Our objective was to examine the neurobiology of social phobia from the perspectives of basic sciences, genetics, immunology, neuroendocrinology, neurotransmission and neuroimaging and to provide an integrated understanding of social phobia in the framework of a hypothetical neural circuit. Family and twin studies provide evidence that social phobia is heritable with significant genetic influence, and molecular genetics offers possibilities in understanding the nature of the trait that is transmitted. The biologic distinctiveness of social phobia from anxiety disorders and physiological validation of differences between generalized and discrete social phobia subtypes have been implicated in genetic, naturalistic and chemical challenge studies. Evidence of specific dysfunction of dopaminergic, serotonergic, noradrenergic and GABAergic (γ-aminobutyric acid) neurotransmitter systems has been presented in animal models, challenge studies and treatment investigations. Preliminary neuroimaging research supports previous studies suggesting striatal dopaminergic dysfunction in social phobia and suggests the importance of functional circuits. A neural circuit involving the striatum, thalamus, amygdala and cortical structures may provide a framework for integrating much of the current knowledge on the neurobiology of social phobia.

Notre objectif était d'examiner la neurobiologie des phobies sociales du point de vue des sciences fondamentales, de la génétique, de l'immunologie, de la neuroendocrinologie, de la neurotransmission et de la neuroimagerie, et de présenter une interprétation intégrée des phobies sociales dans le cadre d'un circuit neural hypothétique. Les études menées auprès de familles et de jumeaux révèlent que les phobies sociales sont héréditaires et associées à une importante influence génétique; la génétique moléculaire offre des possibilités de comprendre la nature du trait psychologique qui est transmis. Des études critiques de nature génétique, naturaliste et chimique laissent entendre que les phobies sociales présentent un caractère biologique distinct des troubles de l'anxiété et que les variations entre les sous-types généralisés et discrets des phobies sociales peuvent être confirmées sur le plan physiologique. Des modèles animaux, des études critiques et des investigations à des fins de traitement ont démontré une dysfonction spécifique des systèmes neurotransmetteurs de la dopamine, de la sérotonine, de la noradrénaline et de la GABA. Des recherches préliminaires par neuroimagerie appuient des études antérieures laissant croire à un lien entre une dysfonction dopaminergique striatale et les phobies sociales, et soulignent l’importance des circuits fonctionnels. Un circuit neural formé du corps strié, du thalamus, du noyau amygdalien et des structures corticales pourrait fournir un cadre susceptible d'intégrer la plupart de nos connaissances actuelles sur la neurobiologie des phobies sociales.

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Introduction

Social phobia (SP), also termed social anxiety disorder, is a disorder characterized by extreme anxiety in social and performance situations. Individuals fear that, while others are watching, they will do something embarrassing, be negatively evaluated or have their excessive anxiety symptoms (e.g., shaking, blushing, sweating) noticed. Because of this persistent fear, social interaction or performance situations are either avoided or endured with intense discomfort, significantly interfering with normal routine or life functioning. SP is classified as either generalized, if the anxiety occurs in most social situations, or discrete, if the anxiety occurs only in specific situations.1

Social phobia has a lifetime prevalence of 13%–16% and, in spite of being the third most common psychiatric disorder, is an under-recognized and undertreated condition.2–5 The mean age of onset is between 11 and 15 years of age — a critical life period — and onset is followed by a chronicity and disability that affects all areas of life. As a result, individuals with SP are more likely to be single, less educated, in lower socioeconomic classes, dependent on welfare and to have unstable employment histories.7 There is also significantly increased comorbidity in SP that includes simple phobia (61% lifetime risk, odds ratio [OR] 8.3), agoraphobia (45%, OR 8.3), alcohol abuse (17%, OR 2.2), major depression (15%, OR 6.8), schizophrenia (13%, OR 13.3), generalized anxiety (26.9%, OR 4.2), panic disorder (11.6%, OR 10.6) and suicide attempts (12%, OR 12.8).4

As a common psychiatric disorder with serious disability and comorbidity, it is surprising that only recently has there been increased research into the neurobiology of SP. There is mounting evidence that SP is a discrete disorder with a genetic basis, but the biological mechanisms underlying the etiology and pathophysiology of SP remain the subject of increasing investigation.

