performance. Thus, the functional neuroanatomy of social phobia involves the activation of a phylogenetically older danger recognition system.

Study III

Functional neuroanatomy of anticipatory anxiety: A PET study of social phobia

Introduction and aim

Anticipatory anxiety is characterized by worry about future events (Barlow, Chorpita, & Turovsky, 1996). Social phobics worry, and it would be of interest to explore neural correlates of anticipatory anxiety in them. Thus, the aim of study III was to examine the neural correlates of anxiety elicited by the anticipation of a public-speaking task in individuals with social

phobia. Recently, we examined brain activity during symptom provocation in social phobics and healthy individuals while speaking in front of an audience and alone (study II). To evaluate anticipatory anxiety we now compared the social phobics who spoke alone before speaking in front of an audience (i.e. the anticipation group) with those who spoke alone after speaking in front of an audience (i.e. the comparison group). During situationally elicited social anxiety rCBF increased more in the amygdaloid complex in those with social phobia than healthy individuals (study II). Because numerous previous studies (see e.g., Davidson et al., 2000a and Davidson & Irwin, 1999 for a review) have also identified the amygdaloid complex as playing a crucial role in the processing of fear and anxiety, we performed a hypothesis driven search for amygdala activation in addition to a whole-brain search using traditional subtractive methodology.

Method

This study was part of a larger investigation of the functional neuroanatomy of social phobia before and after treatment with cognitive-behavioral therapy and citalopram (Furmark et al., submitted; Marteinsdottir et al., submitted; study II). Eighteen right-handed patients (10 men and 8 women) with DSM-IV social phobia with a mean age (± SD) of 35.2 (± 7.34) years (range 23-46) were recruited. Criteria for exclusion were: previous or current organic brain disorders and somatic diseases, current comorbid Axis I disorders, menopause, and pregnancy. Screening included psychiatric (First et al., 1998) and medical histories. Informed consent was obtained.

The PET methodology was the same as in study II. In short, PET and ^{15}O-water was used to measure rCBF in subjects with social phobia during anxiety anticipation. Heart rate and subjective anxiety were also recorded. To evaluate anticipatory anxiety in the social phobics we compared the nine social phobics who spoke alone before speaking in front of an audience (i.e. the anticipation group) with the nine who spoke alone after speaking in front of an audience (i.e. the comparison group).

Subjective and physiological measures of fear and anxiety were analyzed with four unpaired t-tests performed in Statview 4.5 for Macintosh. Because we predicted greater anxiety during anticipation of public speaking than after speaking in front of an audience, a one-tailed alpha level of 0.05 was applied.

An ANOVA (Friston et al., 1995) with one between groups factor (the anticipation group vs the comparison group) was used. To account for between subjects variance and to evaluate anticipatory anxiety, we only used the first of the two normalized rCBF images from the speaking alone condition in order to comply with a random effect model (Petersson et al., 1999). PET-data were normalized for global flow using linear scaling (Andersson, 1997). The contrast generated a t-map that was subsequently converted to a z-score map through a probability preserving transformation (Friston, Frith, Liddle, & Frackowiak, 1991). The significance of the z-score maps was evaluated at an omnibus level

using the mean square z-score (Worsley, Poline, Vandal, & Friston, 1995). Local changes were evaluated using the spatial extent of connected clusters of voxels with a z-score above 2.6 (Friston, Worsley, Frackowiak, Mazziotta, & Evans, 1994). This test takes into account multiple comparisons and has a cluster-localizing power (Friston, Holmes, Poline, Price, & Frith, 1996). The directed search for amygdala activation was performed by comparing the two groups using a z-threshold of 2.58 corresponding to an uncorrected (one-tailed) p of .005.

Results

Heart rate and subjective anxiety measures confirmed anticipatory anxiety in social phobics who performed their private speech before their public (See Figure 4).

