Aspects of Social Phobia

BY

ÍNA MARTEINSDÓTTIR

ACTA UNIVERSITATIS UPSALIENSIS
UPPSALA 2003
Dissertation presented at Uppsala University to be publicly examined in Gustavianum, Uppsala, Monday, May 26, 2003 at 13:15 for the Degree of Doctor of Philosophy (Faculty of Medicine). The examination will be conducted in Swedish.

Abstract

Social phobia is a disabling, lifelong disorder characterised by fear in social settings.
The aim of the present study was to gain more knowledge about diagnostic, neurobiologic and epidemiologic aspects of social phobia.

Thirty-two individuals were assessed by the Structured Clinical Interview for DSM-IV Axis I and II psychiatric disorders, the Karolinska Scales of Personality and the Temperament and Character Inventory. Social phobia was accompanied by concurrent axis I disorders in about 28% of individuals, lifetime axis I disorders in 54%, personality disorders in 60%, and avoidant personality disorder (APD) in 47%. This suggests that there is a high comorbidity between social phobia and APD according to the DSM-IV criteria. The personality profiles associated with social phobia were dominated by anxiety-related traits that were primarily related to social phobia itself and not to the presence of concurrent personality disorders.

Eighteen subjects with social phobia and eighteen controls were investigated with positron emission tomography and the radiolabeled serotonin precursor, [3-11C]-5-HP (5-HTP). Individuals with social phobia demonstrated proportionally lower regional relative whole brain accumulation of 5-HTP in areas of the frontal and temporal cortices as well as the striatum, but higher accumulation in the cerebellum. This suggests that there are imbalances in presynaptic serotonin function in individuals with social phobia, although this could only be confirmed in men, and not in women.

By means of a postal survey, distributed to 2000 randomly selected individuals, social phobia in Sweden was found to be common, with a point prevalence of 15.6%.

Keywords: Social phobia, personality disorders, personality traits, prevalence, serotonin, PET, [3-11C]-5-HTP

Ína Marteinsdóttir, Department of Neuroscience, Box 593, Uppsala University, SE-75124 Uppsala, Sweden

© Ína Marteinsdóttir 2003

ISSN 0282-7476
ISBN 91-554-5551-4
urn:nbn:se:uu:diva-3323 (http://urn.kb.se/resolve?urn=urn:nbn:se:uu:diva-3323)
PAPERS INCLUDED IN THE THESIS

This thesis is based on the following papers, which are referred to in the text by their Roman numerals:


 CONTENT

INTRODUCTION .................................................................................................................. 1
  Background .................................................................................................................... 1
  Definition ..................................................................................................................... 2
  The history of the social phobia concept ..................................................................... 2
  Diagnostic aspects of the co-existence of avoidant personality disorder and social phobia ................................................................. 3
  Social phobia and Avoidant personality disorder, one diagnosis too many? .................. 3
  Subtypes ......................................................................................................................... 4
  The prevalence of social phobia .................................................................................. 5
  Social phobia and Axis I, II, III comorbidity ............................................................... 5
  Demographic aspects .................................................................................................. 6
  Personality traits in social phobia .............................................................................. 7
  The linkage between personality traits and neurotransmitters ................................. 8
  Neurobiology of social phobia .................................................................................. 9
  Serotonin and anxiety ............................................................................................... 11
  Gender differences in social phobia and in the serotonergic system ......................... 12
  Neuroanatomical correlates of anxiety ...................................................................... 13
  Neuroimaging studies on social phobia ..................................................................... 16
  Validation studies of [3-11C]-5-HTP brain imaging .................................................. 16
  Limitations of 5-HTP imaging ................................................................................. 22
  Factors modulating the BBB transport ..................................................................... 24
  The impact of precursor availability on serotonergic neurotransmission ............... 26

AIMS .................................................................................................................................. 28

METHODS .......................................................................................................................... 29
  Study design .................................................................................................................. 29
  Materials, ethics, and statistics ................................................................................... 32
  PET Technique ............................................................................................................ 33

RESULTS ................................................................................................................................ 34
  Sociodemographic findings (studies I and II) ............................................................. 34
  Frequency of Axis I and Axis II diagnoses (studies I and II) ......................................... 34
  General psychopathology measures (study I) ............................................................ 36
  Personality traits according to the KSP (study I) ......................................................... 36
Abbreviations

APA American Psychiatric Association
AADC Aromatic L-amino-acid decarboxylase
ANOVA Analysis of Variance
APD Avoidant Personality Disorder
BA Brodmann Area
BBB Blood Brain Barrier
BDI Beck Depression Inventory
[^123I]beta-CIT [(123)I]2beta-carbomethoxy-3beta-(4-iodophenyl)tropane
CNS Central Nervous System
Cho Choline
Cr Creatine
DIP-Q DSM-IV and ICD-10 Personality Disorder Questionnaire
DSM Diagnostic and Statistical Manual of Mental Disorders
fMRI functional Magnetic Resonance Imaging
GAF Global Assessment of Functioning
5-HIAA 5-hydroxyindoleacetic acid
HPLC High Performance Liquid Chromatography
5-HT 5-hydroxytryptamine (serotonin)
5-HTC 5-hydroxy-L-tryptophan labeled with [11C] in the carboxyl group
5-HTP 5-hydroxy-L-tryptophan labeled with [11C] in the 3-position, [3-11C]-5-HTP
5-HTTLPR The short allele of the serotonin transporter polymorphism
ICD International Classification of Diseases and Related Health Problems
mI myoinositol
ns not significant
k1-3 Rate constants of transport, metabolism, and elimination of the radiotracer, respectively
KSP Karolinska Scales of Personality
L-DOPA L-3,4-dihydroxyphenylalanine
MANOVA Multiple Analysis of Variance
MAO Monoamine Oxidase
NAA N-acetyl aspartate
NEO Neuroticism-Extraversion-Openness Personality Inventory
PET Positron Emission Tomography
rCBF regional Cerebral Blood Flow
SCID Structured Clinical Interview for Psychiatric Disorders
SD Standard deviation
SIAS Social Interaction Anxiety Scale
SPECT Single Photon Emission Computerized Tomography
SFS Social Phobia Scale
SPSQ Social Phobia Screening Questionnaire
SSRI Selective Serotonin Reuptake Inhibitor
[^99mTc-HMPAO] Technetium-99m hexamethylpropylene amine oxime
TCI Temperament and Character Inventory
TRY/LNAA The ratio of plasma concentration of Tryptophan to Large Neutral Amino Acids
INTRODUCTION

Background

People would choose to die rather than make a public speech. This contention comes from The Book of Lists, where public speaking was reported as the number one fear in the population, while fear of death was only number six. Social phobia is an anxiety disorder characterised by fear in social settings. Although social phobia was neglected to a remarkable extent until 15 years ago, it has now been recognised as being among the most common disorders encountered in the general population. In an American national comorbidity survey, social phobia was the third most frequent psychiatric disorder after major depression and alcohol dependence. A similar ranking was reported in a primary care study, although social phobia seemed to be largely undiagnosed and untreated. Social phobia affects most aspects of life, restricting the possibilities for successful social and career development. It is also associated with a high lifetime risk of chronologically superimposed comorbidity with other psychiatric disorders. Additionally, there is an augmented risk of suicide attempts and completed suicides, a risk that appears to increase with each comorbid psychiatric condition that develops secondarily. Social phobia tends to have its onset during adolescence, the average age being between 15 and 18 years. The clinical course is usually chronic, with a mean duration of around 20 years. In other words, social phobia patients may have an almost lifelong impairment in terms of living a normal life. However, only a small fraction of individuals with social phobia identify themselves as having the disorder, and only a small proportion seek treatment. One population study using stringent social phobia criteria reported that only 5.4% of those with uncomplicated social phobia ever sought help from a mental health provider. In view of the high cost of social phobia for the individual, and presumably for society as a whole, due to the loss of productivity of non-institutionalised patients and increased healthcare utilisation, the failure to recognise and treat social phobia...
motivates increased attention and research. This is particularly true now, when efficacious medications and psychological treatments are available.15

Definition
The Diagnostic and Statistical Manual of Disorders, 4th edition (DSM-IV) (American Psychiatric Association, 1994, page 416)18 defines social phobia (also using a synonym, social anxiety disorder) as follows: “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 that will be humiliating or socially embarrassing. The exposure to such situations results in self-understood excessive or unreasonable anxiety and possible panic attacks, leading to avoidance significantly interfering with the person’s normal social or occupational life. The fear or avoidance must not be the direct effect of any substance or general medical condition.”

The history of the social phobia concept
Several researchers have performed a thorough survey of the development of the social phobia concept.2,4,19,21 Briefly, while social anxiety and avoidance have been recognised in medical writings from antiquity,21 the first discussion about social phobia as a distinct clinical syndrome was in the 1960s and was inspired by experiences from behavioural therapy for phobias.22,23 However, it was not until 1980, in the third edition of the Diagnostics and Statistical Manual of Mental Disorders – DSM-III (APA),24 that social phobia was officially included as a psychiatric diagnosis. The DSM-III diagnosis of social phobia was intended for individuals whose fear of scrutiny was restricted to one social performance situation that caused significant distress. Those individuals who suffered from more pervasive social anxiety were assigned the diagnosis of avoidant personality disorder (APD). The diagnostic criteria of social phobia were broadened in the DSM-III-R (1987)25 and DSM-IV (1994)18 as follows. The generalised subtype of social phobia was introduced, thereby incorporating patients with fears in interactional as well as multiple situations, the requirement for significant distress was replaced by interference or marked distress, and comorbid diagnoses of social phobia and APD were allowed. The definitions of social phobia in DSM-IV and ICD-10 are similar except that no subgroups are specified in the ICD-10 and the anxiety reactions described in the DSM-IV as a part of social phobia are not mentioned in the ICD-10 social phobia criteria.
Diagnostic aspects of the co-existence of avoidant personality disorder and social phobia

Millon and Martinez26 expressed the difference between social phobia and APD in this way: APD is essentially a problem in relating to persons, whereas social phobia is largely a problem in performing in situations. This distinction fit the DSM-III definitions fairly well. However, the diagnostic boundaries of the disorders became more blunted in the DSM-III-R version through the addition of the generalised subtype of social phobia as well as the revised APD criteria with increased focus on fear of negative evaluation and discomfort in social situations.27 DSM-IV presents APD as a pervasive pattern of social inhibition, feelings of inadequacy, and hypersensitivity to negative evaluation that begins by early adulthood.18 Thus, there is greater emphasis on social inhibition, feelings of inadequacy, fear of shame and embarrassment than in the previous version.28 Two main theoretical distinctions between APD and social phobia are apparent in the DSM-IV.29 The first one emphasises the requirements in the social phobia diagnosis for somatic anxiety or panic attacks in feared situations, while APD is reserved for avoidance, restraint, and inhibition in feared situations. The second difference stresses that subjects with social phobia have a fear of acting in an embarrassing or humiliating way in specific situations, while those with APD have a generalised fear of being rejected or criticised.

Social phobia and Avoidant personality disorder, one diagnosis too many?

The overlap between social phobia and APD has been a matter of debate. Reich30 concluded after reviewing available empirical evidence that there is indeed no dividing line either diagnostically or pertaining to treatment between social phobia and APD. Johnson and Lydiard31 pointed out that social phobia itself has many characteristics in common with a personality disorder. They supported this contention by means of the seemingly higher rate of personality disorders among patients with social phobia compared with other anxiety disorders. Similarly, after reviewing the literature, Rettew39 found that there are greater distinctions between specific and generalised social phobia than between generalised social phobia and APD. Furthermore, he concluded that with respect to etiology, demographics, phenomenology, course, and treatment, the evidence supporting qualitative differences between generalised social phobia and APD is meagre. The observation that alprazolam treatment of social phobia improved many of the behavioural patterns constituting the APD criteria32 further obliterated the boundary be-
tween axis I and II diagnoses. In contrast, it has been claimed that the diagnosis of APD is superfluous with respect to the more comprehensive social phobia concept. Other researchers have suggested that there is a continuity-spectrum of severity in social discomfort. Thus, generalised social phobia with comorbid APD may represent the severe end of a continuum of shyness, while social phobia is somewhere in the middle. This proposal is deduced from several investigators’ observations that the level of symptom severity, quality of life, prevalence of comorbid disorders and functional impairment becomes aggravated across discrete social phobia, through generalised social phobia without any personality disorder to generalised social phobia with comorbid APD. Also, during speech challenge individuals with both social phobia and APD have shown both more anxiety and fearful cognition, but lower heart rates, than those with social phobia alone. In agreement with this, the presence of avoidant personality disorder has been reported to predict a 41% lower likelihood of social phobia remission.

To summarise, it appears that the conceptualisation of social anxiety requires further work, and that future modifications of the diagnostic criteria of social phobia and APD are to be expected. In this context it is of importance to elucidate whether there are deviant personality traits in social phobia, and if so, how they are related to APD comorbidity.

Subtypes

As mentioned above, there are two types of social phobia, generalised social phobia and specific social phobia. While the generalised subtype represents cases with fear and avoidance extending to a wide range of social situations, the specific subtypes involve fear of only one or a few situations. The generalised subtype is usually predominant in clinical samples, while this is not the case in epidemiological samples. In a German population investigation among adolescents, the generalised subtype was identified in one third of those diagnosed with social phobia. It is associated with earlier onset, more severe impairment, and higher rates of comorbid disorders. Consumption of the healthcare system by individuals with the generalised subtype is high, in contrast to those with non-generalised social phobia. Among the specific social fears, the fear of speaking in front of groups is most prevalent. In population studies, from 15 to 30% admit to having excessive fear of public speaking, while only 3 to 5% have been reported to fulfill the criteria for the diagnosis of social phobia, isolated public speaking subtype. Other frequently feared situations comprise being addressed before a group of people, talking with strangers, interacting with authority figures, and drinking/eating or writing in front of others.
The prevalence of social phobia

Prevalence rates of social phobia show substantial variations. This may be due to repeated modifications of the diagnostic criteria in the different DSM versions, thereby complicating comparisons of studies not using the same version. Also, methodological differences between studies, such as in field procedures, sample composition and different assessment instruments, may be the reason for discrepancies in data.

Most of the DSM-III studies used the Diagnostic Interview Schedule, which assessed social fears as resembling a simple phobia and screened for three potential socially fearful situations. The successor, the World Health Organization’s Composite International Diagnostic Interview (World Health Organization 1990) evaluates all social fears that are specified in DSM-III-R and DSM-IV (six situations), and has a higher threshold for severity. Hence, DSM-III studies generated fairly conservative lifetime and point prevalence rates of social phobia ranging on a worldwide scale between 0.4 and 8.0% and between 0.45 and 2.0%, respectively. The more inclusive DSM-III-R criteria and assessment tools resulted in higher lifetime prevalence estimates varying between 3.1 and 16.0%. Until now there is only one report on DSM-III-R- and one on DSM-IV-based point prevalence rates, both of which are from Canada and show similar figures, 7.1% and 9.8%, respectively. This is in accord with the first impression that the DSM-IV criteria give rise to prevalence estimates that are in the vicinity of those found by DSM-III-R, although no firm conclusions can be drawn, as DSM-IV-based investigations are still scanty.