In this review of the evidence for a genetic contribution to SP and of the primary neurotransmitter systems thought to be involved (i.e., noradrenaline, serotonin, γ-aminobutyric acid [GABA] and dopamine), we will incorporate results from animal models, naturalistic challenges, chemical probes, immunology, neuroendocrinology and treatment studies. By synthesizing this evidence with neuroimaging research, a framework for a current understanding of SP will be presented in the form of a hypothetical neural circuit involving cortical structures, the basal ganglia, thalamus and amygdala.

Genetic studies

Several studies provide strong evidence for the familial transmission of generalized SP (GSP) and also validate the classification of generalized and discrete subtypes as separate entities. In a blinded family study,9 relatives of SP probands were at an increased risk for SP (16.6%, relative risk 3.12, n = 83) but not for other anxiety disorders when compared with relatives of normal controls (5%, n = 231); consequently, the specificity of familial transmission supports the distinctiveness of SP from other anxiety disorders. Providing further evidence of heritability, a study of the children of 26 outpatients with SP found that 23% fulfilled DSM-III-R criteria for SP and another 30% could be diagnosed with overanxious disorder of childhood, one criterion of which is related to concern of social evaluation.10 Specific differences in genetic transmission of generalized and discrete subtypes of SP are suggested by findings that 16% of relatives of probands with the generalized subtype also have SP, compared with 6% of relatives of probands with the discrete subtype, with no differences between the latter and controls.11 Replicating the above findings, Stein et al,12 in a direct interview of relatives (n = 123) of 23 patients with GSP and relatives (n = 74) of 24 control subjects, determined that the relative risks for GSP and avoidant personality disorder were 10-fold higher in the relatives of GSP probands; in contrast, the relative risk for discrete and nongeneralized SP did not differ between the first-degree relatives of the GSP and control groups. Thus, family studies indicate a clear familial transmission for SP, but also underscore that this is true only for the generalized subtype of SP.

Twin studies allow some delineation of the genetic contribution to familial transmission in SP — a higher concordance rate for a syndrome in monozygotic twins, as compared with dizygotic twins (whose genetic material is no more homogeneous than nontwin siblings), suggests a biological causation that is independent of environmental factors. Results from a large study of female twins demonstrated a 44.4% concordance rate for SP in monozygotic twins and a 15.3% concordance rate in dizygotic twins, thus implicating biological factors;13 disease liability variance due to genetic factors was estimated to be 30% for SP. Kendler et al14 expanded these findings and corrected for the unreliabil-
ity of single lifetime assessments by interviewing 1708 female twins on 2 occasions, 8 years apart, and, as such, estimated the corrected total heritability for SP to be 51%, thus suggesting a significant genetic component of at least moderate effect.

Both twin and family studies support that SP is familial with an important genetic component in the transmission; family studies also provide evidence for biological differences between generalized and discrete subtypes, as reflected by their differences in transmission. Expansion of these findings, including adoption studies, and further investigation and clarification of the extent of genetic and environmental contributions, with elucidation of risk factors for the development of SP, is warranted.

Although genetic studies in SP are in relatively early stages, inquiry into the genetic basis of personality traits may guide future research in the neurobiology of SP. When identified in very young children, the trait of behavioural inhibition is associated with increased risk of developing SP in adolescence, and thus may be a precursor of SP. Furthermore, in a study of 200 pairs of twins assessed at 14 months of age, behavioural inhibition was found to have significant genetic heritability. As potential adult correlates of the temperament of behavioural inhibition, avoidant and schizoid personality traits have been reported to be strongly associated with dopamine D2 receptor (DRD2) polymorphisms and weakly associated with dopamine transporter (DAT1) polymorphisms. The convergence of these findings with recent neuroimaging results that also implicate the importance of the D2 receptor and DAT in SP suggest that avoidant and schizoid personality traits and SP symptoms may share common genetic components. Also of potential relevance, the personality trait of novelty seeking, which may be considered opposite to that of social or behavioural inhibition in SP, has been found in 4 studies to be significantly associated with dopamine D4 receptor (DRD4) long-repeat polymorphisms. Although 5 other studies have been unable to replicate these findings, the use of DRD4 exon III polymorphism as a marker for novelty seeking remains. In the most recent addition to the debate, Strobel et al argued that demographic and methodologic differences between studies obscure the small effect of the DRD4 polymorphism on novelty seeking, and after taking these variables into account, report that long DRD4 alleles are significantly associated with increased novelty seeking, exploratory excitability and extravagance.