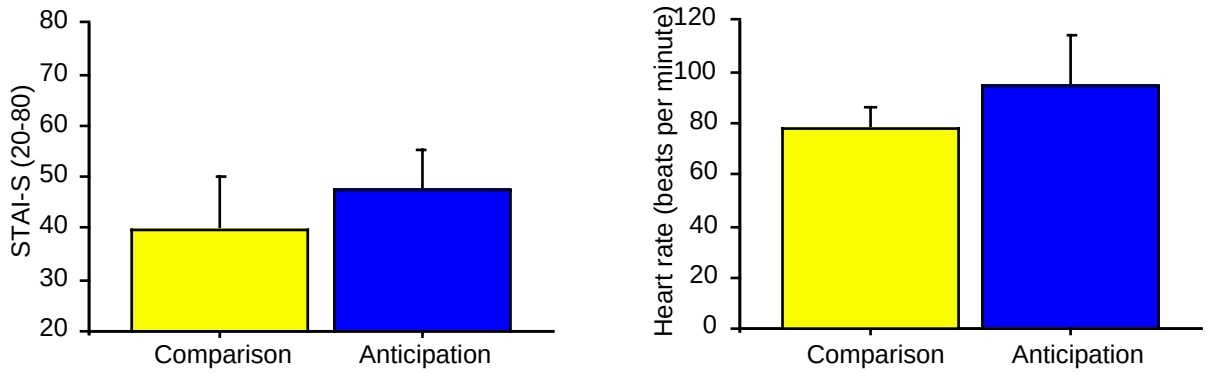

Figure 4. Mean values and standard deviations for subjective measures of negative affect and heart rate during speaking alone before (i.e. the anticipation group) or after (i.e. the comparison group) speaking in public for 18 social phobics.

This was accompanied by enhanced rCBF in the right dorsolateral prefrontal cortex, left inferior temporal cortex and left amygdaloid-hippocampal region. Brain blood flow was lower in the left temporal pole and bilaterally in the cerebellum in the anticipation group (See Table 6).

Table 6. Relative rCBF in social phobics as a function of anticipation of public speaking. Brain areas, Talairach coordinates and maximum voxel z-value for significant rCBF increases and decreases.

Brain areas	x	y	z	Maximum voxel z-value
Regions with higher rCBF				
R Dorsolateral prefrontal cortex (46[a])	38	54	6	3.22
L Inferior temporal cortex (20[a])	-47	-41	-18	4.21
L Amygdaloid-hippocampal region	-27	-13	-13	2.58
Regions with lower rCBF				
L Temporal pole (38[a])	-38	0	-28	4.25
R Cerebellum	36	-66	-27	3.89
L Cerebellum	-41	-69	-27	3.41

R = Right hemisphere, L = Left hemisphere. The coordinates in millimeters correspond to the stereotactic atlas of Talairach & Tournoux (1988). [a] Corresponding Brodmann area.

Because the design is unbalanced in that individuals in the anticipation group always performed their private speech first, we performed a trend analysis to evaluate order effects using rCBF data from all conditions and subjects (n = 18). As a function of repeated performances, rCBF increased bilaterally in the retrosplenial area (maximum z-value = 4.1; x = -1, y = -37, z = 18), in the right parietal cortex (maximum z-value = 3.8; x = 34, y = -51, z = 35), and in the left motor cortex (maximum z-value = 2.6; x = -29, y = -12, z = -12). Attenuated rCBF was observed in the right superior prefrontal cortex (maximum z-value = 4.7; x = 37, y = 43, z = 32). Thus, task repetition did not influence rCBF in structures associated with anticipatory anxiety except in the prefrontal cortex where rCBF was attenuated by task repetition, but enhanced as a function of anticipatory anxiety. Anticipation related rCBF-increases were observed in the dorsolateral prefrontal cortex while repetition related decreases were located in the prefrontal cortex superior to the anticipatory cluster.

Conclusions

Brain regions with altered perfusion presumably reflect changes in neural activity associated with worry about anticipated public performance. We speculate that anticipatory anxiety in social phobics originates in an affect sensitive fear network encompassing the amygdaloid-hippocampal region as well as prefrontal and temporal cortices.

Discussion of the individual studies

The family study

Study I

Probands with DSM-IV diagnoses of social phobia and APD sampled from the general population displayed an increased rate of a positive parental history of excessive social anxiety. This is consistent with both previous studies in clinical populations (Fyer et al., 1993; 1995; Mannuzza et al., 1995; Reich & Yates, 1988; Stein et al., 1998; Stemberger et al., 1995) and a recent community study (Lieb et al., 2000), finding higher rates of social phobia in relatives of social phobia probands. Having an affected family member resulted in a two- to threefold risk increase for both social phobia and APD. Further, this pattern was also observed for different diagnostic cut-off levels, indicating a robust effect. Finally, we observed increased rates of social phobia similarly in both sexes as a function of both paternal and maternal excessive social anxiety. This is not congruent with Skre and colleagues (1994) who reported that significantly more female than male relatives of persons with anxiety disorders suffered from anxiety syndromes themselves. This divergence could be due to the fact that we investigated a general population sample whereas Skre et al. (1994) used a clinical sample. Moreover, we examined probands with social anxiety problems only, while Skre and coworkers (1994) examined probands with a variety of anxiety disorders. In addition, even if the familial mediated risk of developing social phobia in study I was neither affected by the sex of the parents nor by the sex of the probands, it would be interesting to examine if there are any sex differences with regard to brain perfusion or presynaptic serotonin function in social phobics, since there is a distinct sex difference in prevalence.