Social phobia and Axis I, II, III comorbidity

Prevalence estimates of comorbid personality disorders in social phobia have ranged from 37 to 100%. Likewise, the prevalence rate of the most common concurrent personality disorder, APD, has shown large variability across studies that is probably attributable to differences in patient populations and diagnostic tools. Thus, the prevalence ranges from 17 to 100% in social phobia, from 25 to 89% in the generalised subtype of social phobia, and from 0 to 44% in the nongeneralised subtype of social phobia. Conversely, the prevalence of comorbid generalised social phobia in subjects with APD has varied between 25 and 100%.

While social phobia is usually the first axis I disorder to appear, it commonly occurs with other axis I disorders. This may have several explanations, such as a common predisposing factor, the early age at onset of social phobia, and the distress and impairments in interpersonal relationships and
occupational life following social phobia that in turn may give rise to secondary conditions.\textsuperscript{38}

In an American national comorbidity survey, 81% of the subjects with social phobia reported at least one other lifetime disorder and of these, 18.9% had only one other diagnosis, 14.1% had two others, and 48% three others.\textsuperscript{6} Most common were the other anxiety disorders (56.9%), the affective disorders (41.4%), and the substance abuse disorders (39.6%). Epidemiological studies have shown that simple phobia is the most frequent comorbid anxiety disorder, followed closely by agoraphobia, generalised anxiety disorder, and obsessive-compulsive disorder.\textsuperscript{4,67} Axis I comorbidity tends to be less extensive in epidemiological studies than in clinical studies, although the pattern is similar. Thus, in clinical samples the comorbidity rates are high for major depression (40-85\% current, 50-90\% lifetime), dysthymia (20–50\%), other anxiety disorders and substance-induced disorders, particularly in men.\textsuperscript{5} The increased symptom severity, social disability and suicide rates indicate that social phobia with a comorbid axis I disorder is a more severe condition than the isolated social phobia.\textsuperscript{68}

Furthermore, it may be speculated that social phobia is a burden for somatic health, since individuals with social phobia rate their health as fair or poor and visit a doctor more frequently than healthy individuals.\textsuperscript{9,69}

**Demographic aspects**

Gender has persistently been shown to be the strongest modulating factor among demographic variables. Women are 1.5 times more likely to have social phobia than men.\textsuperscript{48,76} Paradoxically, the highest lifetime estimates of social phobia have been reported among young adults and the lowest among those over 65 years.\textsuperscript{4,6,57,77} This has raised the question as to whether social phobia is truly a lifelong condition, although it is conceivable that the elderly have habituated to such a degree that they do not identify it as a problem.\textsuperscript{15} This could also reflect that social phobia is increasing in society.\textsuperscript{78} Urbanity, on the other hand, does not appear to influence prevalence figures.\textsuperscript{48}

Social phobia strikes both occupational and family life. It has been linked to poor school and work performance, school dropout, less educational attainment, unemployment, and lower levels of income.\textsuperscript{6,9,15,58,79-83} In addition, individuals with social phobia are more likely to have poor social support, fewer friendships, and to be living alone.\textsuperscript{4,6,79,84}
Personality traits in social phobia

The diagnostic boundaries of social anxiety and the diagnostic group to which it belongs are a matter of continuously ongoing revision, i.e. whether there should be one or two diagnoses (social phobia and APD), and whether it should belong to Axis I or Axis II. Nevertheless, the research on personality traits in social phobia and their relation to co-existing APD is limited. However, the exact connection between personality disorders and personality traits in general is not clear, even though research in this area has been conducted. By investigating 136 psychiatric patients, Svrakic confirmed an earlier hypothesis that the Temperament and Character Inventory (TCI) character factors, Self-Directedness (low) and Cooperativeness (low), predicted the presence of personality disorders, while the temperaments differentiated between them. Patients with cluster A, B and C personality disorders were differentiated by low Reward dependency, high Novelty seeking and high Harm avoidance, respectively.

Notably, levels of avoidant personality symptoms have been shown to correlate positively to Harm avoidance and negatively to Persistence, Self-directedness, Cooperativeness and Self-transcendence in undergraduate students as measured by TCI. Curiously, a similar pattern has been noted in 20 individuals with social phobia, i.e. high levels of Harm avoidance and low levels of Novelty seeking, Self-directedness and Cooperativeness. In parallel with this, elevated harm avoidance and reduced reward dependency, as well as a tendency for lower Novelty seeking, were observed in 20 patients with social phobia by using the Tridimensional Personality Questionnaire. However, only increased Harm avoidance and lower Self-directedness were observed in a group of 178 social phobics as compared to controls. By using another instrument, the Dutch Personality Questionnaire, higher levels of introversion and neuroticism were shown to characterise those social phobia patients with comorbid APD as compared to those with generalised social phobia without APD. Furthermore, the introversion level could predict the presence of APD in social phobia individuals. Similarly, Bienvenu observed high levels of neuroticism and low extraversion in social phobics by using the revised NEO Personality Inventory. Finally, Fahlén reported that patients with social phobia showed specific avoidant social behavior and more unspecific general depressive-anxious traits as compared to healthy individuals.

Collectively, these data suggest that there are deviant personality traits in social phobia that may be more apparent in the presence of comorbid APD. Further studies are necessary to confirm this and to explore the relations between APD comorbidity and personality traits in social phobia.
Shyness is a concept originating in the common parlance of ordinary people and is presumed to describe a normally occurring personality trait. The boundary between shyness and social phobia is obscure. There are reports that up to 40 to 50% of the normal population label themselves as shy. This is of course a much higher prevalence than that of social phobia. However, the overlap between social phobia and shyness may be considerable. For example, St Lorant documented an almost 100% overlap in individuals seeking treatment for chronic shyness. Chavira found that among highly shy people (>90th percentile), 49% had social phobia, 36% generalised social phobia and 14% avoidant personality disorder, while among normatively shy individuals (40-60th percentile) the corresponding prevalances were 18, 4, and 4%, respectively. Further information regarding the relation between social phobia and shyness may be attained by employing TCI in social phobia research, as shyness is a subscale of the TCI personality dimension Harm avoidance.

The linkage between personality traits and neurotransmitters

The TCI personality dimensions, Novelty seeking, Reward dependency, and Harm avoidance have been proposed to be influenced by the dopaminergic, serotonergic and norepinephrine systems, respectively. Recent neurobiological investigations have confirmed this in most respects.

Some but not all molecular genetics studies have suggested a relationship between Novelty seeking and polymorphisms of the dopamine D4 receptor in particular, but also of the dopamine transporter and the dopamine D3 receptor. In addition, individuals with high Novelty seeking scores have exhibited heightened sensitivity to psychophysiological and subjective effects of the dopamine release by d-amphetamine. After administration of the dopamine agonist bromocriptine, the levels of prolactin and growth hormones have been shown to be correlated to Novelty seeking scores. Also, the bindings of both the dopamine striatal D2 receptor and of the transporter have been associated with the KSP personality trait detachment, which has been reported to resemble low Novelty seeking and Reward dependency. These findings offer some support for the hypothesised relationship between Novelty seeking and the dopamine system. However, this personality dimension may be a function of a more complex neurotransmitter composition, as there is some evidence of a potential involvement of the noradrenergic system in Novelty seeking as well.

Reward dependency has shown significant correlations with both adrenaline and urinary levels of the noradrenaline metabolite, 3-methoxy-4-hyd-
oxyphenylglycol.105 A similar finding is the correlation of Reward dependency scores to growth hormone levels after challenge by the α2-adrenergic receptor agonist, clonidine.106 These data suggest that Reward dependency is under the influence of the nor/adrenergic system.

Serotonin has been postulated to participate in anxiety related traits such as Harm avoidance. Thus, several serotonergic indices have shown an association to Harm avoidance, such as serotonin transporter promoter region polymorphism (5-HTTLPR),106,107 the platelet 5-HT2 receptor binding in depressive patients,108 the ratio of plasma concentration of tryptophan to large amino acids (TRY/LNAA) in alcoholics,109 and the prolactin and/or cortisol responses to serotonergic challenge.110-112 In addition, successive antidepressant treatments have been observed to reduce Harm avoidance scores concurrently.113,114

There is also some evidence suggesting that the TCI character dimensions may be linked to neurotransmitter functioning. For instance, both Self-directedness and Cooperativeness have been related to the 5-HTTLPR.115,116 The Self-directedness level has been shown to correlate positively to the TRY/LNAA.109 Finally, SSRI treatment has been reported to increase the scores for both Self-directedness and Cooperativeness in patients with generalised anxiety disorder117 and the scores for Self-directedness in healthy individuals.118 In summary, it appears that the serotonin system is implicated in character dimensions.

Controversially, drug challenging of the 3 neurotransmitter systems in social phobia patients did not reveal any notable relationship between TCI personality dimensions and monoamine functioning.119 Likewise, Chatterjee could not find any link between the TCI dimensions and 5HT2 receptor binding in social phobics.87 Although these studies are few and are based on rather small groups, the question might be raised as to whether there is a neurobiological link between the social phobia disorder and the personality traits. This field needs further exploration.

Neurobiology of social phobia

The neurobiological underpinnings of social phobia are largely unknown. The growing body of social phobia investigations in recent years may, however, provide some clues. The firmest knowledge arises from the fact that medications targeting the monoaminergic systems show beneficial efficacy in the treatment of social phobia.120,121

Those agents (CO2, cholecystokinin, pentagastrin, flumazenil), which have been used successfully to induce panic attacks in individuals with panic disorder, have also been administered to patients with social phobia. Such
challenge studies have revealed increased sensitivity to panicogenic agents in subjects with social phobia compared with healthy volunteers, while the responses are not equivalent to those observed in patients with panic disorder.\textsuperscript{122}

Investigations of the hypothalamic–pituitary–adrenal axis have not revealed any clear-cut evidence of abnormalities in social phobia patients.\textsuperscript{123,124} Recently, however, dichotomous salivary cortisol responses to a speech task were shown in social phobia patients as compared to controls, i.e. the social phobics showed either lower or higher responses than the controls.\textsuperscript{125} On the other hand, an increased pressor effect of thyrotropin-releasing hormone stimulation has been observed in subjects with social phobia as compared to healthy individuals, suggesting disturbances in the hypothalamic-pituitary-adrenal axis.\textsuperscript{126}

There are some indices of disturbance in the adrenergic system in patients with social phobia. Subjects with social phobia as compared to healthy individuals have displayed a smaller immediate drop in blood pressure,\textsuperscript{83} a higher mean change in diastolic blood pressure on standing,\textsuperscript{127} higher resting as well as 5-minute plasma norepinephrine concentrations following an orthostatic challenge,\textsuperscript{127} an enhanced blood pressure response to Valsalva maneuver, and exaggerated vagal withdrawal in response to exercise, while cardiovascular reactions and plasma norepinephrine levels were normal in response to other naturalistic challenges.\textsuperscript{83,128} These last three items could indicate an increased parasympathetic tone relative to adrenergic activity.\textsuperscript{129} The overall picture of adrenergic function in social phobia is somewhat discordant, as also shown by the inconsistent results achieved by challenges with the $\alpha_2$-adrenoreceptor agonist, clonidine.\textsuperscript{130,131}

The high incidence of social phobia in patients with Parkinson’s disease implicates a dopaminergic involvement in social phobia.\textsuperscript{132} The finding of low cerebrospinal fluid concentrations of the dopamine metabolite, homovanillic acid, in social phobics with comorbid panic disorder, is in line with such a hypothesis.\textsuperscript{131} In contrast, challenging the dopamine system with levodopa did not differentiate between social phobics and healthy volunteers.\textsuperscript{119}

The favourable response to SSRIs in the treatment of social phobia would suggest that serotonin is implicated in social phobia.\textsuperscript{133} Several lines of evidence support such a notion. Individuals with social phobia display enhanced anxiety and increased cortisol response as compared to controls on exposure to fenfluramine, a serotonergic releasing agent.\textsuperscript{19} Metachlorophenylpiperazine, a serotonergic agonist, also elicited relatively increased anxiety in social phobics.\textsuperscript{134} A hypersensitivity in the postsynaptic 5HT$_{2A}$ serotonin receptors could account for these findings, while the normal prolactin responses to both of these agents suggest normal 5HT$_{1A}$ receptor

10
functioning in social phobia. Controversially, a greater prolactin response to buspirone (a 5HT1A partial agonist) challenge was documented in 14 subjects with generalised social phobia as compared to controls. Similarly, no differences were found in platelet 5-HT2 receptor density between socially anxious and healthy individuals, and no genetic bonds were shown between generalised social phobia and the 5-HTTLPR and 5HT2A receptor genes.

The postulated role of serotonin in social dominance and affiliated behaviour is another aspect worth considering in the context of social phobia. Thus, high serotonin levels have been linked to dominant social status and, conversely, low levels have been linked to subordinate status. Also, increased sociability in healthy individuals has been noted following SSRI treatment. Taken as a whole, there is reason to believe that serotonin is involved in social phobia, although its exact neurobiological role is unknown.

Serotonin and anxiety

Most theories of anxiety suggest that the serotonergic raphe nuclei afferents modulate activity in the brain structures involved in the experience of anxiety. However, the mechanisms by which serotonin participates in anxiety are elusive, and reported findings are conflicting. While a substantial body of preclinical observations indicates a relationship between elevated serotonergic neurotransmission and anxiety, human data tend to point to the reverse relationship. The most compelling evidence is the fact that the SSRI induced enhancement of serotonergic neurotransmission usually results in anxiolysis in humans, although initially the treatment may aggravate anxiety.

Conceivably, there are methodological explanations for this paradox concerning the relation between serotonin and anxiety, such as the limited number of studies examining the same questions, small group sizes, and species differences.

Also, the intrinsic properties of the serotonergic system might be the basis for the above controversy. For example, the immediate effect of SSRI administration presumably is an increase of serotonin in the synapse that in turn should induce rapid inhibitory feedback via the 5HT1A and 5-HT1B receptors. Accordingly, studies on rodents have demonstrated that serotonergic activity is attenuated during the first period of tricyclic/SSRI antidepressive treatment, and that it first becomes elevated after chronic treatment when the negative feedback mediating receptors are functionally down-regulated.
Hence, attenuated serotonergic activity could account for the initial aggra-
vation of anxiety during administration of antidepressants or serotonin agon-
ists, and enhanced serotonin activity could account for the anxiolysis accom-
ppanying more long-term treatment. In other words, the same pharma-
cological agent may have opposing effects on the serotonergic system
depending on the time-point in the treatment. In addition to the time-point,
the quantity of administrated substance may also lead to antagonistic results
in serotonergic experiments. For instance, administration of 5-hydroxy-L-
tryptophan showed a dose-reliant biphasic effect on anxiety in rats where the
lower dose was anxiolytic and the higher dose was anxiogenic.\textsuperscript{168}

Further progress towards an understanding of the complex relation be-
tween serotonin and anxiety may be obtained from anxiety models postulat-
ing a functional division of the serotonin system by the two raphe nuclei and
their functional units.\textsuperscript{143,145} For instance, Deakin and Graeff\textsuperscript{143} proposed that
increased dorsal raphe nucleus input to the amygdalo-hippocampal areas
would enhance learned anxiety while the innervations to the periventricular
and periaqueductal gray matter would inhibit unconditioned fear/panic reac-
tions.\textsuperscript{147} The median raphe nucleus connections with hippocampus were sup-
posed to promote resistance to chronic stress by preventing aversive events
from evoking psychobiological chains in the brain.\textsuperscript{169} Hence, it is plausible
that serotonin may influence distinct forms of anxiety differently,\textsuperscript{149} which
could clarify some reports that at first sight appear to be incoherent com-
ments on the topic.