Thus, although research is in the early stages, the genetic nature of heritable traits, such as behavioural inhibition, avoidant and schizoid personality traits, and possibly novelty seeking, is being elucidated, with potential relevance to understanding the familial transmission and genetic mechanisms of SP.

### Neuroendocrine studies

Abnormalities in thyroid and adrenal function have been demonstrated in panic disorder and depression. Similar studies of the hypothalamic-pituitary-adrenal (HPA) axis and hypothalamic-pituitary-thyroid (HPT) axis have been done in SP to search for neuroendocrine alterations that would differentiate SP patients from healthy controls and patients with other psychiatric disorders. Two studies of the HPA axis measuring urinary free cortisol levels and another measuring salivary cortisol revealed no differences between patients with SP and controls; similarly, when using the dexamethasone suppression test, SP subjects had patterns of suppression no different from normal controls. Although there have been no observations of specific HPA dysfunction in SP patients, the integrity of the HPA axis could be tested in future studies using corticotrophin releasing factor. With respect to the HPT axis, Tancer et al found no differences between SP subjects and controls on plasma T3, T4, free T4 and thyroid stimulating hormone levels. However, in another study, of the effect of thyroid stimulating hormone (TRH) on blood pressure and heart rate, SP patients had significantly greater increases in blood pressure 1 minute after TRH infusion than did patients with panic disorder or normal controls. Although studies of the HPA axis have revealed little that is specific to SP, 1 study of the HPT axis using TRH challenge revealed an increased pressor response that differentiated SP from panic disorder and normal controls, suggesting a possible biological mechanism specific to SP involving a disturbance of noradrenaline and hyperactivity of the autonomic nervous system. Future research directions include more clearly defining the role of autonomic dysfunction in SP, searching for neuroendocrine markers, investigating the HPA axis using corticotrophin releasing factor stimulation, and examining the HPA and HPT axes with the purpose of distinguishing between generalized and discrete subtypes of SP.
Neurotransmitter systems

Noradrenaline

Research on the neurobiology of SP initially focused on the role of noradrenaline (NA) because SP patients experience blushing, tremor, palpitations and sweating — symptoms characteristic of adrenergic overactivity. The 3 main methodologies that have been employed to date in an attempt to elucidate the importance of NA in SP are naturalistic challenge, neuroendocrine and chemical challenge and treatment studies.

Naturalistic challenge studies have used postural change (orthostatic challenge) and public speaking to investigate possible NA dysfunction in SP. Stein et al36 found that after orthostatic challenge, SP subjects had significantly higher plasma NA levels than patients with panic disorder and controls. A subsequent study by the same investigators, however, suggested increased NA levels in response to isometric exercise, but noradrenergic hyperactivity and exaggerated vagal activity, as demonstrated by increased blood pressure and growth hormone responses compared with controls,43,44 thus suggesting sympathetic hyperactivity.

Although a somewhat discordant pattern emerges, naturalistic challenges in SP have implicated both sympathetic and parasympathetic hyperactivity and, in 1 study, increased NA reactivity.

A study using public speaking challenge found no differences in heart rate between patients with generalized SP and controls,39 but reported, in concordance with another study, that there was increased heart rate reactivity in discrete SP in the first minute of public speaking.40 A later study by Hofmann et al41 using a public speaking challenge also revealed differences in heart rate between generalized and discrete SP, but also found that the heart rates of SP patients without avoidant personality disorder were higher than either controls or social phobics with avoidant personality disorder. These 3 naturalistic studies demonstrating physiological differences between the 2 subgroups of SP reinforce the importance for future research, not only to clarify the neurobiological differences between the 2, but also to take into account their distinctiveness in the study design. In overview, however, although naturalistic challenges have suggested increased autonomic activity, findings specifically differentiating generalized SP and healthy controls have not been consistently reproduced.