Since we observed a two- to threefold risk of social phobia as well as APD as a function of a positive family history we conclude that the two disorders reflect dimensions of social anxiety rather than separate categories with different heritable transmission patterns. Generally, none of the previous distinctions reported between social phobia and APD have pointed to qualitative differences between the two conditions (see e.g., Boone et al., 1999; Moutier & Stein, 1999; and Wideger, 1992 for a review). If we are dealing with only one disorder the question arises whether the condition belongs on axis I or axis II. Hence, the topic is important and has clinical implications for both diagnosis and choice of treatment. This question also taps a broader ongoing debate in psychiatry regarding the validity of using categorical versus dimensional diagnostics.

Because family studies do not distinguish genetic from environmental contributions to a given trait or state, the present results can not separate learning from genetic mechanisms. This would require twin or adoption studies. The strongest evidence of a heritable contribution to social phobia comes from two epidemiological twin studies, where Kendler and coworkers (1992; 2001) reported that the variability in familial transmission of social phobia

seemed to be determined both by genetic (ranging from 24 to 30 percent in men and women, respectively) and environmental factors. As previously discussed in this thesis, some family studies (Fyer et al., 1995; Reich & Yates, 1988) suggest that social phobia runs in families in a specific fashion, i.e. independently of other anxiety disorders, whereas a number of genetic studies of anxiety disorders (see e.g., Hudson & Rapee, 2000 for a review) provide evidence for a general predisposition toward anxiousness. Speculatively, it is plausible that the specific familial transmission of social phobia results from the family environment rather than from specific genetic loading. Taken together, this points to the importance of conducting preventive strategies among relatives of individuals suffering from social anxiety.

A potential limitation worthy of note in Study I is that we could not properly evaluate whether the social phobia could be better accounted for by other disorders. Yet, in a validation study using a diagnostic interview as a reference, the sensitivity for social phobia of the questionnaire of the present study was 100 percent and the specificity 95 percent (Furmark et al., 1999). Furthermore, because the DIP-Q questionnaire is a screening instrument the sensitivity is high but the specificity lower. However, varying numbers of APD criteria (4-7) did not affect the parental history rate. Lastly, the concept "social anxiety" used to collect information about the probands' relatives is broad, and affirmative answers might represent the presence of subsyndromal cases of social phobia as well as other anxiety disorders. However, some studies have observed that by including subsyndromal cases the familial and/or genetic aspects of the anxiety disorder become more apparent (e.g., Smoller & Tsuang, 1998).

To the extent that the concept "social anxiety" included subsyndromal cases, study I points to the possibility that having shy or introverted parents may also be associated with an increased risk of developing pathological anxiety. Partial support for this comes from the investigation of parental history using the most liberal cut-off level (including 245 subjects resulting in a point-prevalence of 20.4%), which probably includes subsyndromal cases of social phobia. A two- to threefold relative risk of social anxiety was still observed among persons with social phobia and APD.

To summarize, a robust two- to threefold relative risk of social anxiety was observed for all diagnostic groups.

The brain imaging studies

Study II

Results showed that situationally elicited anxiety in social phobics in comparison with healthy individuals was characterized by increased rCBF in the right amygdaloid complex, consistent with a wealth of data identifying the amygdaloid complex as playing a crucial role in emotional processes, particularly fear and anxiety (e.g., Davidson et al., 2000a; Davis & Whalen, 2001). Additionally, this is also consistent with theories of emotion and motivation emphasizing the right hemisphere as being dominant in negative affect (e.g., Davidson & Irwin, 1999; Sutton &

Davidson, 1997). Cortically, brain blood flow decreased in social phobics and increased in comparison subjects more during public than private speaking in the orbitofrontal and insular cortices as well as in the temporal pole, and increased less in the social phobia group compared to the comparison group in the parietal and secondary visual cortices. Further, rCBF increased in the comparison group but not in social phobics in the perirhinal and retrosplenial cortices. This neural pattern most likely reflects emotional processes since we evaluated the interaction between phobics vs comparison subjects and public vs private performance, i.e. ruling out rCBF alterations resulting from perceptual or anatomical differences. Comparison of the present results with previous anxiety provocation PET-studies on social anxiety (Bell et al., 1999; Reiman, 1997; Van Ameringen et al., 1998) is difficult because the complete data sets have not yet been published.