In summary, it seems that the relationship between serotonin and anxiety
is complicated, and it may be that no simple answers are to be found, thus
emphasising that further investigations in this area are warranted.

\section*{Gender differences in social phobia and in the
serotonergic system}

Women as compared to men have a higher prevalence of most disorders
comprising social phobia that are known to be responsive to SSRI treat-
ment.\textsuperscript{7,150} Social phobia has not only been reported to be more common in
women than in men,\textsuperscript{7} but also to be more severe.\textsuperscript{170} In addition, the specific
social situations that generate fears in social phobics have been reported to
show gender differences.\textsuperscript{170}

Several lines of evidence suggest sex dimorphism in the presynaptic sero-
tonin function in specific. First, the tryptophan depletion test preferentially
evokes symptoms in healthy women as compared to men, indicating a relatively more vulnerable serotonin system in females.\textsuperscript{151,171} For instance, speech anxiety has been induced by tryptophan depletion in female but not
in male volunteers, suggesting that vulnerability in presynaptic serotonin function is involved in social phobia in women.\textsuperscript{172} Moreover, L-5-hydroxytryptophan loading elicited a hypothermic reaction in men, and on the contrary, a hyperthermic reaction in women.\textsuperscript{173} Also, 5-hydroxy-L-tryptophan loading induced a higher cortisol response in healthy men than in women, while depressive women had a higher cortisol as well as prolactin response than depressive men.\textsuperscript{174}

Sex differences have not only been reported presynaptically but also in other parts of the serotonin system. For instance, the highly selective serotonin 5-HT\textsubscript{2c}-receptor agonist, metachloro-phenylpiperazine, elicited a higher level of anxiety and greater hormone response in women than in men. The men, on the other hand, had more physical symptoms.\textsuperscript{175}

Although some of the findings described above may suggest proportionally lower serotonergic activity in women, results from animal experiments,\textsuperscript{176} as well as the observation of a relatively higher 5-hydroxyindoleacetic acid (5-HIAA) cerebrospinal level in healthy women,\textsuperscript{177} seem to contradict such a notion.

Collectively, it appears plausible that the higher prevalence of social phobia in women may be attributable to sex differences in the brain serotonin system that might be located presynaptically. Such a theory warrants further exploration.

**Neuroanatomical correlates of anxiety**

The amygdala and its functional brain units are of utmost interest in anxiety research, as amygdala is postulated to serve a coordinating function in the acquisition and expression of fear/anxiety (see Figure 1).\textsuperscript{178} With this in mind, its neuroanatomic position provides excellent possibilities, as it is widely interconnected with other brain regions.\textsuperscript{179} It receives direct sensory information from thalamus, but also more processed and specific information through the thalamo-cortico-amygdala pathways encompassing cortical areas such as the cingulate, the orbitofrontal, the medial prefrontal and the insular cortices. Also, the amygdala receives additional memorial and contextual input from hippocampus and the surrounding temporal cortex layers. The amygdala projects to areas that play different roles in anxiety reactions such as: the basal ganglia, mediating motor responses; the locus coeruleus, modulating the norepinephrine system; the hypothalamus, inducing adrenocorticoid release and sympathetic nervous system activation; the periaqueductal gray, initiating postural freezing or defensive behaviour; the parabrachial nucleus and the dorsal motor nucleus of the vagus, areas involved in respiratory and cardiovascular control.\textsuperscript{144,179}
Figure 1. Anxiety pathways. The figure is a modified version of a model previously presented by Charney and Deutch (1996).
Table 1. Brain imaging studies showing regional alterations in patients with social phobia.

<table>
<thead>
<tr>
<th>First author</th>
<th>Method</th>
<th>Tracer</th>
<th>Paradigm</th>
<th>Alterations in social phobics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stein180</td>
<td>SPECT</td>
<td>99mTc-HMPAO</td>
<td>Resting.</td>
<td>No significant alterations.</td>
</tr>
<tr>
<td>Van der Linden181</td>
<td>SPECT</td>
<td>99mTc-HMPAO</td>
<td>Resting.</td>
<td>Left sided decreases in the anterior and lateral temporal cortex, the left anterior, lateral and posterior mid frontal cortices and the left cingulum after 8 weeks of SSRI treatment. *7</td>
</tr>
<tr>
<td>Tiihonen182</td>
<td>SPECT</td>
<td>[123I]-beta-CIT</td>
<td>Resting.</td>
<td>Reduced striatal dopamine reuptake site densities in the striatum.</td>
</tr>
<tr>
<td>Schneier183</td>
<td>SPECT</td>
<td>[123I]-iodobenzamide</td>
<td>Resting.</td>
<td>Lower striatal D2-receptor binding potential</td>
</tr>
<tr>
<td>Li184*</td>
<td>SPECT</td>
<td>[123I]-epidepride</td>
<td>Resting.</td>
<td>Positive correlation between SIAS and striatal to frontal cortex ratio of postsynaptic D2 density.</td>
</tr>
<tr>
<td>Potts185</td>
<td>MR</td>
<td></td>
<td>Resting.</td>
<td>Age dependent decreases in putamen volumes.</td>
</tr>
<tr>
<td>Davidson186*</td>
<td>MR</td>
<td></td>
<td>Resting.</td>
<td>Reduction in Cho and Cr in subcortical, thalamic and caudatus areas. NAA was lower in cortical and subcortical regions.</td>
</tr>
<tr>
<td>Birbaumer188</td>
<td>IR</td>
<td></td>
<td>Resting.</td>
<td>Amygdala activity elicited selectively.</td>
</tr>
<tr>
<td>Schneider189</td>
<td>IMRI</td>
<td>Neutral faces versus aversive odor stimuli</td>
<td>Resting.</td>
<td>Negative odor elicited increased activations in amgudla and hippocampus in social phobics while the activity decreased in control subjects.</td>
</tr>
<tr>
<td>Veit190</td>
<td>IMRI</td>
<td>Neutral faces versus painful pressure unmanipulated air</td>
<td>Resting.</td>
<td>Increased activity in amygdala and orbitofrontal cortex during habituation, suggesting an overactive frontolimbic system in social fear.</td>
</tr>
<tr>
<td>Stein191*</td>
<td>IMRI</td>
<td>Human facial stimuli from photographs</td>
<td>Resting.</td>
<td>Greater percent blood oxygen level dependent signal change in amygdala for both contemptuous and angry faces in comparison with happy faces.</td>
</tr>
<tr>
<td>Malizia192*</td>
<td>PET</td>
<td>15O</td>
<td>Autobiographic script describing a feared situation</td>
<td>Increased cerebral blood flow (rCBF) in the right dorsolateral prefrontal cortex and left parietal cortex.</td>
</tr>
<tr>
<td>Kent193*</td>
<td>PET</td>
<td>(+)11C McNeil-5652</td>
<td>Resting</td>
<td>No abnormalities in serotonin transporter binding.</td>
</tr>
<tr>
<td>Van Ameringen194*</td>
<td>PET</td>
<td>15O</td>
<td>Viewing an interview of patient/others with experts</td>
<td>Increased rCBF in the lingual and the medial frontal gyrus.</td>
</tr>
<tr>
<td>Kelsey195*</td>
<td>PET</td>
<td>15O</td>
<td>Social and performance anxiety inducing imaginary script.</td>
<td>Social anxiety correlated positively with rCBF in the bilateral insular, right middle temporal gyrus, frontal pole, and lateral orbital frontal cortices as well as in the nucleus caudate, but negatively with rCBF in the middle frontal gyrus.</td>
</tr>
</tbody>
</table>
Neuroimaging studies on social phobia

Neuroimaging data on social phobia are being collected, although more research is needed in order to reveal the neural circuits involved. Available data, as shown in Table 1, suggest participation of the striatum and the dopaminergic system in social phobia. Functional imaging studies have subcortically outlined the amygdaloid complex in particular, but also the thalamus, hippocampus and striatum. Cortically, those areas most often noted are situated in the frontal cortex, including the medial, dorsolateral, and orbito-lateral prefrontal cortices as well as the insular cortices. Also, the regions of the temporal cortices encompassing the anterior and medial temporal gyrus as well as the rhinal, parahippocampal and periamygdaloid cortices have been repeatedly observed to participate in social phobia. In addition, some researchers have noted territories in the parietal and visual cortices (see Table 1).

Validation studies of [3-\textsuperscript{11}C]-5-HTP brain imaging

The tracer used for assessment of serotonin synthesis, [3-\textsuperscript{11}C]-5-HTP, is the immediate precursor of serotonin, i.e. 5-hydroxy-L-tryptophan, labeled with \textsuperscript{11}C in the 3-position (5-HTP) (see Figure 2). It follows the endogenous tryptophan pathway as it crosses the blood-brain-barrier (BBB) via the same saturable, carrier-mediated transport mechanism as tryptophan, in competition with the other large neutral amino acids (LNAA). Because it
bypasses the rate limiting conversion of tryptophan to 5-hydroxy-L-tryptophan by tryptophan hydroxylase, 5-HTP is converted directly by aromatic amino acid decarboxylase (AADC) into serotonin in the brain. Finally, it is degraded to $^{11}$C-5-hydroxyindoleacetic acid ($^{11}$C-5-HIAA) by monoamine oxidase.\textsuperscript{202}

\textbf{Figure 2.} The tracerkinetics of 5-HTP as compared to the serotonin metabolism in the central nervous system

Although there are several lines of evidence demonstrating that 5-HTP is used in central serotonin synthesis, there are some methodological questions worth considering regarding the use of $^{11}$C-5HTP as a tracer for studying serotonin synthesis in the brain by positron emission tomography (PET). These questions can be addressed by several methods such as:

I. Tracerkinetic modeling, whereby using mathematical approximations the different steps of serotonin metabolism in the brain are mimicked by rate coefficients ($k_i$) (see Figure 2). Thus, $k_1$ represents the inflow to the brain, $k_2$ the outflow from the brain, $k_3$ the conversion to serotonin, $k_4$ the degradation to 5-HIAA, and $k_5$ the elimination of 5-HIAA from the brain tissue. Hence, in order to reveal how many $k_{i,iii}$ best explain the obtained PET data, different models are set up using different numbers of $k_i$. Subsequently, statistical analysis is performed to find out which model best fits the measurements. The results for 5-HTP showed that a 3-compartment model
best fitted the 5-HTP PET-data obtained in humans. This suggests that the tracer can be used to estimate in-transport and out-transport through the BBB and the conversion to serotonin, while there were no signs of tracer loss from the brain tissue during the time span of a PET investigation.\textsuperscript{203} Also, the tracerkinetic modeling results showed that the half-life of the tracer for plasma to brain equilibrium is 7–12 minutes and that the dynamic equilibrium across the BBB is reached within 35–60 minutes.\textsuperscript{203} This may be a limiting factor for the interpretation of the present results in terms of direct measures of alterations in serotonin synthesis, as the analysis was started at about 15 minutes. On the other hand, the 5-HTP accumulation between 15 and 30 minutes showed a high correlation with the rate of tracer trapping, $k_3$.

II. Bioanalysis. Microdialysis in vivo in animals is probably the most used method to date for determining the fate of a tracer in the brain. So far, no such data exist on 5-HTP, as the amounts of radiolabeled serotonin and its metabolites that are synthesised in the brain after a single administration of the precursor are so small that they are difficult to measure by currently available microdialysis equipment. However, by using high performance liquid chromatography of brain tissue, determination of the tracer and its in vivo formed radiolabelled metabolites in rats immediately after execution has demonstrated that 40 minutes after administration of the tracer, 95\% of the brain tissue radioactivity originated from $[^{11}C]$-HTP, $[^{11}C]$-serotonin and $[^{11}C]$-5HIAA (see Table 2.).\textsuperscript{202} The major part, 75\%, was in the form of $[^{11}C]$-5HIAA, and the rest was equally divided between $[^{11}C]$-HTP and $[^{11}C]$-serotonin.\textsuperscript{202} These data suggest that after peripheral administration of the tracer, it will participate in the cerebral serotonergic metabolism and that the $[^{11}C]$ is retained in the brain tissue long enough to perform a PET investigation. Conceivably, an even smaller proportion of the tracer is catabolised to $[^{11}C]$-5HIAA in humans, as the metabolism is presumed to be slower in humans than in animals. Therefore, the half-life of 5-HIAA in the brain tissue in humans may be presumed to be longer than 40.8 minutes, which has been reported in rats.\textsuperscript{204}

III. Pharmacological perturbations. Several approaches have been used such as: selective pharmacological blockage of enzymatic steps, manipulations of the tracer’s in-transport to the brain by altering the plasma concentrations of tryptophan or LNAA, and radiolabelling the 5-hydroxy-L-tryptophan in different positions. This last method, where the carboxyl group of 5-hydroxy-L-tryptophan has been radiolabeled with $[^{11}C]$, (5-HTC) instead of the 3-position as in 5-HTP, has been used for validation of the tracer’s function. Thus, the radiolabel is eliminated from the tissue as carbon dioxide when the decarboxylation to serotonin takes place, enabling selective depiction of the BBB passage of the tracer (see Table 2).
Table 2. Overview of studies illustrating the functional value of cerebral 5-HTP PET imaging.