Chemical challenge studies have attempted to delineate the nature of autonomic hyperactivity in SP at the level of receptor function. These studies have been based on the hypothesis that excessive anxiety is associated with enhanced firing of the locus ceruleus, causing increased NA release into the synaptic cleft. More specifically, the α2-adrenergic receptor has been investigated at the level of the hypothalamus, and it would be predicted that if there is increased NA release in the synaptic cleft secondary to pervasive social anxiety, there should be a downregulation of postsynaptic α2-adrenergic receptors and a blunting of growth hormone secretion (which is dependent on stimulation of hypothalamic α2-adrenergic receptors).42 Unfortunately, however, there have been discrepant findings on the role of the α2 receptor in SP; although 1 study showed that patients with SP and panic disorder had blunted growth hormone responses compared with controls,43 these findings were not replicated in a later study using a different dose and route of administration of clonidine.44 Furthermore, a small crossover study of 6 SP patients given infusions of saline or yohimbine (an α2 antagonist) reported a significant increase in anxiety in response to yohimbine, with concomitant elevation of NA levels, thus suggesting adrenergic hyperactivity and heightened α2 sensitivity in SP patients.44 Thus, although 2 of 3 chemical challenge studies have reported possible abnormalities of the α2 receptor in SP, there remains controversy about whether these receptors are supersensitive or subsensitive.

Other approaches have been employed in an attempt to clarify the role of NA in SP, but still have not yielded findings specific to SP. An investigation of lymphocyte β-adrenergic receptors, which serve as a possible indirect measure of central adrenergic neuroceptors, did not identify differences between patients with SP and controls.45 Measurement of plasma neuropeptide Y, an indicator of peripheral sympathetic activity and plasma NA, also did not reveal any differences during resting conditions or after hand immersion in ice water among SP, panic disorder and control groups.46-48

Although initial research into the neurobiology of SP has provided support for autonomic hyperactivity, increased NA reactivity to orthostatic and yohimbine...
challenges, possible dysfunction of α₂ receptors, and differential heart rate reactivity between discrete and generalized SP, there are many inconsistencies among the studies and results have not always been reproducible. Further research is warranted, but the nonspecificity of results suggests that NA may not play a primary role in the etiology of SP. In fact, strong evidence against primary NA dysfunction in SP includes 3 placebo-controlled trials of β-adrenergic blockers that failed to demonstrate clinically significant effects in generalized SP. Nevertheless, the effective use of β-blockers for performance anxiety symptoms (e.g., tremor, sweating, tachycardia, and dizziness preceding public speaking), particularly for discrete SP, reinforces the possibility that NA dysfunction in SP may be the end pathway in the expression of primary dysfunctions of other neurotransmitter systems. Furthermore, unlike patients with panic disorder, those with SP have different responses to lactate, carbon dioxide and epinephrine challenges, which underscores that there are distinct neurobiological mechanisms underlying each disorder. However, their frequent co-occurrence, overlapping clinical characteristics (e.g., panic attacks and pervasive anxiety) and evidence of autonomic overactivity intimates that both disorders may share a common anxiety circuit, with NA system dysfunction. Accordingly, Stein et al state that techniques employed to investigate NA in panic disorder and posttraumatic stress disorder, including fear-potentiated startle, have yet to be employed in SP, and there remains a relative paucity of research in NA and its associated neural circuitry. Consequently, although support for NA abnormalities in SP exists, clarification of its particular role awaits disorder-specific, repeatable findings.

Serotonin

The role of serotonin (5-hydroxytryptamine [5-HT]) in the neurobiology of SP has been implicated in animal models and chemical challenge studies and by the treatment efficacy of selective serotonin reuptake inhibitors (SSRIs). The role of 5-HT in modulating exploratory activity and anxiety is suggested by decreased exploration and increased fear-related behaviours in 5-HT₁A receptor-deficient mice — although no specific measure of social interaction was reported. More specifically, studies employing the social interaction test have demonstrated that 5-HT₁C antagonists increase social interaction of rats, whereas 5-HT₂₃, 5-HT₁B, 5-HT₁B, 5-HT₁D, and 5-HT₃ antagonists have no such effect on social interaction. Interestingly, paroxetine administration in rats also significantly increased the time spent in social interaction, an effect that only occurred after 3 weeks, therefore suggesting increased 5-HT presynaptic function or downregulation of 5-HT postsynaptic receptors or both. Stein discusses how 5-HT and cortisol may be important for establishing social dominance in primates, and how primate social submissiveness may be a useful model for SP; accordingly, the administration of 5-HT enhancers such as fluoxetine or tryptophan promotes social dominance acquisition in monkeys. Although it is difficult to convincingly argue that current 5-HT animal models can be directly extrapolated to SP, the models strongly suggest that exploratory activity, social interaction and submissiveness and dominance — traits with significant correlates in SP — are regulated by 5-HT function. Similarly, the importance of 5-HT in the regulation of human social activity was demonstrated in a study in which paroxetine was administered to 26 healthy subjects who showed a significant increase in the social affiliation index (a measure of sociability) relative to controls after 4 weeks of treatment.