In social phobics, emotion related neural activations of the amygdaloid complex have been reported in processing of neutral faces (Birbaumer et al., 1998), and in classical aversive conditioning (Schneider et al., 1999). Further, in a recent PET-study (Furmark et al., submitted) preliminary evidence indicated that anxiolytic effects in social phobia are mediated by decreased rCBF in the amygdala, hippocampus, and neighboring cortical areas. This is in agreement with the anxiety provocation reaction in untreated social phobia associated with increased rCBF in the amygdaloid complex in this study. The amygdala together with the hippocampus have also been postulated by Reiman (1997) to serve as an external alarm center suggested to alter an individual's attention to outside threat. Taken together, this suggests that untreated social phobia manifests in a highly sensitive fear network with the amygdaloid-hippocampal area playing a significant role. Because the evaluative process in non-fearful individuals was attributed to cortical areas, there may be a fear-related shift from cortical to subcortical processing in pathological anxiety. Recently Paradiso and coworkers (1999) reported that observing and assigning emotional value to unpleasant stimuli activated subcortical limbic regions, whereas evaluation of pleasant stimuli activated cortical paralimbic areas. They suggested that the former reflects activity in an archaic danger recognition system and the latter a phylogenetically younger system. Thus, in anxiety disordered subjects the fear-related shift to subcortical processing may reflect activation of a phylogenetically older danger recognition system.

Our group recently performed PET assessments of cerebral 5-HTP derived radioactivity in the same 18 untreated subjects with social phobia that participated in study II as well as in 18 healthy individuals (Marteinsdottir et al., submitted). Preliminary results suggest that social anxiety is characterized by regionally attenuated accumulations of 5-HTP mainly in the periamygdaloid and rhinal cortices. Speculatively, one possible mechanism underlying the increased rCBF in the amygdaloid complex expressed in enhanced anxiety during public-speaking in social phobics, as compared to healthy subjects, could be compromised serotonin synthesis in this area. This suggests that the suppressed normalized 5-HTP at the level of the

amygdaloid complex fails to inhibit the excitatory inputs from cortical pathways, resulting in easily triggered alarm reactions. A further interesting topic to investigate is whether presynaptic serotonin function is altered as a result of treatment with SSRIs and cognitive behavior therapy. This is currently underway in our laboratory.

The functional connections between the ventromedial/orbitofrontal cortex and the amygdala have been considered important in emotional regulation of negative affect (e.g., Davidson et al., 2000a; 2000b; LeDoux, 1996). The finding of lower neural activity in the orbitofrontal cortex and higher activity in the amygdaloid complex in social phobics compared with healthy comparison subjects during public speaking, suggests that a reciprocal relationship may be altered in persons with social phobia, probably reflecting emotional dysregulation linked with failure to inhibit anxiety. An issue for future research is whether top-down or bottom-up processes influence the neural circuitry underlying negative affect.

Notable limitations include that these data are preliminary and that a small comparison group was used. However, as previously outlined, the results are consistent with a wealth of data that alterations in the amygdala are associated with fear and anxiety (e.g., Davidson et al., 2000a; Davidson & Irwin, 1999). Furthermore, the rCBF alterations in all areas studied were theoretically predicted based on previous independent research, and therefore we believe that they are unlikely to reflect statistical type I errors. Of course, independent replication of the present data would strongly support findings and interpretations.

To conclude, we speculate that subcortical activations observed in social phobics during symptom provocation represent anxiety related activation of a phylogenetically older danger recognition system, whereas cortical activity in non-phobics represent evaluative activity in a phylogenetically younger system.