<table>
<thead>
<tr>
<th>First author</th>
<th>Subjects</th>
<th>Method</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hartvig205</td>
<td>1 rhesus monkey</td>
<td>5-HTC</td>
<td>The radioactivity was homogeneously distributed, indicating a uniform transport of the tracer, 5-HTP, over the BBB and into the nerve terminals in the brain.</td>
</tr>
<tr>
<td></td>
<td>2 rhesus monkeys</td>
<td>[3-11C]-L-tryptophan</td>
<td>Homogeneous distribution of the radioactivity. The ( K_3 ) value, describing the activity of the hydroxylase, was close to zero.</td>
</tr>
<tr>
<td></td>
<td>1 rhesus monkey</td>
<td>Pretreatment with carbidopa, 30 min before the tracer.</td>
<td>Peripheral decarboxylase inhibition did not affect 5-HTP measurements.</td>
</tr>
<tr>
<td></td>
<td>1 rhesus monkey</td>
<td>Pretreatment with NSD 1015.</td>
<td>Central decarboxylase inhibition resulted in homogeneous distribution in the brain, and indicating a uniform transport of 5-HTP through the BBB and nerve terminals. ( K_3 ) value approached zero.</td>
</tr>
<tr>
<td></td>
<td>1 rhesus monkey</td>
<td>Pargyline chloride for 2 days.</td>
<td>Nonselective MAO inhibition did not affect 5-HTP measurements.</td>
</tr>
<tr>
<td></td>
<td>1 rhesus monkey</td>
<td>Pretreatment with Clorgyline, 10 minutes before the tracer.</td>
<td>Selective MAO-A inhibition did not affect 5-HTP measurements.</td>
</tr>
<tr>
<td>Hartvig206</td>
<td>4 rhesus monkeys</td>
<td>5-HTP + unlabelled 5-hydroxy-L-tryptophan 0.5, 3, 5 or 10 mg/kg.</td>
<td>Doses from 3.0 mg/kg of unlabelled 5-hydroxy-L-tryptophan decreased the ( K_3 ) value dose-dependently.</td>
</tr>
<tr>
<td></td>
<td>3 rhesus monkeys</td>
<td>5-HTP+unlabelled L-DOPA, 4, 15 or 30 mg/kg.</td>
<td>The addition of unlabeled L-DOPA resulted in decreased ( K_3 ) value only at high doses &gt; 15 mg/kg.</td>
</tr>
<tr>
<td></td>
<td>3 rhesus monkeys</td>
<td>[11C]-L-DOPA with unlabelled 5-hydroxy-L-tryptophan 3 or 30 mg/kg.</td>
<td>No major effect on ( K_3 ) value.</td>
</tr>
<tr>
<td></td>
<td>2 rhesus monkeys</td>
<td>[11C]-L-DOPA with unlabelled L-DOPA, 4 or 30 mg/kg.</td>
<td>The addition of unlabeled L-DOPA resulted in decreased ( K_3 ) value only at high doses &gt; 30 mg/kg.</td>
</tr>
<tr>
<td>Hartvig207</td>
<td>8 rhesus monkeys</td>
<td>5-HTP and pyridoxin hydrochloride 10 mg/kg</td>
<td>Pyridoxin increased the ( K_3 ) suggesting a regulatory role of pyridoxin on the AADC</td>
</tr>
<tr>
<td>Lindner202</td>
<td>4-6 rats</td>
<td>5-HTP</td>
<td>Equal distribution of the radioactivity in cerebellum and striatum. A high liquid chromatographic system (HLPC) analysis of the brain after execution 40 minutes after 5-HTP administration revealed that 95% of the radioactivity emanated from ([1^{11C}])-HTP, ([1^{11C}])-HT and ([1^{11C}])-5HIAA.</td>
</tr>
<tr>
<td></td>
<td>4-6 rats</td>
<td>Carbidopa or NSD 1015 pretreatment</td>
<td>AADC inhibition increased the radioactivity in cerebellum and striatum. HLPC measurements showed that the fraction of ([1^{11C}])-HTP was increased while ([1^{11C}])-5HT and ([1^{11C}])-5HIAA were decreased. The ( K_3 ) value decreased markedly with NSD 1015 but increased with Carbidopa.</td>
</tr>
<tr>
<td></td>
<td>4-6 rats</td>
<td>Probenecid pretreatment</td>
<td>Inhibition of ([1^{11C}])-5HIAA clearance from the central nervous system (CNS) increased 5-HTP derived radioactivity in cerebellum and striatum. Measurements by HLPC showed that the fraction of ([1^{11C}])-5HIAA tended to increase. The ( K_3 ) value increased.</td>
</tr>
<tr>
<td>Study</td>
<td>Subjects</td>
<td>Intervention</td>
<td>Findings</td>
</tr>
<tr>
<td>-------</td>
<td>----------</td>
<td>--------------</td>
<td>----------</td>
</tr>
<tr>
<td>Reibring208</td>
<td>3 humans</td>
<td>5-HTP, administrated at 2 occasions.</td>
<td>Good reproducibility of brain measurements.</td>
</tr>
<tr>
<td></td>
<td>1 human</td>
<td>Benserazide</td>
<td>Peripheral AADC inhibition increased accumulation of global brain radioactivity in the brain. Tracer utilisation (K3) unaffected.</td>
</tr>
<tr>
<td></td>
<td>1 human</td>
<td>p-Chlorophenylalanine</td>
<td>Tryptophan hydroxylase inhibition increased accumulation of global brain radioactivity. K3 value unaffected.</td>
</tr>
<tr>
<td></td>
<td>1 human</td>
<td>Triple experiments with 5-HTP alone or concomittant with 0.1 or 10 mg of unlabeled 5-HTP</td>
<td>The accumulation of global brain 5-HTP derived radioactivity increased dose-dependently with the addition of unlabeled 5-HTP. K3 value unaffected.</td>
</tr>
<tr>
<td>Reibring209</td>
<td>4 humans</td>
<td>Tryptophan depletion performed prior to the 5-HTP investigation</td>
<td>No change in mood, plasma hormones or in cerebral 5-HTP measurements.</td>
</tr>
<tr>
<td>Ågren210</td>
<td>6 humans</td>
<td>5-HTP</td>
<td>Lower accumulation of global brain radioactivity in depressive patients compared with controls (6).</td>
</tr>
<tr>
<td>Ågren211</td>
<td>15 humans</td>
<td>Both 5-HTP and [11C]-L-DOPA</td>
<td>Specific utilisation of 5-HTP and [11C]-L-dopa detected in medial prefrontal cortex and basal ganglia. Increased utilisation of cerebral 5-HTP in depressive patients but not of [11C]-L-DOPA in lower medial prefrontal cortex as compared with controls (15).</td>
</tr>
<tr>
<td>Eriksson212</td>
<td>7 humans</td>
<td>5-HTP</td>
<td>High tracer accumulation in neuroendocrine tumours and signs of binding in metastasis.</td>
</tr>
<tr>
<td>Ahlstrom213</td>
<td>22 humans</td>
<td>[15C]-L-DOPA and 5-HTP</td>
<td>Accumulations of 5-HTP in pancreatic neuroendocrine tumours correlated well with that of [15C]-L-DOPA but tended to be higher.</td>
</tr>
<tr>
<td>Bergström214</td>
<td>6 rats</td>
<td>5-HTP</td>
<td>HLPC separation of urine showed that 64% of the radioactivity was in the form of [11C]-5HT within 20 minutes from administration.</td>
</tr>
<tr>
<td>Kälknera215</td>
<td>10 humans</td>
<td>5-HTP</td>
<td>Bone uptake of 5-HTP in prostatic adenocarcinoma identified metastatic lesions.</td>
</tr>
<tr>
<td>Kälknerb216</td>
<td>2 humans</td>
<td>5-HTP as well 5-HTC.</td>
<td>The uptake in prostatic adenocarcinoma tumours did not differ between the tracers indicating that decarboxylation of 5-HTP may not take place in the tumours.</td>
</tr>
<tr>
<td>Örlefors217</td>
<td>18 humans</td>
<td>5-HTP</td>
<td>In gastrointestinal neuroendocrine tumours, changes in 5-HTP transport rate constant during treatment correlated with changes in urinary 5-HIAA.</td>
</tr>
</tbody>
</table>

Some important validation studies are presented in Table 2. Nevertheless, the possibility of drawing firm conclusions from the results is limited by the small group sizes as well as by species differences. There are, however, several points that should be highlighted.

Pretreatment with pharmacological agents acting upon the serotonin system immediately before the 5-HTP investigation may shed some light on the
significance of 5-HTP and PET findings in the brain. Administration of a cerebral decarboxylase inhibitor yielded homogeneous 5-HTP derived radioactivity in Rhesus monkeys, whereas the serotonin synthesis rate was low or close to zero. Notably, the same distribution of radioactivity was observed when radiolabelled tryptophan, [3-11C]-L-tryptophan, or 5-HTC, was used instead of 5-HTP. This suggests that regional alterations in the brain identified by 5-HTP reflect changes in serotonin synthesis. The remaining uniformity in the brain accumulation of radioactivity appearing when visualisation of the decarboxylation is blocked suggests that the BBB transport is equable throughout the brain. This seems reasonable, since the BBB transport is mainly regulated by LNAA concentrations in plasma, the volume of distributions of which are probably similar in all brain areas.

Accordingly, accumulation of radioactivity in carcinoid tumours has only been observed after administration of 5-HTP but not 5-HTC. This suggests that detectable 5-HTP in the tumours reflects serotonin synthesis. Notably, a strong correlation between changes in 5-HTP transport rate constant in the tumours and changes in 5-HIAA urinary excretion during treatment has also been reported.

Pretreatment with selective and non-selective monamine oxidase (MAO) inhibitors did not affect 5-HTP measurements in monkeys, while in rats the above mentioned bioanalytically measured concentration of [11C]-5HIAA decreased and that of [11C]-HTP and [11C]-HT increased. It seems that there is tracerkinetic modeling, bioanalytical and pharmacological evidence suggesting that during the time span of the PET investigation (60 minutes), there is no tracer loss from the brain tissue in humans and larger animals, although not all findings are congruous. Tracer trapping is an important condition for interpretation of 5-HTP data, because otherwise it would be difficult to discriminate between alterations in serotonin synthesis and alterations in serotonin catabolism/5-HIAA clearance from brain tissue. Contradictory to this, inhibition of 5-HIAA egress from CNS by probenecid in rats increased the accumulation of 5-HTP radioactivity in the brain, the serotonin synthesis rate and the concentration of [11C]-5HIAA. At first glance, it appears that there is actually a loss of 5-HIAA derived radioactivity during a PET investigation in rats. However, there could be another explanation, as probenecid itself increases the cerebral tryptophan levels and thus may stimulate serotonin synthesis.

In summary, existing experimental findings suggest that 5-HTP and PET may be used to probe serotonin synthesis, although more validation studies are needed.
Limitations of 5-HTP imaging

Some of the keys to an understanding of 5-HTP derived radioactivity measurements may be obtained by studying the characteristics of the enzyme AADC. In general, the distribution of AADC in the brain corresponds quite well to the synthesis of monoamine neurotransmitters. Its concentration is high in the striatum, substantia nigra, and hypothalamus, but lower in the cortex and cerebellum. AADC is not only found in serotonergic nerves but also in all monoaminergic nerves and so-called D-cells as well. Hence, it is plausible that the 5-HTP tracer is metabolised to serotonin in non-serotonergic nerve cells, limiting the possibilities of using 5-HTP in order to mirror activity in the serotonergic system. For example, 5-HTP derived radioactivity in basal ganglia may reflect AADC activity in dopaminergic nerves as well, and likewise, radioactivity in cerebellum might partly reflect AADC activity in nor-adrenergic cells. In order to clarify this issue, it might be beneficial to find out whether the dopaminergic/adrenergic nerves take up 5-hydroxy-L-tryptophan in the first place. No definite answers are available to date, but there are some clues. Mandell and Knapp reported regulation of serotonin synthesis by high affinity uptake of tryptophan into the serotonergic neurons, suggesting that the serotonergic precursors are mainly used by the serotonin system. On the other hand, the immediate neurotransmitter precursors, L-DOPA (L-3,4-dihydroxyphenylalanine) and 5-hydroxy-L-tryptophan, have been found to share the same in-transporter and exert a competitive type of inhibition upon each other in Opossum kidney cells, which synthesise both dopamine and serotonin. Nonetheless, the uptake mechanisms in serotonergic neurons are not necessarily identical, since the neurons are usually single monoamine producers.

Another facet of this enigma is whether AADC displays substrate specificity, which is supported by several lines of evidence. First, the fact that the ratio of L-dopa to 5-hydroxy-L-tryptophan decarboxylation activities between different tissues and brain regions is not constant, as well as the differential loss of L-dopa and 5-hydroxy-L-tryptophan decarboxylation activities following a variety of treatments, suggest that a single enzyme protein cannot be responsible for the syntheses of both dopamine and serotonin. Second, serotonin formation from exogenous 5-hydroxy-L-tryptophan has been reported to markedly decrease following lesioning of the raphe system, implying that 5-hydroxy-L-tryptophan is used primarily by serotonergic nerves. Third, studies of rodents illustrate that 5-hydroxy-L-tryptophan in low doses is predominantly taken up and decarboxylated in serotonergic neurons, and that in vitro 5-hydroxy-L-tryptophan releases synaptosomal serotonin but not catecholamines. Finally, PET and 5-HTP
investigations provide some pieces of information pertinent to this question. Ågren et al. reported an overall parallelism between utilisation of the tracers 5-HTP and L-DOPA in healthy individuals, while in depressive patients the utilisation of 5-HTP but not L-DOPA was increased in lower areas of medial prefrontal cortex. Hartvig et al. showed that the activity of AADC in striatum of monkeys was blocked by relatively low doses of unlabeled 5-hydroxy-L-tryptophan but only at high doses of unlabeled L-DOPA, irrespective of whether 5-HTP or [11C]-L-DOPA was used as a tracer. This suggests that AADC displays different affinities for the two substrates.

In conclusion, there appears to be experimental evidence supporting a substrate selectivity of AADC, suggesting that 5-HTP may be used to obtain an estimate of the activity presynaptically in the serotonergic system. Furthermore, it may be speculated whether 5-HTP in tracer doses could have a pharmacological effect of its own on the dynamic balance in the serotonergic system that should be considered in data interpretation. For example, does the tracer have to compete with the endogenous 5-hydroxy-L-tryptophan for conversion to serotonin by AADC? In that case, the obtained 5-HTP PET values would be inversely correlated with the endogenous 5-hydroxy-L-tryptophan pool and probably also the actual serotonin synthesis. However, the quantity of endogenous 5-hydroxy-L-tryptophan is restricted by the rate limiting conversion of tryptophan to 5-hydroxy-L-tryptophan by tryptophan hydroxylase, which has only a low affinity for tryptophan. And bearing in mind that AADC is traditionally thought to work far from saturation, any such competition between the tracer and the endogenous substance appears improbable. Accordingly, Reibring et al. by administrating 5-HTP in humans concomitantly with either 0.1 mg or 10 mg of unlabeled 5-hydroxy-L-tryptophan, showed that changes in plasma 5-hydroxy-L-tryptophan concentration did not affect the serotonin synthesis rate. Nonetheless, similar experiments on monkeys revealed that administration of unlabeled 5-hydroxy-L-tryptophan in high doses of about 3 mg/kilo or more decreased the rate of AADC. However, such mass effects seem to be an irrelevant concern for the experiments described in this paper, where the 5-HTP human doses ranged from 1 to 5 micrograms.

Also, it might be questioned whether 5-HTP administration could increase the amount of synthesized serotonin, and if so whether the presynaptic 5-HT$_{1A}$ or the terminal 5-HT$_{1B}$ autoreceptors would consequently respond by negative inhibition during the investigation. Taking into account the low tracer doses used and the short investigation time, which restricted the number of biological/metabolic steps that could be undertaken concurrently, the likelihood of any such pharmacological effects seems minimal. Also, studies on humans as well as animals have shown elevated
serotonergic activity after 5-hydroxy-L-tryptophan loading, which contradicts any significant negative receptor feedback mechanisms even at high doses.235-238

Factors modulating the BBB transport

Several factors have been noted to influence the transport of tryptophan across the BBB that might be valuable to keep in mind in regard to study design and data interpretation. For example, the nutritional composition may affect the TRY/LNAA ratio. A high-carbohydrate and low-protein diet, for instance, has been shown to increase the serotonin level in the brain of rodents.239,240 probably through modulation of the TRY/LNAA ratio. This is due to a carbohydrate mediated insulin release, which in turn removes all of the LNAA from plasma into tissues except tryptophan, which is 80–90% protein bound and not readily removed from plasma.239,240 Hence, the TRY/LNAA ratio will be elevated, facilitating the entry of tryptophan into the brain. Interestingly, such a diet has been reported to increase personal control during stressful situations.241

Similarly, an increment in the concentration of free fatty acids in plasma leads to decreased tryptophan binding to albumin, thus augmenting the free plasma tryptophan level and facilitating the passage of tryptophan into the brain. This may occur, for example, during fasting and immobilisation, but may also be an effect of drugs such as the isoprenaline, noradrenaline, heparin and tricyclic antidepressants.242,243 Protein ingestion has the opposite effect as it increases the more abundant LNAA relatively more than tryptophan, thus lowering the TRY/LNAA ratio.