The role of 5-HT in SP is supported by placebo-controlled trials showing moderate-to-marked improvement in patients treated with sertraline, fluvoxamine and paroxetine. Furthermore, it has been suggested that the efficacy of monoamine oxidase inhibitors (MAOIs) in SP may be primarily due to their serotonergic component.

Attempts to delineate the nature of 5-HT dysfunction in SP have been made using fenfluramine and m-chlorophenylpiperazine (m-CPP) challenges. SP patients challenged with fenfluramine, a 5-HT-releasing agent, showed increased anxiety and cortisol response over controls, though prolactin responses were normal; similarly, challenge with m-CPP, a partial 5-HT receptor agonist, resulted in increased cortisol response in SP patients and normal prolactin responses compared with controls. These results suggest that anxiety in SP may be due to hypersensitive post-synaptic 5-HT; receptors and that 5-HT, receptors, responsible for prolactin response, are functioning normally.

Given the importance of 5-HT in anxiety disorders such as panic disorder and obsessive–compulsive disorder, it is not surprising that 5-HT also has a role in social anxiety. The challenge remains, however, to
further define intricacies of the neural circuitry and the 5-HT receptor subtypes involved in SP. On the basis of the obsessional quality of the ruminative negative cognitions in SP and the high comorbidity of obsessive–compulsive disorder in SP (18.6% or 8.6), hypothetical neural circuits in SP may include 5-HT pathways that parallel those thought to be of importance in obsessive–compulsive disorder (e.g., thalamic – basal ganglia – frontal cortex loop). In addition, Stein suggests that SP may result from a deficiency in integrating social information from mesolimbic reward pathways originating in the ventral tegmental area (VTA), such that the “risk” of social interaction exceeds any “reward.” Accordingly, the midbrain raphe nuclei have 5-HT projections to the VTA that modulate dopamine release, and treatment with fluoxetine enhances dopamine neurotransmission in this mesolimbic pathway — thus potentially increasing the “reward” of social interaction with theoretical relevance to SP.

γ-aminobutyric acid (GABA)

Evidence that GABA may play a role in SP originates with the clinical observation that alcohol decreases social anxiety and inhibition and is reinforced by the high incidence of comorbid alcohol abuse in SP (17.2%) and by the demonstrated efficacy of benzodiazepines to treat SP. Also, in a 14-week placebo-controlled study of 69 patients with SP, gabapentin significantly reduced SP symptoms, and although the mechanism of action of gabapentin is not well established and includes activity at voltage-sensitive Na+ and Ca2+ channels, its efficacy in SP is probably due to increases in central GABA.

Although studies are few in number, there are 2 that attempt to directly examine the GABAergic system in SP. Peripheral benzodiazepine receptors (PBRs) are important in the regulation of stress responses and are reduced in panic disorder, post-traumatic stress disorder and generalized anxiety disorder, but not in obsessive–compulsive disorder or major depression. In a study of 53 patients with SP, there was a significant decrease in PBRs compared with controls, suggesting that PBRs may be part of a common mechanism of GABA dysfunction in several anxiety disorders. To further explain the specific nature of GABA dysfunction in anxiety disorders, it has been suggested that panic responses to flumazenil, a benzodiazepine receptor antagonist, may be associated with situational fears such as social cues.

To test this hypothesis, Coupland et al, using a double-blind crossover challenge design, infused flumazenil and placebo in SP patients (n = 14) and matched controls but did not find an increase in panic symptoms in patients versus controls. Thus, although GABAergic agents have been shown to diminish SP symptoms and PBRs may represent a site of GABAergic dysfunction shared with other anxiety disorders, future studies delineating the specific role of GABA in SP are required. To this end, recent advances in the imaging of benzodiazepine receptors with 123I-iomazenil single-photon emission computed tomography (SPECT) or 11C-flumazenil positron emission tomography (PET) hold promise for investigating GABA in SP.