Study III

The current findings in study III revealed that anticipatory elicited anxiety was accompanied by enhanced rCBF in the dorsolateral prefrontal and inferior temporal cortices as well as in the amygdaloid-hippocampal region in social phobics who performed their private speech before their public (i.e. the anticipation group) as compared to after (i.e. the comparison group). This is consistent with previous studies emphasizing the prefrontal cortex, the amygdala, and the hippocampus as important components underlying the circuitry of negative affect (e.g., Davidson et al., 2000a; Gorman et al., 2000). Hence, anticipatory anxiety in social phobics may be mediated by a neural reciprocal functional system comprising the prefrontal cortex and the amygdaloid-hippocampal area. Moreover, rCBF was lower in the temporal pole and in the cerebellum in the anticipation group. Results from the trend analysis generally supported that anticipatory anxiety rather than task repetition accounts for the observed rCBF alterations. Further, it is not likely that the rCBF alterations are due to anatomical differences between the two groups since all individual CBF images were normalized into a standard atlas using the

cerebral brain atlas software (Thurfjell, Bohm, & Bengtsson, 1995). Thus, the present neural pattern probably reflects emotional processes.

Because anticipatory anxiety is characterized by worry about future events but may also activate memory of the past, we speculate that the enhanced perfusion in the right dorsolateral prefrontal cortex reflects affective working memory, a process suggested to be critical during anticipating future affective outcomes (e.g., Davidson et al., 2000a). Further support for the importance of the prefrontal cortex in anticipatory anxiety comes from a recent study by Davidson and coworkers (2000c) examining the electroencephalogram in social phobics while they anticipated a public speech. A right-sided activation was observed in the prefrontal area.

In previous PET-studies, anticipatory anxiety has been associated with: i) deactivations of modality-specific primary sensory areas in animal phobics (Drevets et al., 1995; Wik, Fredrikson, & Fischer, 1996), and ii) enhanced rCBF in the anterior cingulate, insula, temporal, prefrontal, and orbitofrontal cortices as well as the thalamus and the cerebellum in healthy subjects (Benkelfat et al., 1995; Chua, Krams, Toni, Passingham, & Dolan, 1999; Reiman, 1997; Reiman, Fusselman, Fox, & Raichle, 1989). Hence, it seems that the neural patterns of anticipatory anxiety in social phobics and healthy individuals are relatively similar and might involve activation of affective working memory (e.g., Davidson et al., 2000a; Davidson & Irwin, 1999). However, one distinctive region separating "normal" from "pathological" anxiety seems to be the amygdala because it does not appear to be engaged by anticipatory anxiety in normal individuals but only in social phobics. An explanation could be that pathological anxiety originates in an affect sensitive fear network centered in the amygdaloid-hippocampal region involving interaction with the prefrontal cortex (e.g., Gorman et al., 2000). Finally, in social phobics the amygdaloid complex seems highly sensitive (study II) and an anxiety reaction may be more easily elicited by decreased orbitofrontal/ventromedial inhibition or increased dorsolateral prefrontal excitation than in non-anxious individuals. Although the present data are preliminary and rather small sample sizes were used, the altered perfusion in both the amygdaloid-hippocampal area and the prefrontal cortex have previously been associated with negative affect in the literature (e.g., Davidson et al., 2000a; Davidson & Irwin, 1999).

To summarize, an affect sensitive fear network encompassing the amygdaloid-hippocampal region, prefrontal and temporal areas characterizes anticipatory anxiety in social phobics.

General discussion

To conclude, study I demonstrates that having an affected family member is associated with an increased risk of developing social anxiety. Hence, the relation is present not only in clinical populations but also in the general population. Both family and twin studies support a hereditary contribution to social phobia resulting from genetic and environmental factors, which

most likely operate in an interactive way rather than acting in isolation. The challenge for future research is then to disentangle the relative contribution of genetic and environmental factors in the development of social anxiety. Early emotional experiences most likely have implications for individual differences in emotional reactivity later in life, particularly for persons with a susceptibility to anxiety. For example, animal data indicate that disruption of early attachment between mothers and infants produce persisting behavioral and biological changes indicative of increased stress sensitivity, and conversely that parental care expressed in licking and grooming is stress protective (e.g., Caldji et al., 1998; Francis & Meaney, 1999). A future topic for research to deal with would be to clarify how early emotional experiences interact and influence the maturing human nervous system. For example, a tendency toward general fearfulness could be described behaviorally by constructs such as shyness or behavioral inhibition, which may facilitate conditionability to fear relevant stimuli. The contributions from the environment, including parental style and modeling as well as negative and positive reinforcement factors provided from social experiences may affect the tendency to exhibit social fears. Moreover, avoidance behaviors and cognitive biases could maintain these social fears.