The B-vitamin pyridoxin phosphate is implicated in serotonin metabolism in two different ways. It is a coenzyme of AADC and it inhibits the oxidative liver metabolism of tryptophan, thereby increasing both the plasma concentration and the brain uptake of tryptophan.244 Accordingly, a PET and 5-HTP investigation demonstrated that pyridoxin administration increased the central serotonin synthesis.207

The tryptophan-LNAA metabolism is also under hormonal influences. One hypothesis is that the brain uptake of LNAA is under beta-adrenergic control, which may be exerted both through regulation of the tryptophan binding to albumin and the LNAA levels.245 Paradoxically, isoprenaline (beta-adrenergic agonist) administration in rats has been reported both to attenuate the LNAA levels in plasma246 as well as to enhance the cerebral levels.245 Glucocorticosteroids have been found to induce the liver pyrrolase, resulting in reduced plasma levels and availability of tryptophan to the brain.247,248 These latter two findings might be of particular interest in
research on the impact of stress on brain functions. Moreover, prolactin may diminish plasma amino acid levels by augmenting liver utilisation and subsequently affecting the TRY/LNAA ratio.249

Consideration of additional factors such as circadian rhythms in the tryptophan/serotonin metabolism may be relevant regarding study design. In humans, the LNAA plasma levels are lowest in the morning and highest in the evening, although the tryptophan concentration is relatively higher in the morning.250 Moreover, there is evidence indicating the presence of circadian rhythm in the cerebral serotonin metabolism of rodents.251,252 Comparisons of subjects participating in the current PET studies were matched according to the time of day when the experiments were performed in order to exclude effects of diurnal rhythms on the results. Moreover, increased body mass index is accompanied by a lowered TRY/LNAA ratio.253 However, none of the participants in our studies was overweight.

Also, non-endogenic chemicals may influence the peripheral TRY/LNAA transport. Tricyclic antidepressants have been shown to reduce the plasma and cerebral concentrations of LNAA in rats,254 and may increase the tryptophan concentration in plasma as well by inhibiting the hepatic tryptophan pyrrolase.255 In other words, the antidepressants may influence the TRY/LNAA ratio in favour of enhanced tryptophan in-transport to the brain. Furthermore, an addition of tricyclic antidepressants to peripheral tryptophan administration has been shown to amplify the tryptophan mediated increase in the cerebral tryptophan concentration in rats.255 Ethanol activates the liver tryptophan pyrrolase in humans, causing a lower plasma tryptophan concentration with a secondary risk of acute cerebral brain depletion in susceptible individuals.256 Also, caffeine has been reported to increase tryptophan, serotonin and 5-HIAA levels in the brain.257

Thus, there are a number of factors, including food composition, fasting, diurnal rhythms, hormones and stress levels, recent alcohol intake, and drug treatment, which may influence the availability of tryptophan and thus cerebral serotonin synthesis, and these should be standardised in experiments on the serotonin system and taken into account in data interpretation. In order to avoid interference with measurements due to different LNAA concentrations, the participants in the studies were fasting for at least 5 hours and potential differences in LNAA between the investigated groups were analysed.
The impact of precursor availability on serotonergic neurotransmission

Depending on how calculations of 5-HTP derived radioactivity are performed, results may not only reflect serotonin synthesis but BBB transport to some degree as well, according to the tracer kinetic modeling experiments.\textsuperscript{203} The BBB transport of tryptophan and 5-HTP is regulated by the TRY/LNAA ratio in plasma. Consequently, the plasma TRY/LNAA ratio may have a role in modulating serotonin synthesis. The relationship between serotonergic neurotransmission and peripheral tryptophan-LNAA metabolism/BBB transport has been investigated in numerous studies with methods focusing on alteration of the supply of precursors to the brain such as the tryptophan depletion and 5-hydroxy-L-tryptophan loading tests.

By employing a tryptophan-free diet and thereby achieving significant tryptophan depletion in plasma, patients recovered from depression have been made to relapse, especially those who were treated with SSRI.\textsuperscript{258,259} Also, the tryptophan depletion has been reported to lower mood in healthy women\textsuperscript{151} as well as in healthy men with a family history of depression.\textsuperscript{171} Further emphasising the important role of peripheral tryptophan metabolism in serotonin related psychiatric disorders are reports on attenuated intestinal uptake of L-tryptophan,\textsuperscript{260,261} and reports on low plasma L-tryptophan concentrations\textsuperscript{262,263} in depressive patients.

A substantial number of studies indicate that the cerebral serotonin activity in rodents can be augmented by systematically administrated 5-hydroxy-L-tryptophan loading.\textsuperscript{235-237,264} Moreover, it has been shown in rats that concomitant 5-hydroxy-L-tryptophan loading may even further increase the observable enhancement in the cerebral serotonin extracellular level evoked by either 5-HT\textsubscript{1A} antagonist or SSR\textsubscript{1}.\textsuperscript{265} In humans, 5-hydroxy-L-tryptophan loading has been shown to mediate mood elevation and temperature changes as well as to increase the cortisol, prolactin, adrenocorticotropic and growth hormone levels, although there are some incongruencies between studies.\textsuperscript{173,174,266-268} These phenomena most likely reflect altered central serotonergic activity where, for example, the increased cortisol response may be secondary to enhanced serotonin function at the 5-HT\textsubscript{2} receptors.\textsuperscript{174} The cortisol and prolactin responses to 5-hydroxy-L-tryptophan challenge have been used as a measure of the antidepressant’s effects on the serotonergic system. Meltzer\textsuperscript{269} noticed enhanced cortisol and prolactin responses in patients with depression and obsessive-compulsive disorders with and without chronic antidepressant treatment. However, it was preferentially marked in those treated with the SSRI substance fluoxetine, and the explanation was thought to be that fluoxetine may differ from the tricyclic antidepressants by increasing serotonergic activity via presynaptic rather than postsynaptic...
mechanisms. Also, an increased cortisol response was noted after one week of administration of SSRI (paroxetine), both in healthy as well as depressive individuals, while chronic treatment resulted in normalisation in the controls but not in the patient groups. Notably, van Praag revealed that lower probencid-induced cerebrospinal 5-HIAA accumulation characterised those depressive patients who could be treated with 5-hydroxy-L-tryptophan, thus suggesting that they suffered from an underlying central serotonin deficiency. Additionally, Ågren et al observed lower uptake of 5-HTP across the BBB in depressed patients. Taken together, these studies illustrate that peripherally administrated 5-hydroxy-L-tryptophan may influence the serotoninergic neurotransmission. However, in our PET studies, such effects of administration of 5-HTP are unlikely to happen due to the small dosages used.

In summary, the results of the above-described presynaptic serotoninergic investigations suggest that there is a close relationship between the precursors’ supply to the brain and cerebral serotoninergic tonus.
AIMS

The main purpose of the study was to gather more knowledge about the social phobia disorder.

The concrete aims formulated in the beginning were as follows:

1. To examine how common avoidant personality disorder is among social phobia subjects according to DSM-IV.
2. To clarify whether social phobia is accompanied by specific personality traits.
3. To elucidate any potential association between personality traits and the occurrence of personality disorders in individuals with social phobia.
4. To investigate whether there are imbalances in presynaptic serotonin function in social phobics by means of PET and the radiotracer 5-HTP.
5. To evaluate plausible sex differences in presynaptic serotonin function in individuals with social phobia as imaged by PET and the radiotracer 5-HTP.
6. To estimate the prevalence of social phobia in Sweden.
METHODS

Study design

STUDY DESIGN
Study I-IV

Inclusions criteria
DSM-IV criteria for social phobia fulfilled
Aged 18-40 years. Right handed. Drug free
No concurrent medical or psychiatric disorders. Non pregnancy

Newspaper advertisements

Short screening of inclusions criteria by telephone
(120)

Self-report scales were mailed out
(60 assumed to fulfill inclusions criteria)
The Social Anxiety Interaction Scale
The Swedish versions of the Social Phobia Scale
The Beck Depression Inventory
The Social Screening Phobia Questionnaire
(48 returns)

Clinical evaluation
(36 assumed to fulfill inclusions criteria)
Public speaking behavioral test
The Structured Clinical Interview for DSM-IV (SCID I and II)
(35 fulfills social phobia criteria)
Study I
(35)
KSP
(32 returns)
(16 male/16 female, mean age: 33.7 years)

Study II
(35)
TCI
(31 returns)
(15 male/16 female, mean age: 33.5 years)

Study III
(18 selected according to behavioral test:
gender + inclusions criteria)
Social phobics:
(10 men/8 female, mean age: 35.2 years)
Controls:
(10 male/8 female, mean age: 30.0 years)
recruited among the hospital staff
and through advertisements
5-HTP PET investigation

Study IV
(16 selected for acquiring
an equal number of the sexes)
Social phobics:
(8 male/8 female, mean age: 33.9 years)
Controls:
(8 male/8 female, mean age 28.9 years)
5-HTP PET investigation
The design of study V was as follows: The authors constructed a self-report questionnaire, identifying symptoms of social fears (SPSQ). The SPSQ constitutes several sections. First, there is a diagnostic section. The presence of social phobia is determined by means of six true/false statements covering criteria A-D in the DSM-IV. Impairment, according to the E-criterion, was estimated in different life domains (3) and levels (0-3). Yes/no questions were applied in order to determine whether comorbid psychiatric disorders and medication were present according to the G and H criteria. The SPSQ also evaluates the level of social distress in 14 potentially phobic situations, each situation rated from 0–4 (min–max) on a distress scale, thus yielding a maximal distress score of 56. This part generated information on the frequency of social fears in general and the degree to which the “marked distress” DSM-IV criteria were fulfilled. The questions concerning the 14 phobic situations were repeated after each of the 6 diagnostic statements. The *a priori* cut-off criteria were set in order to define social phobia as follows: (a) a rating of distress ≥3 for at least one of the 14 phobic situations, (b) this situation had to be confirmed throughout all questions assessing the DSM-IV social phobia criteria, and (c) there had to be impairment or marked distress due to social anxiety in at least one of the three life domains assessed by the E-criterion question. The point prevalence of social phobia was estimated across different cut-off levels, i.e. by varying the degree of distress and impairment in the diagnostic questions. Second, the SPSQ assessed sociodemographic characteristics. The last two sections explored family history of social anxiety as well as APD with the aid of diagnostic questions from the DSM-IV and ICD-10 Personality Disorder Questionnaire, DIP-Q.271

In a preliminary assessment, the SPSQ identified all 35 cases of social phobia in a sample of 55 individuals who had been screened with the structured clinical interview for axis I disorders (SCID; First et al., 1998). However, there was one false positive identification. Thus, the sensitivity and specificity of the SPSQ were 100% and 95%, respectively. Subsequently, the SPSQ was mailed to 2000 randomly selected adults (1000 males and 1000 females, aged 18–70) from a population-based registry (Enator). Subjects were selected in equal proportions from the larger Stockholm area and from Gotland in order to evaluate urban-rural differences. Completed questionnaires were obtained from 1202 respondents, i.e. 60.1% (541 men, 661 women; mean age=41.8, SD=14.1; 621 from Stockholm and 581 from Gotland).
Table III. Materials/instruments and statistics.

<table>
<thead>
<tr>
<th>Study</th>
<th>Instruments</th>
<th>Statistics used</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>SCID I and II interview</td>
<td>Chi-square test</td>
</tr>
<tr>
<td></td>
<td>SCID I, severity grade of social phobia</td>
<td>Chi-square test</td>
</tr>
<tr>
<td></td>
<td>The Social Screening Phobia Questionnaire:</td>
<td>Student’s t-test</td>
</tr>
<tr>
<td></td>
<td>Number of impaired life domains</td>
<td>Student’s t-test</td>
</tr>
<tr>
<td></td>
<td>Global Assessment of functioning, self report</td>
<td>Student’s t-test</td>
</tr>
<tr>
<td></td>
<td>The Social Anxiety Interaction Scale</td>
<td>Student’s t-test</td>
</tr>
<tr>
<td></td>
<td>The Swedish versions of the Social Phobia Scale</td>
<td>Student’s t-test</td>
</tr>
<tr>
<td></td>
<td>The Beck Depression Inventory</td>
<td>Student’s t-test</td>
</tr>
<tr>
<td></td>
<td>KSP</td>
<td>Student’s t-test</td>
</tr>
<tr>
<td>II</td>
<td>SCID I and II interview</td>
<td>Student’s t-test</td>
</tr>
<tr>
<td></td>
<td>TCI</td>
<td>Logistic regression analyses</td>
</tr>
<tr>
<td>III</td>
<td>SCID I and II interview</td>
<td>Pixelwise multiple linear regression</td>
</tr>
<tr>
<td></td>
<td>PET</td>
<td>One-way ANOVA</td>
</tr>
<tr>
<td></td>
<td>H$_2^{15}$O</td>
<td></td>
</tr>
<tr>
<td></td>
<td>[3-11C]−5-HTP*</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>SCID I and II interview</td>
<td>Chi-square test</td>
</tr>
<tr>
<td></td>
<td>SCID I, social phobia subgroups</td>
<td>Two-way ANOVA</td>
</tr>
<tr>
<td></td>
<td>Large neutral amino acids</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PET</td>
<td></td>
</tr>
<tr>
<td></td>
<td>H$_2^{15}$O</td>
<td></td>
</tr>
<tr>
<td></td>
<td>[3-11C]−5-HTP *</td>
<td></td>
</tr>
<tr>
<td>V</td>
<td>The Social Screening Phobia Questionnaire</td>
<td>Chi-square test</td>
</tr>
<tr>
<td></td>
<td>Confidence interval calculations.</td>
<td></td>
</tr>
</tbody>
</table>

* Preprocessing of data included transforming of the individuals’ brain [3-11C]−5-HTP images to a standardised brain atlas, the Talairach-Tournoux atlas, with aid of the H$_2^{15}$O image for anatomical orientation. The pixelwise multiple linear regression identified brain areas with significantly (p<0.05) altered normalised [3-11C]−5-HTP in the group comparisons.

Materials, ethics, and statistics

Materials/diagnostic instruments are presented in Table III. For more detailed descriptions regarding the methodological approaches other than the PET technique (see Figure 3), see papers I–V.