Dopamine

Making SP distinct from other anxiety disorders, Liebowitz et al first suggested that diminished central dopamine (DA) may play a key role in the neurobiology of SP, and this has been subsequently supported by evidence from animal models, clinical studies and neuroimaging studies. In a study of depressed patients, introversion, a characteristic of social anxiety, was found to be significantly associated with decreased cerebrospinal fluid DA levels. Similarly, the levels of homovanillic acid (HVA), a metabolite of DA, were significantly lower in the cerebrospinal fluid of 49 patients with panic disorder and SP than controls; in addition, a trend toward lower levels of HVA was also noted in patients with SP compared with those with panic disorder.

In a treatment study of depressed patients with increased rejection sensitivity, a trait seen in SP, phenelzine had significantly greater efficacy over imipramine, and this may be secondary to DA enhancing effects of phenelzine which are absent with imipramine. More specifically, research has implicated dysfunction in the striatal DA system in SP. A timid mouse strain was found to have markedly decreased DA in the caudate nucleus. Clinical observations have noted that some patients with Tourette’s syndrome, a disorder associated with dopaminergic dysfunction in the basal ganglia, develop social anxiety and avoidance after treatment with the DA antagonist haloperidol. A magnetic resonance imaging study measuring brain volumes in SP patients and healthy controls revealed no significant differences with respect to cerebral, caudate, putamen and thalamic volumes, but did find greater age-related reductions in putamen volumes in
SP patients compared with controls. This possible age-related atrophy of the putamen in SP may provide some explanation for observations of a higher than expected incidence of SP that predates the onset of Parkinson’s disease — an illness that involves loss of dopaminergic neurons in the basal ganglia. Furthermore, novelty seeking, an attribute opposite to social inhibition, has been correlated with striatal uptake of DA precursor and, as previously discussed, inversely correlated with short alleles of the DAD4 receptor.

Although support exists for the importance of diminished central DA in SP, much of it is based on indirect evidence, and there are few replicated studies. Crucial weaknesses in the DA hypothesis of SP include a paucity of research that directly investigates the role of DA at a receptor level, a lack of evidence demonstrating the efficacy of dopaminergic agents in treating SP and a poor understanding of the functional role of DA in SP — especially given the evidence for concomitant involvement of NA, 5-HT and GABA.

Accordingly, although limited in number, neuroimaging studies provide considerable potential for clarifying and increasing our understanding of the role of striatal DA in SP. In addition to the reported association between primate dominance and 5-HT cortisol levels, female monkeys with low social status were found to have significantly lower striatal D2 binding, suggesting that both diminished striatal DA and 5-HT cortisol may be significant in modulating social behaviour in this potential animal model of SP.

In humans, a study using SPECT and 123I-β-CIT (123I-labelled 2β-carboxymethoxy-3β-[4-iodophenyl] tropane), a radioligand for the DA and 5-HT transporters, demonstrated markedly lower striatal presynaptic DA reuptake site densities in those with SP compared with controls. With respect to striatal postsynaptic DA function, a SPECT study with the D2 radioligand 123I-IBZM (123I-labelled iodobenzamide) found diminished striatal D2 receptor binding in 10 patients with SP relative to controls. We also investigated striatal DA in 12 SP patients and 10 controls using SPECT and the D2 radioligand 123I-epidepride, preliminary analysis shows that striatal postsynaptic D2 receptor binding is significantly associated with SP symptom severity, as measured by the Liebowitz Social Anxiety Scale (unpublished data).

Evidence for the importance of striatal DA in SP continues to grow; both pre- and postsynaptic abnormalities have been correlated with clinical symptoms in SP. Further studies are needed to clarify whether D2 binding abnormalities reflect receptor abnormalities or differences in synaptic levels of DA. In addition, it will be important to examine other basal ganglia neurotransmitters, such as glutamate, and to incorporate pre- and post-treatment arms to test the response of the striatal DA system to therapy.

Of particular interest, striatal dopamine has not only been correlated with SP symptoms, but several studies suggest associations with other related personality attributes, including avoidant and schizoid traits and detachment. Studies have shown that the density of striatal D2 receptors varies considerably among healthy subjects, and this may be related to differential participation of DRD2 genotypes. As discussed earlier, Blum et al found an association between polymorphisms of the dopamine D2 receptor and dopamine transporter genes with schizoid–avoidant behaviours. On a similar note, a PET study using [11C]raclopride, a D2 radioligand, found that the personality trait of detachment, as measured by the Karolinska Scales of Personality, was significantly associated with decreased D2 receptor binding. These findings were not only replicated in a later PET study of 18 adults, but were extended to include findings that D2 receptor density was specifically related to the trait of detachment as defined by the Karolinska Scales of Personality, but not to forms of detachment defined by the Tridimensional Personality Questionnaire. Results of another recent PET study indicate that DAT binding in the putamen correlate negatively with detachment scores on the Karolinska Scales of Personality.