Study II and III suggest that social phobia has a neuroanatomical basis in a highly sensitive fear network centered in the amygdaloid-hippocampal region and encompassing the prefrontal cortex. This highly sensitive fear network found in social phobics in the present thesis has recently been posited by Gorman and coworkers (2000) to be abnormal also in panic disorder, posttraumatic stress disorder, and in generalized anxiety disorder. This pattern is congruent with genetic studies proposing that the genetic component comprises a general vulnerability to fearfulness rather than social phobia itself. Further, according to Gorman et al. (2000) such reasoning could explain the high levels of comorbidity observed among the anxiety disorders.

The right and the left lateralized activations in the amygdaloid-hippocampal region in study II and III, respectively, may concur with studies trying to distinguish between types of anxiety, where panic as compared to worry seems to be associated with an asymmetry in favor of the right hemisphere. A left-lateralized pattern is associated with worry (Heller, Nitschke, Etienne, & Miller, 1997). This suggests laterality differences, but strong conclusions on laterality require that the left and the right brain blood flow are statistically compared (see e.g., Davidson and Irwin 1999 for a review). Both situationally elicited and anticipatorily determined anxiety in social phobics seems to be mediated by a neural reciprocal functional system comprising the amygdaloid-hippocampal area and the prefrontal cortex. Because a reciprocal relation between rCBF in the subgenual cingulate and the prefrontal cortex has been described for depression and normal sadness, it could be speculated that negative affect in general is associated with limbic-cortical reciprocity (Mayberg et al., 1999). Morgan, Romanski, and LeDoux (1993) demonstrated that lesions to the ventromedial prefrontal cortex prolonged fear extinction, which could imply that there is a descending inhibitory pathway from the ventromedial prefrontal cortex to the amygdaloid complex. Further, Davidson and colleagues

(e.g., 2000a) suggest that the major inhibitory control of the amygdaloid complex may derive from the left prefrontal cortex. Generally, this is in agreement with study II since we found bilateral rCBF reductions in the orbitofrontal cortex together with enhanced activity in the amygdaloid complex, probably reflecting emotional dysregulation linked with failure to inhibit negative affect. However, it remains to be clarified whether the association between the prefrontal cortex and the amygdaloid complex is only inhibitory or if excitatory influences exist as well. In study III we interpreted the enhanced brain perfusion in the dorsolateral prefrontal cortex to reflect the latter. However, an alternative explanation may be that increased worry and rumination, reflected in dorsolateral prefrontal activation, modulates the orbitofrontal cortex resulting in reduced inhibition of the amygdaloid complex. Thus, both an indirect pathway and a more direct connection between the prefrontal cortex and the amygdaloid complex may account for the data in the neurobiological studies in this thesis.

Recently, Thomas and coworkers (2001) investigated the amygdala response to facial expressions in healthy adults and children. Generally, they observed that adults displayed increased neural activity in the left amygdala when exposed to fearful faces relative to neutral faces. The opposite pattern was observed in children who showed larger and more bilateral amygdala activation to neutral as compared to fearful faces. In addition, boys but not girls showed decrease in amygdala activity with repeated presentations of fearful faces. Thus, it would be of interest to investigate the neural pattern in anxious infants, particularly in children and/or adolescents with an increased (positive family history) risk of developing social phobia as compared to those with a negative family history, to determine whether an enhanced amygdala reactivity predates or follows the development of pathological anxiety.

CONCLUDING REMARKS

- Having an affected family member is associated with a robust two- to threefold risk increase for both social phobia and APD, also at various diagnostic cut-off levels. The familial mediated risk of developing social phobia was neither affected by the sex of the parents or by the sex of the probands.

- Family history data imply that social phobia and APD may represent a dimension of psychopathology rather than qualitatively distinct disorders.

- The functional neuroanatomy of social phobia involves the activation of a phylogenetically older danger recognition system, manifested in enhanced brain perfusion in the amygdaloid complex during anxiety provocation in social phobics relative to healthy individuals.

- Situationally and anticipatorily elicited anxiety in social phobics seem to be characterized by a highly sensitive fear network centered in the amygdaloid-hippocampal region involving interaction with the prefrontal cortex.

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