All subjects participating in studies I–IV gave informed consent. The Uppsala University Ethics Committee approved the study protocols.
Statistical analyses in studies I and IV were performed with the SPSS programme for Macintosh 5.0. Statview 5.0 for Macintosh was employed in paper V. The statistical methods used are shown in Table 3.

**PET Technique**

![PET procedure diagram](image)

**Figure 3.** PET procedure. Grafik: (c) Thomas Molén/Svenska Dagbladet
RESULTS

Sociodemographic findings (studies I and II)

Sociodemographic characteristics are presented in Table IV.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Study I (n=32)</th>
<th>Study II (n=31)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>9</td>
<td>28.2</td>
</tr>
<tr>
<td>Living together</td>
<td>10</td>
<td>31.2</td>
</tr>
<tr>
<td>Single</td>
<td>13</td>
<td>40.6</td>
</tr>
<tr>
<td>Educational level</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low¹</td>
<td>4</td>
<td>12.6</td>
</tr>
<tr>
<td>Medium²</td>
<td>14</td>
<td>43.7</td>
</tr>
<tr>
<td>High³</td>
<td>14</td>
<td>43.7</td>
</tr>
<tr>
<td>Occupational status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Working</td>
<td>19</td>
<td>59.4</td>
</tr>
<tr>
<td>Student</td>
<td>12</td>
<td>37.5</td>
</tr>
<tr>
<td>Unemployed</td>
<td>1</td>
<td>3.1</td>
</tr>
</tbody>
</table>

Notes: 1 = grades 1–9 or elementary school; 2 = high school, trade school or technical education below university level; 3 university or university college.

Frequency of Axis I and Axis II diagnoses (studies I and II)

The distribution and frequency of lifetime and current Axis I disorders for the groups investigated in studies I (n=32) and II (n=31) are presented in Table V. Nine of the 32/31 subjects (28.1/29.0 %) received a current axis I diagnosis and 17 subjects (53.1/54.8%) received a lifetime axis I diagnosis. The most common lifetime diagnosis was major depression.

The distribution of personality disorders is presented in Table VI. Concurrent personality disorder was diagnosed in 19 (59.4/61.3%) of the subjects.
### Table V. Distribution and frequency of lifetime and current axis I disorder in studies I (n=32) and II (n=31).

<table>
<thead>
<tr>
<th>Axis I disorder</th>
<th>Lifetime</th>
<th></th>
<th></th>
<th>Current</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I</td>
<td>II</td>
<td>I</td>
<td>II</td>
<td>I</td>
<td>II</td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Panic disorder with agoraphobia</td>
<td>2</td>
<td>6.2</td>
<td>1</td>
<td>3.1</td>
<td>3.1</td>
<td>3.2</td>
</tr>
<tr>
<td>Agoraphobia</td>
<td>1</td>
<td>3.1</td>
<td>1</td>
<td>3.1</td>
<td>3.1</td>
<td>3.2</td>
</tr>
<tr>
<td>Generalised Anxiety disorder</td>
<td>1</td>
<td>3.1</td>
<td>1</td>
<td>3.1</td>
<td>3.1</td>
<td>3.2</td>
</tr>
<tr>
<td>Specific phobia</td>
<td>3</td>
<td>9.4</td>
<td>2</td>
<td>6.2</td>
<td>6.2</td>
<td>6.4</td>
</tr>
<tr>
<td>Obsessive-Compulsive disorder</td>
<td>2</td>
<td>6.2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Anxiety disorder UNS</td>
<td>1</td>
<td>3.1</td>
<td>1</td>
<td>3.1</td>
<td>3.1</td>
<td>3.2</td>
</tr>
<tr>
<td>Affective disorder</td>
<td>11</td>
<td>34.4</td>
<td>3</td>
<td>9.4</td>
<td>9.4</td>
<td>9.7</td>
</tr>
<tr>
<td>Major depressive disorder</td>
<td>8</td>
<td>25.0</td>
<td>2</td>
<td>6.2</td>
<td>6.2</td>
<td>6.4</td>
</tr>
<tr>
<td>Dysthymic disorder</td>
<td>3</td>
<td>9.4</td>
<td>1</td>
<td>3.1</td>
<td>3.1</td>
<td>3.2</td>
</tr>
<tr>
<td>Anorexia nervosa</td>
<td>1</td>
<td>3.1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Alcoholic dependence</td>
<td>1</td>
<td>3.1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hash dependence</td>
<td>2</td>
<td>6.2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Somatoform disorder</td>
<td>1</td>
<td>3.1</td>
<td>1</td>
<td>3.1</td>
<td>3.1</td>
<td>3.2</td>
</tr>
<tr>
<td>Any axis I disorder</td>
<td>17</td>
<td>53.1</td>
<td>9</td>
<td>28.1</td>
<td>29.0</td>
<td></td>
</tr>
</tbody>
</table>

### Table VI. Distribution and frequency of co-existing axis II disorders in studies I (n=32) and II (n=31).

<table>
<thead>
<tr>
<th>Personality disorders</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Study</td>
<td>I</td>
<td>II</td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Cluster A</td>
<td>3</td>
<td>9.4</td>
</tr>
<tr>
<td>Paranoid</td>
<td>1</td>
<td>3.1</td>
</tr>
<tr>
<td>Schizoid</td>
<td>2</td>
<td>6.3</td>
</tr>
<tr>
<td>Schizotypal</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cluster B</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Histrionic</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Narcissistic</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Borderline</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cluster C</td>
<td>16</td>
<td>50.0</td>
</tr>
<tr>
<td>Avoidant</td>
<td>15</td>
<td>46.9</td>
</tr>
<tr>
<td>Dependant</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Obsessive-compulsive</td>
<td>2</td>
<td>6.3</td>
</tr>
<tr>
<td>Personality disorder, unspecified</td>
<td>2</td>
<td>6.3</td>
</tr>
<tr>
<td>Negativistic</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Depressive</td>
<td>2</td>
<td>6.3</td>
</tr>
<tr>
<td>Any personality disorder</td>
<td>19</td>
<td>59.4</td>
</tr>
<tr>
<td></td>
<td>61.3</td>
<td></td>
</tr>
</tbody>
</table>
APD was the most common, occurring in 15 (46.9/48.4%) of the subjects. All the 15 subjects with comorbid APD were also diagnosed with a generalised social phobia. Generalised social phobia is a subtype of social phobia which was diagnosed by the SCID I interview in 21 (65.6%) of the participants.

**General psychopathology measures (study I)**

The 15 subjects with a comorbid APD had significantly higher scores on the BDI and SIAS scales than those without APD. Social phobics with APD exhibited functional impairments in significantly more life domains as compared to those without APD (Table VII).

**Table VII.** Measures of social anxiety symptoms, depression and impairment in social phobics with and without avoidant personality disorder (APD)

<table>
<thead>
<tr>
<th></th>
<th>Social phobics with APD (n=15)</th>
<th>Social phobics without APD (n=17)</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPS</td>
<td>mean 30.1 SD 14.0</td>
<td>mean 25.8 SD 15.8</td>
<td>0.80</td>
<td>ns</td>
</tr>
<tr>
<td>SIAS</td>
<td>mean 44.7 SD 8.9</td>
<td>mean 26.6 SD 17.1</td>
<td>3.73</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BDI</td>
<td>mean 11.9 SD 5.1</td>
<td>mean 6.2 SD 4.8</td>
<td>3.04</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>GAF</td>
<td>mean 66.6 SD 10.7</td>
<td>mean 75.0 SD 13.7</td>
<td>1.87</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>Symptom severity</td>
<td>n %</td>
<td>n %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mild</td>
<td>1 11.8</td>
<td>2 11.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>moderate</td>
<td>2 35.3</td>
<td>3 35.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>severe</td>
<td>3 52.9</td>
<td>9 52.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of domains</td>
<td>affected</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1 52.9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>2 29.4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>3 17.6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ns, not significant.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Personality traits according to the KSP (study I)**

As compared to the normative sample, social phobic subjects were characterised by higher scores on all anxiety scales as well as the scales measuring irritability, indirect aggression, and detachment, but lower scores on the scales for socialisation and social desirability (Table VIII). Social phobics with an APD scored significantly higher on the scales for psychic anxiety and inhibition of aggression than those without an APD (Table VIII).
Table VIII. Personality traits measured by means of the KSP in 32 subjects with social anxiety syndrome with and without avoidant personality disorder (APD) as compared to the normative sample.

<table>
<thead>
<tr>
<th>KSP scales</th>
<th>Social phobia (n=32)</th>
<th>Social phobia subgroup with APD (n=15)</th>
<th>Social phobia subgroup without APD (n=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>t</td>
</tr>
<tr>
<td>Somatic anxiety</td>
<td>61.2</td>
<td>9.1</td>
<td>6.18 ***</td>
</tr>
<tr>
<td>Psychic anxiety</td>
<td>59.2</td>
<td>9.5</td>
<td>5.03 ***</td>
</tr>
<tr>
<td>Muscular tension</td>
<td>61.2</td>
<td>12.7</td>
<td>4.83 ***</td>
</tr>
<tr>
<td>Psychasthenia</td>
<td>54.9</td>
<td>10.0</td>
<td>2.7 **</td>
</tr>
<tr>
<td>Inhibition of aggression</td>
<td>54.4</td>
<td>10.4</td>
<td>2.41 *</td>
</tr>
<tr>
<td>Impulsiveness</td>
<td>48.2</td>
<td>9.1</td>
<td>0.98</td>
</tr>
<tr>
<td>Monotony avoidance</td>
<td>49.6</td>
<td>8.9</td>
<td>0.22</td>
</tr>
<tr>
<td>Socialisation</td>
<td>42.4</td>
<td>9.2</td>
<td>4.16 ***</td>
</tr>
<tr>
<td>Social desirability</td>
<td>45.3</td>
<td>8.2</td>
<td>2.6 **</td>
</tr>
<tr>
<td>Indirect aggression</td>
<td>54.3</td>
<td>9.7</td>
<td>2.34 *</td>
</tr>
<tr>
<td>Verbal aggression</td>
<td>47.4</td>
<td>8.6</td>
<td>1.42</td>
</tr>
<tr>
<td>Irritability</td>
<td>53.8</td>
<td>9.2</td>
<td>2.07 *</td>
</tr>
<tr>
<td>Suspicion</td>
<td>52.2</td>
<td>10.5</td>
<td>1.2</td>
</tr>
<tr>
<td>Guilt</td>
<td>48.4</td>
<td>10.2</td>
<td>0.85</td>
</tr>
<tr>
<td>Detachment</td>
<td>54.6</td>
<td>11.1</td>
<td>2.47 *</td>
</tr>
</tbody>
</table>

Personality test scores are given as T-scores, which are standardised to have a mean of 50 (SD=10) in the KSP normative sample.

* p<0.05; **p<0.01; *** p<0.001 social phobia subjects as compared to the normative sample.

# p<0.05; ## p<0.01 social phobia group with versus without avoidant personality disorder

Personality traits according to the TCI (study II)

The subjects with social phobia exhibited significantly higher scores on the TCI personality dimension Harm avoidance, but significantly lower scores on Persistence, Self-directedness, Cooperativeness and Self-transcendence as compared to healthy volunteers of the same age (Table IX). Social phobics with comorbid APD scored higher on Harm avoidance and its subscales Fear of uncertainty and Shyness with strangers, but lower on the Novelty seeking subscales Exploratory excitability and Extravagance, and the Reward dependence subscale Attachment, as compared to those without APD (Table IX).
**Table IX.** Comparison of personality traits according to the Temperament and Character Inventory in subjects with social phobia (n=31) and healthy volunteers (n=400) of the same age as well as in social phobics with (n=15) and without (n=16) avoidant personality disorder (APD).

<table>
<thead>
<tr>
<th>Trait</th>
<th>Healthy controls</th>
<th>Subjects with social phobia</th>
<th>Social phobics with APD</th>
<th>Social phobics without APD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Novelty seeking</td>
<td>15.3±3.8</td>
<td>14.2±4.0</td>
<td>13.4±3.5</td>
<td>14.9±4.4</td>
</tr>
<tr>
<td>Exploratory excitability</td>
<td>7.3±2.3</td>
<td>6.0±2.3</td>
<td>5.2±2.6</td>
<td>6.8±1.6</td>
</tr>
<tr>
<td>Impulsiveness</td>
<td>4.5±2.5</td>
<td>5.1±2.5</td>
<td>5.5±3.1</td>
<td>4.8±1.8</td>
</tr>
<tr>
<td>Extravaganza</td>
<td>5.5±2.1</td>
<td>5.1±2.0</td>
<td>4.3±2.2</td>
<td>5.8±1.6</td>
</tr>
<tr>
<td>Disorderliness</td>
<td>4.6±1.9</td>
<td>4.4±2.0</td>
<td>4.3±2.0</td>
<td>4.4±2.0</td>
</tr>
<tr>
<td>Harm avoidance</td>
<td>13.4±6.3</td>
<td>20.9±6.0</td>
<td>23.1±4.7</td>
<td>18.8±6.4</td>
</tr>
<tr>
<td>Anticipatory worry</td>
<td>3.8±2.3</td>
<td>5.6±2.5</td>
<td>5.8±2.5</td>
<td>5.4±2.6</td>
</tr>
<tr>
<td>Fear of uncertainty</td>
<td>3.7±1.8</td>
<td>5.5±1.7</td>
<td>6.3±0.8</td>
<td>4.8±2.0</td>
</tr>
<tr>
<td>Shyness with strangers</td>
<td>3.1±2.1</td>
<td>6.0±1.9</td>
<td>7.1±1.1</td>
<td>4.9±1.9</td>
</tr>
<tr>
<td>Fatigability and asthenia</td>
<td>2.8±2.0</td>
<td>3.8±2.1</td>
<td>3.9±1.7</td>
<td>3.7±2.4</td>
</tr>
<tr>
<td>Reward dependence</td>
<td>6.4±2.0</td>
<td>6.4±2.0</td>
<td>6.7±2.1</td>
<td>6.2±1.9</td>
</tr>
<tr>
<td>Sentimentality</td>
<td>5.2±2.1</td>
<td>3.8±2.5</td>
<td>2.6±2.4</td>
<td>4.9±2.1</td>
</tr>
<tr>
<td>Attachment</td>
<td>3.7±1.5</td>
<td>3.9±1.3</td>
<td>4.1±0.8</td>
<td>3.8±1.6</td>
</tr>
<tr>
<td>Dependence</td>
<td>4.2±2.0</td>
<td>3.5±1.7</td>
<td>3.2±1.7</td>
<td>3.8±1.8</td>
</tr>
<tr>
<td>Self-directedness</td>
<td>31.1±6.9</td>
<td>26.9±8.8</td>
<td>25.2±8.4</td>
<td>28.5±9.1</td>
</tr>
<tr>
<td>Responsibility</td>
<td>6.4±1.8</td>
<td>5.9±2.0</td>
<td>5.7±1.9</td>
<td>6.1±2.2</td>
</tr>
<tr>
<td>Purposefulness</td>
<td>5.5±1.8</td>
<td>3.9±2.2</td>
<td>3.3±2.0</td>
<td>4.5±2.4</td>
</tr>
<tr>
<td>Resourcefulness</td>
<td>4.0±1.2</td>
<td>3.3±1.3</td>
<td>3.9±1.4</td>
<td>3.8±1.1</td>
</tr>
<tr>
<td>Self-acceptance</td>
<td>7.1±1.5</td>
<td>7.4±2.8</td>
<td>7.3±3.2</td>
<td>7.5±2.5</td>
</tr>
<tr>
<td>Congruent second nature</td>
<td>8.2±2.5</td>
<td>6.3±3.1</td>
<td>5.9±3.1</td>
<td>6.7±3.1</td>
</tr>
<tr>
<td>Cooperativeness</td>
<td>33.1±5.2</td>
<td>29.7±5.7</td>
<td>30.2±3.7</td>
<td>29.1±7.1</td>
</tr>
<tr>
<td>Social acceptance</td>
<td>7.0±1.3</td>
<td>6.5±1.6</td>
<td>6.3±1.6</td>
<td>6.7±1.5</td>
</tr>
<tr>
<td>Empathy</td>
<td>5.0±1.2</td>
<td>4.0±1.6</td>
<td>3.9±1.5</td>
<td>4.1±1.7</td>
</tr>
<tr>
<td>Helpfulness</td>
<td>6.5±1.3</td>
<td>5.9±1.4</td>
<td>6.1±0.8</td>
<td>5.7±1.8</td>
</tr>
<tr>
<td>Compassion</td>
<td>7.4±2.4</td>
<td>6.2±2.4</td>
<td>6.5±2.3</td>
<td>5.9±2.5</td>
</tr>
<tr>
<td>Integrated conscience</td>
<td>7.1±1.5</td>
<td>7.0±1.7</td>
<td>7.3±1.5</td>
<td>6.7±1.8</td>
</tr>
<tr>
<td>Self-transcendence</td>
<td>11.7±5.4</td>
<td>6.8±4.3</td>
<td>7.3±5.2</td>
<td>6.3±3.3</td>
</tr>
<tr>
<td>Self-forgetfulness</td>
<td>3.7±2.2</td>
<td>2.8±2.2</td>
<td>3.5±2.6</td>
<td>2.1±1.5</td>
</tr>
<tr>
<td>Transpersonal identification</td>
<td>2.6±1.4</td>
<td>1.4±1.0</td>
<td>1.4±1.2</td>
<td>1.4±0.8</td>
</tr>
<tr>
<td>Spiritual acceptance</td>
<td>5.4±3.3</td>
<td>2.6±2.1</td>
<td>2.5±2.4</td>
<td>2.7±2.0</td>
</tr>
</tbody>
</table>
The logistic regressions analyses revealed that the only dimension that showed an independent but weak relation to APD was Harm avoidance (p values close to 0.05). Furthermore, of the five subscales differentiating significantly between social phobia individuals with and without comorbid APD, only Shyness with strangers was significantly related to APD (R²=0.39, p<0.01), thus explaining 39% of the variance.