The convergence of research from the perspective of SP, avoidant–schizoid personality traits and detachment suggests that the avoidance of people (or avoiding giving and taking confidences in others [as defined by the Karolinska Scales of Personality]) is the specific trait or behaviour that is associated with striatal D2 receptor and DAT abnormalities. Accordingly, it would be helpful for future SP neuroimaging research to incorporate the Karolinska Scales of Personality into the protocol, with further efforts made to understand the specific nature of the trait that is associated with striatal dopamine in SP.

**Toward an integrative hypothesis of social phobia**

A current review of the primary neurotransmitter
systems in SP reveals that only striatal DA has been shown to distinguish SP patients from healthy controls and to be correlated with clinical symptoms; as a result, the centrality of striatal DA in SP emerges as a key concept. A hypothetical model for integrating much of the current knowledge base of SP in the form of cortical – basal ganglia – thalamic neural circuit may be suggested by comorbidity research and preliminary neuroimaging results. This, in turn, could provide a framework for understanding the interwoven involvement of the primary neurotransmitter systems in SP.

The importance of cortical – basal ganglia – thalamic circuit has been described for obsessive–compulsive disorder and schizophrenia, and the close proximity of parallel cortical-subcortical pathways may account for the relatively high comorbidity of these 2 disorders. Interestingly, Cosoff and Hafner report that the comorbidity of SP in schizophrenia (17%) may be just as high as that of obsessive–compulsive disorder in schizophrenia (13%); furthermore, Davidson et al note that the lifetime prevalence rate of schizophrenia in SP is 13% (OR 13.3), which is remarkably high. As a result, perhaps a cortical – basal ganglia – thalamic circuit exists in SP that parallels, in close proximity, certain components of the neural circuitry in schizophrenia.

Neuroimaging data can provide foundational support for a hypothetical cortical – basal ganglia – thalamic neural circuit in SP. Magnetic resonance spectroscopy (MRS), which provides access to the biochemistry, physiology and metabolism of brain regions, offers significant potential for elucidating the pathophysiology of SP. Magnetic resonance studies report an association between SP and increased choline and myo-inositol (relative to creatine and N-acetylaspartate) in both cortical and subcortical (i.e., caudate, putamen, thalamus) gray matter. The significance of these results is unclear, but increased choline may suggest abnormalities in the phospholipase C second messenger pathway activated by DA and serotonin, whereas increased myo-inositol can result from cytoskeleton breakdown or inositol triphosphate second messenger dysfunction. The largest differences were found in cortical gray matter, a region of higher cognitive function and integration, which may ultimately be the source of cognitive distortions in anxiety disorders.

Of particular interest, SP symptom severity was correlated with decreased choline and myo-inositol in subcortical gray matter, which includes the caudate, putamen and thalamus — providing further evidence, in accordance with previously discussed SPECT results, for the involvement of basal ganglia circuits in the symptoms of SP.

Regional cerebral blood flow in SP has been examined using both SPECT and PET. In a SPECT study measuring brain perfusion with technetium-99m-hexamethyl-propyleneamineoxime (99mTc-HMPAO), no significant differences in regional cerebral blood flow were demonstrated between those with SP and healthy subjects. This study highlights the necessity for future research to incorporate brain perfusion studies with social anxiety challenges. Accordingly, in a PET study using 15O, cerebral perfusion in a group of SP subjects was imaged during anxiety provoked by reading a script of a feared social situation. Compared with a previous study of conditioned anticipatory anxiety in normal volunteers, both SP and conditioned anxiety groups had increased blood flow in the anterior cingulate gyrus and the insulae. Notably, however, only the SP group had increased blood flow in the right dorsolateral prefrontal cortex (DLPFC) and left parietal cortex. As Nutt et al discuss, these results point to potential neural circuits in SP involving the anterior cingulate gyrus and insulae for regulating anticipatory anxiety and autonomic response, whereas neural circuit more specific for the negative cognitions and pervasive social anxiety possibly reside in the right DLPFC and the left parietal cortex.