Presynaptic serotonin metabolism in subjects with social phobia (study III)

The global 5-HTP values, defined as the individual whole brain 5-HTP derived radioactivity concentration divided by the injected radioactivity and multiplied by the subject’s weight in order to reflect standard uptake values, were evaluated for individuals with social phobia and healthy volunteers. No significant differences (ANOVA, F=0.268; df=1; p=0.60) between the social phobia subjects (mean±SD: 1.11±0.23) and the controls (1.15±0.19) were found.

Table X. Alterations in regional 5-HTP derived radioactivity in patients with social phobia in comparison to healthy controls.

<table>
<thead>
<tr>
<th>Brain areas:</th>
<th>Coordinates</th>
<th>Max Z-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lower 5-HTP accumulation in social phobia</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R Temporal Cortex (34, 36, 38)</td>
<td>31 -16 -29</td>
<td>3.30</td>
</tr>
<tr>
<td>L Temporal Cortex (21, 34, 36)</td>
<td>-36 -26 -22</td>
<td>2.47</td>
</tr>
<tr>
<td>R Frontal Cortex (13, 14, 15, 44, 45, 47)</td>
<td>47 19 0</td>
<td>3.44</td>
</tr>
<tr>
<td>L Frontal Cortex (15)</td>
<td>-11 5 -12</td>
<td>2.87</td>
</tr>
<tr>
<td>R+L Anterior Cingulate Cortex (25, 33)</td>
<td>-6 14 -16</td>
<td>2.37</td>
</tr>
<tr>
<td>L Basal Ganglia (N. Accumbens, N. Caudate, Pallidum, Putamen)</td>
<td>-12 4 -8</td>
<td>2.75</td>
</tr>
<tr>
<td><strong>Higher 5-HTP accumulation in social phobia</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebellum</td>
<td>-14 -75 -27</td>
<td>3.51</td>
</tr>
<tr>
<td>Pons</td>
<td>-6 -22 -17</td>
<td>4.06</td>
</tr>
</tbody>
</table>

L = left hemisphere, R = right hemisphere; _= where the maximum voxel value is located; approximate Brodmann areas within parentheses; coordinates in millimeters correspond to the stereotactic atlas of Talairach & Tournoux; all Z-scores correspond to p<0.05 or better when corrected for multiple comparisons except *, p=0.0002 uncorrected.

In contrast, pixel-wise linear regression analysis revealed a group-specific difference (omnibus p=0.000001) in the normalised 5-HTP values (regional values relative to whole brain radioactivity). Regions with significantly (p<0.05) lower normalised 5-HTP in social phobia, relative to controls, were
found in the temporal lobes including the perirhinal, entorhinal and peri-
amygdaloid cortices bilaterally as well as the right anterior and the left
inferior temporal cortices.

Furthermore, there were significant diminutions bilaterally in the anterior
cingulate and inferior frontal cortices, the right insular cortex, and the left
basal ganglia nuclei. The normalised 5-HTP was significantly higher bilate-
raly in the cerebellum in patients than in controls (Table X).

Impact of gender on presynaptic serotonin metabolism
in individuals with social phobia (study IV)

In the present group of subjects, the frequency of the generalised subtype of
social phobia did not differ between men and women (p=0.6).

There were significantly less sex-related differences in normalised 5-HTP
in patients with social phobia than in healthy individuals (Male controls –
Female controls) – (Male phobics – Female phobics); omnibus level; p <
0.000001) in areas of the frontal lobes including the right medial/orbito-
lateral prefrontal cortices and the left inferior frontal cortex. Men with social
phobia as compared to healthy men exhibited significant, lower, normalised
5-HTP values (p<0.000001 at the omnibus level) in the same frontal regions
in addition to most of the cortical territories noted in the mixed gender
analysis that are described above (study III). In addition, they had higher
normalised 5-HTP in the cerebellum. Healthy women showed significantly
(p < 0.000001 at the omnibus level) lower normalised 5-HTP compared to
healthy men in the left inferior frontal cortex as well as in the right
periamygdaloid and anterior temporal cortices. In contrast, there were no
significant differences in normalised 5-HTP between females and males with
social phobia, or between female social phobics and female controls (Table
XI).

The plasma levels of LNAA were significantly higher in male than
female subjects (F=8.0; df=1; P<0.01; 2-way ANOVA), but the main effects
for group and group-by-gender interaction were not significant. The global
brain 5-HTP derived radioactivity did not differ significantly depending on
group, gender or group-by-gender interaction (P>0.1; 2-way ANOVA).
Table XI. Significant gender differences in regional 5-HTP derived radioactivity in women and men with social phobia (n=8+8) as compared to healthy women and men (n=8+8).

<table>
<thead>
<tr>
<th>Brain areas</th>
<th>Coordinates</th>
<th>Max Z-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>x   y   z</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Healthy females &lt; healthy males</th>
</tr>
</thead>
<tbody>
<tr>
<td>R Temporal cortex (15, 34, 38)</td>
</tr>
<tr>
<td>L Frontal cortex (44, 50)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Social phobia males &lt; healthy males</th>
</tr>
</thead>
<tbody>
<tr>
<td>R Temporal cortex (15, 34, 36, 38)</td>
</tr>
<tr>
<td>L Temporal cortex (22, 34, 38)</td>
</tr>
<tr>
<td>R Frontal cortex (10, 13, 44, 46, 47)</td>
</tr>
<tr>
<td>L Frontal cortex (15, 43, 44, 47, 50)</td>
</tr>
<tr>
<td>R+L Anterior Cingulate cortex (25, 33)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Social phobia males &gt; healthy males</th>
</tr>
</thead>
<tbody>
<tr>
<td>[Healthy males – healthy females] &gt; [social phobia males – social phobia females]</td>
</tr>
<tr>
<td>R + L Cerebellum</td>
</tr>
</tbody>
</table>

L = left hemisphere, R = right hemisphere; _= where the maximum voxel value is located; approximate Brodmann areas within parentheses; coordinates in millimeters correspond to the stereotactic atlas of Talairach & Tournoux; all Z-scores correspond to p<0.01 or better when corrected for multiple comparisons.

Swedish epidemiological data (study V)

The point prevalence of social phobia was 15.6% (95% confidence interval (13.5–17.6%) obtained by using the *a priori* definition. However, the prevalence rates varied between 1.9–20.4% when different levels of distress and impairment were tested. Eighty-eight (14%) individuals from the Stockholm area and 100 (17%) from Gotland fulfilled the social phobia criteria. Prevalence estimates from Stockholm and Gotland (χ²=2.1, df=1, n.s.) were compared, as were those from Gotland’s urban and rural regions (χ²=4.6, df=2, n.s.). Nonetheless, there were no significant geographical differences. Public speaking was the most common social fear in social phobic (77%) as well as non–social phobic individuals (14%). Comparisons between social phobic and non-phobic individuals revealed that female gender (χ²=8.8, df=1, p<0.005), low educational attainment (χ²=11.3, df=2, p<0.005), psychotropic medication use (χ²=20.1, df=1, p<0.0001), lack of social support (χ²=29.2, df=1, p<0.0001) and younger age (χ²=7.7, df=2, p<0.05, (non-significant after Bonferroni correction)) were linked to the presence of social phobia. An attrition analysis, performed by means of telephone interviews of 80 nonresponders, showed that 12 (12%) met the social phobia impairment
(E) criterion, which was significantly fewer than for the questionnaire responders ($\chi^2=9.1$, df=1, p<0.005).
DISCUSSION

The first part of the study described psychopathology, comorbidity and personality traits in 32/31 (studies I and II) individuals with social phobia. The prevalence of concurrent personality disorders was close to 60% and for APD it was close to 47%, and these figures are in the range of previously reported data. Comparisons are, however, problematic due to the high variance in prior prevalence estimates. In addition, since reports based on these latest criteria are still scarce, it is too early to draw any definitive conclusions as to whether the DSM-IV criteria have influenced the occurrence of APD and social phobia, although there still seems to be a considerable overlap.

The frequency of comorbid lifetime Axis I disorders was around 54% and for concurrent Axis I disorders it was around 28%. In line with previous reports, the most common lifetime comorbid Axis I disorders were affective and anxiety disorders observed in 35% and 32%, respectively. Interestingly, the reported prevalence rate of comorbid APD is about the same as noted in a recent Swedish epidemiological study, also using the DSM-IV criteria. Lifetime Axis I comorbidity was found in more than half of the group, although the purpose of using advertisements for recruitment was to select participants without any such comorbidity. However, the Axis I comorbidity is lower than that described by most social phobia investigators, suggesting that this method of recruitment has advantages when doing research on this disorder. Since the characteristics of the present group are in accord in all other aspects with previous descriptions of clinical social phobia samples, it seems that the reported data are representative for clinical populations of social anxiety disorder.

The social phobics as compared to a normative sample were characterised by significantly higher muscular tension, psychasthenia, detachment, irritability, indirect aggression, psychic and somatic anxiety, but lower socialisation and social desirability on the KSP. Furthermore, they showed significantly higher Harm avoidance as well as lower Persistence, Self-directedness, Cooperativeness and Self-transcendence on the TCI. The KSP and TCI findings seem to converge in most aspects, although traits defined by the two different scales are not easily compared. Most notably, relatively high scores in anxiety-related scales were noted in individuals with social...
phobia on both the TCI and KSP. Collectively, the KSP and TCI results indicate personality traits in social phobia subjects characterised by anticipatory worry, fear of uncertainty, hypersensitiveness, shyness and fatigability, lack of confidence, autonomic disturbances, lack of self-assertiveness and avoidance of involvement with others.

These results are largely consistent with earlier reports on personality traits in social phobics, although once again, making comparisons across different inventories of temperament traits is complicated. Nevertheless, high levels of Harm avoidance and low levels of Self-directedness, Novelty seeking, and Cooperativeness in individuals with social phobia are replications of earlier findings.

The social phobia subjects with APD were distinguished from those without APD by enhanced inhibition of aggression as well as psychic anxiety on the KSP, and by elevated Harm avoidance on the TCI. Thus, it may be suggested that there are only minor differences between social phobics with and without comorbid APD with regard to personality traits. Svrakic implied that Harm avoidance is associated with personality disorders in cluster C. Logistic regression analyses of the present TCI data revealed, however, a low predictive value of Harm avoidance for the presence of comorbid APD in social phobic subjects, while its subscale, *Shyness with strangers*, was a strong predictor. Individuals, who score high on the subscale *Shyness with strangers*, are described as unassertive and shy in most situations and often actively avoid meeting people they do not know well. This description seems to partially overlap with the APD criteria. The observation of enhanced shyness in social phobics correlating positively with the presence of comorbid avoidant personality is congruent with a recent version of the continuum hypothesis. This hypothesis suggests that the social phobia disorder represents the severe part of a continuum of shyness where generalised social phobia with comorbid APD is at the endpoint. Accordingly, the measures on personality traits, functional impairment, severity of symptoms and psychopathology indicated more severity and impairment in the generalised social phobia subtype with comorbid APD than in discrete social phobia, in agreement with the continuum hypothesis.

The pattern of personality traits presented here for social phobia does not seem to be unique for social anxiety disorders, as similar findings have also been reported in patients with other anxiety and depressive disorders. It is noteworthy that these disorders have in common with social phobia, as well as certain personality disturbances, the fact that they are responsive to treatment with SSRIs. In addition, the TCI dimension Harm Avoidance, has been linked to serotonergic imbalances in several studies. It might thus be speculated that disturbances in serotonergic
neurotransmission are the connecting link between the described personality pattern and these often co-existing SSRI responsive disorders.4,6

In summary, the clinical results suggest that there are maladaptive personality traits in subjects with social phobia that are not primarily related to APD comorbidity. However, the results are to be considered explorative due to the small sample and the Axis I comorbidity. Replication studies using larger samples without Axis I comorbidity are warranted to clarify whether deviant personality traits are features of social phobia.

The second part of the study investigated the presynaptic serotonin function in 16/18 individuals with social phobia in comparison with healthy controls, with and without respect to potential gender differences, by means of 5-HTP and PET.

The results revealed that the regional accumulation relative to the whole brain accumulation of 5-HTP, i.e. the normalised 5-HTP, was significantly \( (p<0.05) \) lower in social phobics as compared to healthy controls in the temporal periamygdaloid, entorhinal and perirhinal cortices in both hemispheres, as well as in the right anterior and left inferior temporal cortices. Also, there were attenuations in the anterior cingulate and inferior frontal cortices bilaterally, as well as in the right anterior insular cortex and subcortically in the left basal ganglia. In contrast, the normalised 5-HTP was relatively higher in the cerebellum in the social phobia subjects.

Hence, social phobia was characterised by regionally suppressed presynaptic serotonin function. This appears to be in line with recent hypotheses suggesting that anxiety is associated with low rather than high cerebral serotonin activity,148,286 which is best supported by the beneficial effect of SSRI mediated serotonin enhancement on social anxiety.153

The implicated regions have been proposed to have different anxiety-related roles: the anterior cingulate cortex has been suggested to be involved in the attentional and behavioural response of threat and/or in the conscious experience of anxiety;196 the inferior frontal cortex in affective working memory;287 and behavioural integration of emotionally relevant exteroceptive information;288 the anterior insula in evaluation of interoceptive sensory stimuli and bodily sensations that signal potential internal danger;196 the temporal periamygdaloid/rhinal cortices in attaching emotional significance to exteroceptive stimulation178 as well as participating in anxiety or bodily alarm reactions to threatening stimulation with the amygdalo-hippocampal structures.178,196,285 While the brain territories mentioned above may subserve afferent functions in the brain fear circuit, the basal ganglia have been thought to serve efferent motor functions.179

The findings are of interest in light of the postulated serotonergic regulation of neural activity in fear pathways of the brain,144 where the
The amygdala has been postulated to function as an integrative center of anxiety.\textsuperscript{178} Since serotonin is predominantly an inhibitory neurotransmitter,\textsuperscript{160} and assuming that the normalised 5-HTP values offer an index of serotonin synthesis, it appears plausible that the regional decrements of normalised 5-HTP in social phobia subjects are associated with relatively less inhibition of excitatorial inputs to the amygdala. Thus, the amygdala and subsequently the afferent part of the fear circuit are more easily activated in social phobics, thereby probably lowering the threshold of anxiety.\textsuperscript{190}

It became apparent when the impact of gender was analysed, that observed decrements of normalised 5-HTP in the mixed gender social phobic group were mainly derived from the social phobic men. Thus, the social phobic men as compared with healthy men exhibited lower normalised 5-HTP in all the brain areas revealed in the mixed gender analysis except the anterior cingulate cortex and basal ganglia. In addition, they had lower normalised 5-HTP in the right medial/orbitolateral prefrontal cortices and the left inferior frontal cortices. In contrast, no notable differences were identified between the social phobic and the healthy women. Methodological limitations may account for this gender difference, and these include the small size of the subgroups and/or the fact that the female participants were not matched according to their menstrual phase. The healthy women displayed significantly lower normalised 5-HTP in the left inferior frontal cortex and the right periamygdaloid and anterior temporal cortices compared to healthy men. It is thus also conceivable that the regional attenuations in normalised 5-HTP in the healthy women may have restricted the possibility of detecting differences between the women with social phobia and healthy women. Otherwise, a plausible interpretation is that social phobia in men is linked to presynaptic serotonergic disturbances but in women this link is not a certainty. In that context, it would be of interest to examine whether there is a sex difference in SSRI responsiveness in social phobic individuals.

The absence of sex differences in normalised 5-HTP in the social phobics in contrast to healthy individuals suggests that the presynaptic serotonin function is more similar across the sexes in social phobia than in the healthy state and that this low level of presynaptic function may have a role in social phobia, in line with the above proposal. In parallel, it may be speculated that the regional suppressed presynaptic function in healthy women as compared to men is associated with women’s vulnerability to tryptophan depletion\textsuperscript{151,171,172} as well as to a predisposition for SSRI responsive disorders.\textsuperscript{7} This distinction between social phobia and healthiness was most pronounced in areas of the frontal lobes including the right medial/orbitolateral prefrontal cortices and the left inferior frontal cortex. From a functional point of view, these regions might be of importance regarding social anxiety. The left
inferior frontal gyrus, as a linguistic processing region, could participate in fear of public speaking, which characterised all of the social phobia participants. Activity in medial/orbitofrontal areas has been hypothesised to inhibit the amygdala, thereby enabling a modulatory role regarding anxiety. Accordingly, neuroimaging evidence has delineated the right prefrontal regions as a neural substrate of emotions, where presynaptic serotonin function might be involved.

The frontal lobes have been pointed out in prior studies of brain activity as a site with gender differences, in accordance with the present data. In particular, sex differences have been shown in the inferior frontal gyrus. However, recent MRI studies only indicate neuroanatomical sex dimorphism as an underlying genesis of the present findings in Brodmann area 46.

In general, the results of the PET studies should be regarded as explorative due both to the small samples investigated as well as to some of the assumptions made concerning the validity of 5-HTP in probing serotonin synthesis. The latter issue is discussed in detail in the introduction. There are, however, several points that ought to be mentioned. Thus, while there were no differences between social phobics and healthy individuals in the concentration of LNAA, there were significant LNAA gender differences. Conceivably, this may have influenced the final results, because the BBB transport of 5-HTP is regulated by LNAA plasma concentrations. Nonetheless, such effects may in part be disregarded, as the analysis that was performed is based on the regional 5-HTP accumulations after normalisation to whole brain tracer accumulation. While LNAA-plasma levels may potentially affect the global brain 5-HTP uptake, the regional levels should not, since any such influence is adjusted for by the normalisation procedure. Since no gender or group-related differences in global brain 5-HTP accumulations were observed in the present study, such arguments are even further weakened. In spite of these findings, a small imprecision may remain if some local differences in tracer-transport persist after normalisation. In that case, the normalised 5-HTP, as an index of serotonin synthesis, may be influenced by variation in tracer availability in the brain.

Collectively, the neuroimaging results suggest a dysfunction in the presynaptic serotonin system in subjects with social phobia, primarily in men. Furthermore, our findings suggest relatively lower presynaptic serotonin function regionally in healthy women. This may be related to their vulnerability to SSRI responsive disorders including social phobia. Besides replicated studies on larger samples, the present data motivate further studies on the possible role of the presynaptic serotonin function in social phobia as well as on potential gender differences in presynaptic
serotonin function in healthy as well as social phobic subjects. Finally, the present results suggest that by investigating both genders concurrently, their sex distinctive neural pattern is lost. Thus, sex should be incorporated as a possible modulating factor in future studies of brain functions.

The third study comprised an epidemiological investigation performed by postal surveys in two distinct Swedish regions, Stockholm and Gotland. The obtained point prevalence rate of 15.6% in the total sample suggests that social phobia, defined by the DSM-IV criteria, is a common disorder in Swedish society. However, the estimate varied between 2 and 20%, depending on the defined threshold of distress and impairment, which is in agreement with prior observations. This highlights the need for more detailed research criteria, since the DSM-IV does not clearly define the extent of impairment or distress needed to fulfill the social phobia criteria.

Comparisons with prior epidemiological findings are complicated due to great variability. This may be explained by the above-mentioned uncertainty in determining the social phobia diagnosis as well as by methodological differences in the studies concerning factors such as culture, instruments and DSM versions. Nevertheless, the Swedish figure presented here seems relatively high, although a number of lifetime prevalence estimates based on the DSM-III-R criteria are in the same range e.g., those from the USA (13.3%), Switzerland (16%), and Norway (13.7%). Hence, it seems that the results are in agreement with the contention that the two latest versions of the DSM system, the DSM-IIIR and the DSM-IV, generate similar but higher rates than the pioneer version, DSM-III, although assessments based on different time intervals may not be totally compatible. It is plausible that the limited response frequency (60%) had escalating effects on the prevalence rate, since a significantly larger proportion of responders than non-responders met the impairment criterion. Nevertheless, prior reports rather suggest over-representation of the disorder among non-responders. In addition, speculations could be made concerning the effect of postal survey methodology on the results. Nevertheless, the weighing of pros and cons regarding different methodological techniques in epidemiological research on social phobia has to date not indicated any specific method as superior. However, the comparison between the SPSQ, with established social phobia scales, and the SCID I interview regarding the capability of identifying true social phobia cases suggested that the SPSQ is a satisfactory assessment instrument, although the interview cohort was relatively small.

In most aspects, however, the current data are in accordance with previous reports including the following observations: that public speaking is the most common social fear, that urbanity did not affect the prevalence of social phobia, and that social phobia is associated with
female gender,\textsuperscript{4,6} low educational attainment,\textsuperscript{4,6,58} and little social support.\textsuperscript{84} On the other hand, the expected relations between social phobia and marital status\textsuperscript{4,6} as well as occupational status,\textsuperscript{15,58,82} were not found. There are no apparent explanations for this, although cultural factors could conceivably be involved.

As a whole, the results of the study suggest that social phobia is common in Sweden, although the diagnostic thresholds for the disorder need better definitions to allow for comparisons over time as well as between cultures.
CONCLUSIONS

- Comorbid avoidant personality disorder was noted in 47% of social phobia cases in the clinical sample. In light of the relatively small size of the group this figure should be interpreted cautiously, but it suggests that there is a substantial overlap between social phobia and APD according to the DSM-IV criteria.
- The results of the studies investigating individuals with social phobia with the TCI and the KSP suggest that social phobia is accompanied by specific personality traits.
- The personality profiles associated with social phobia were primarily related to social phobia itself and not to the presence of APD.
- Individuals with social phobia were characterized by significantly lower regional accumulation of the PET-tracer, 5-HTP, suggesting imbalances in presynaptic serotonin function in anxiety-related regions of the brain. This could only be confirmed in men with social phobia, and not in women.
- There appeared to be less gender differences in presynaptic serotonin function in subjects with social phobia than in healthy subjects.
- The epidemiological survey revealed a point prevalence of 15.6% for social phobia in Sweden. The prevalence estimate varied, however, between 2 and 20%, depending on the distress and impairment cut-off levels used to define cases. This suggests that while the exact prevalence rates may be difficult to determine with the present DSM-IV criteria, excessive anxiety in social settings is common among Swedish people, in particular public speaking anxiety.
ACKNOWLEDGEMENTS

This journey began with my keen interest in understanding the human being. It has also offered many chances for more in-depth comprehension. Most important of all, this journey has made me realize the value of being surrounded by honest and helpful people, and it has made me feel very rich in that regard. I want to express my sincere gratitude to all of you.

Hans Ågren, my supervisor, for guiding me through the years and for showing confidence in my ability to carry on my work independently.
Gisela Hagberg, my supervisor, for inviting me to join you on the voyage to an understanding of the track of 5-HTP. Your incredible sharpness of mind has enriched my thinking and my work. Thank you for your loyalty and friendship as well as for our discussions about science and life in general, which I hope will continue in the future, although I don’t know where. Perhaps in Sweden, Italy, or even Iceland?
Per Hartvig, my supervisor, for being a warm-hearted and loyal friend. Without your support this thesis would not have been possible.
Lisa Ekselius, my supervisor, for introducing me to methodological approaches that characterise work of the highest quality. For your friendship and guidance as well as for sincerely safeguarding my interests.
Lars von Knorring, for not hesitating to invite me to come to Uppsala to do research. For many supportive discussions in which you always managed to find a solution to every possible situation.
Bengt Långström, for your kindness, for supporting my work in every way possible, and for giving me the strength to continue by radiating unbelievable energy, enthusiasm and knowledge.
Mats Fredriksson, for sharing your superb skills in methodology and in writing scientific papers in a kind and patient manner that will mark my future work.
Carina Stenfors, my supervisor and dear friend, for never-ending encouragement and invaluable discussions regarding the serotonin system.
Lars Oreland, for excellent advice concerning my scientific work and for being an exemplary leader, combining social and scientific skills with humanity.
Frits-Axel Wiesel, for being supportive when I needed it most, and for always managing to say exactly what I needed to hear, even though I sometimes did not realize it myself, and finally for good, honest collaboration, which I hope will continue.

Maria Tillfors and Tomas Furmark, for successful collaboration, which always included humour and laughter along with the hard work, as well for your generous guidance in the wilderness of PET technology.

Ulla Maria Anderberg, my colleague, coworker and friend, for me excellent advice. And with a few more years than I in the scientific field, you have been my idol, never giving up and always finding a way out of all difficulties.

Susanne Bejerot and Ola Gefvert, for excellent collaboration, honesty and friendship.

Stephan Hjorth, for proving to be a true serotonin friend, generously sharing your time and sound knowledge.

Lars Reibring, for support and for generosity in sharing your experiences from your prior 5-HTP works.

Göran Tidbeck, head of psychiatric services at Huddinge, for a superb staff policy, including understanding and looking after scientists, a policy that is almost better than I could imagine.

Ann-Christine Trost von Werder, my former head of psychiatric services, for being an excellent chief, and for your support and faith in me throughout the years.

Hannes Pétursson, my former chief of clinical services in Iceland, for evoking my interest in science by continuously combining daily clinical work and scientific discussions.

Jarmila Hallman, for your honesty and support.

The staff at the PET Centre, for your willingness to help regardless of how busy you all are, for managing to make the impossible possible, and for the many good times I have shared with you. In particular I want to thank Anders Wall, Harald Schneider, Lars Lindsjö, Rita Öhrstedt, Karin Lidström, Anders Grundström and Anna Nilsson.

Svante Ross, Jesper Anderson, Håkan Fischer, Pinelopi Merachtsaki, Hans Arinell, Olle Eriksson, Anna Pissiota and Lena Bohlin, for invaluable discussions and help.

Karin Sparring and Bengt Björksten, for opening their home and hearts to me whenever I needed it, and for inspiring cultural, ethical, moral, and professional discussions.

The staff of former 88A and 88B, for your positive attitudes towards me and for your assistance with this scientific work.

My friends and colleagues, Rúna Geirsdóttir, Ragnheidur Bragadóttir, Kamilla Portala, Ewa Lundborg, Gudlaug Thorsteinsdóttir, Ýr Logadóttir, Ólöf
Sigurdardóttir, Anna Geirsdottir, Maj-Liz Person, Eva Frykman, Britt Lindström and Rut Larsson, for being there for me.
My family, and most of all Bengt, for believing in me, and supporting and helping me in every possible way.
My cats, and especially Lisa, who over the years has sat in my lap, watching every step of this work come to fruition, except for those times when I was seemingly getting nowhere, and she decided to help by taking a walk over my keyboard. Unfortunately, readers will not be able to look at this thesis as the first scientific production by a cat, as that help was not always particularly appreciated.
The patients, for participating in this trying study, thereby making this work possible.


130. Tancer M., Stein M. B., Uhde T. W. Growth hormone response to IV clonidine in social phobia; comparison to patients with panic disorder and healthy volunteers. Biol Psychiatry 1994;34:252-256.


63


van Wijk M., Sebens J. B., Korf J. Probenecid-induced increase of 5-hydroxytryptamine synthesis in rat brain, as measured by formation of 5-hydroxytryptophan. Psychopharmacology (Berl) 1979;60(3):229-35.


269. Meltzer H., Bastani B., Jayathilake K., Maes M. Fluoxetine, but not tricyclic antidepressants, potentiates the 5- hydroxytryptophan-mediated increase in plasma