Taking into account the above neuroimaging results, a hypothetical cortical – basal ganglia – thalamic neural circuit can be formulated that also incorporates an understanding of the primary neurotransmitter systems involved in SP. The centrality of striatal DA dysfunction has been discussed, and both SP and symptom severity have been correlated with striatal abnormalities in SPECT and MRS studies. With DA being a key neurotransmitter system involved, basal ganglia circuits may provide the biological substrate for the development of SP and also determine the degree to which symptoms are experienced. Acting as a gate or filter of input from cortical circuits responsible for awareness of body position and social space (e.g., left parietal cortex), basal ganglia – thalamic circuits may modulate output to the (dorsolateral) prefrontal cortex, where excessive input may result in the recurrent negative cognitions of social evaluation and where 5-HT and GABAergic systems may be of primary importance. The output of pervasive anxiety and adrenergic symptoms may correspond to activation of neural
circuits involving the anterior cingulate gyrus and insulae — which could be a final common pathway for other anxiety disorders and the site for NA overactivity\textsuperscript{111,113} (Fig. 1).

The cortical – basal ganglia – thalamic circuit in SP is probably influenced significantly by key connections with the amygdala. The amygdala function to register the emotional significance of stimuli and are fundamental to forming both conditioned associative and emotional memories.\textsuperscript{114,115} Converging with evidence that the striatum is important in SP, exciting research by Heimer et al\textsuperscript{116} demonstrates that amygdala – ventral striatal circuitry is particularly critical for associating complex sensory stimuli with positive and negative rewards.\textsuperscript{117} In SP, there may be a constitutional predisposition of excessive conditionability to social fear and anxiety,\textsuperscript{63} the origins of which would probably reside in amygdala – ventral striatal circuitry; furthermore, the influence of development and experience on the facilitation of social fears is probably associated with the role of the amygdala in the formation of emotional memories.\textsuperscript{118} Although this hypothesis requires future investigation, support for the role of the amygdala in SP is suggested by Schneider et al\textsuperscript{119} who found, in a functional magnetic resonance imaging study of 12 patients with SP and 12 controls, that the activation of the amygdala and hippocampus differs significantly between social phobics and normal controls when conditioned aversive stimuli are processed.

In overview, impaired striatal – thalamic filtering and excessive “conditionability” of ventral striatal – amygdala circuitry may form the biological substrate for the constitutional predisposition and development of SP, and interconnections among the cortical – basal ganglia – thalamic loop and the amygdala might provide the pathways necessary for conditioned fear and reinforcement of negative cognitions — ultimately resulting in the behavioural avoidance seen in SP.

Conclusion

In recent years, significant progress has been made in understanding the neurobiology of SP. Making it unique among the anxiety disorders, there is persuasive evidence that pre- and postsynaptic striatal dopaminergic dysfunction plays a chief role in the neurobiology of SP and in possibly determining the severity of social anxiety experienced. Drawing from

\begin{figure}[h]
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\caption{Components of a hypothetical neural circuit in social phobia (SP). The chief biological substrate of SP in this model is hypothesized to include impaired basal ganglia – thalamic filtering and/or excessive conditionability of ventral striatal – amygdala circuitry. Impaired basal ganglia – thalamic filtering may result in excessive input of information (related to body position and image) to the frontal cortex, where negative cognitions occur and behavioural avoidance is planned. The subsequent output of anxiety in social situations reinforces these pathways, and fear conditioning and learning takes place through amygdala – ventral striatal circuitry.}
\end{figure}
neuroimaging results, it may be theorized that basal ganglia – thalamic circuits may act as a gate, controlling social information travelling from sensory cortices to the frontal cortex, and that impairment of this filter may result in the recurrent negative cognitions of SP. Striatal connections with the amygdala may also play a role in the predisposition, memory and processing of emotions (e.g., fear and shame) related to social cues. 5-HT has also been shown to be important for regulating exploratory activity, sociability and social hierarchy, and there is early evidence that hypersensitive 5-HT receptors may contribute to anxiety in SP. The well-documented treatment efficacy of the SSRIs in SP may be secondary to actions at cortical structures in the aforementioned circuit or may be related to input to the VTA mesolimbic reward system where 5-HT modulates DA. Although efforts at delineating the role of NA have produced discrepant findings, there is evidence for autonomic hyperactivity, increased NA response to orthostatic and yohimbine challenges, possible dysfunction of α receptors and a differential heart rate reactivity between discrete and generalized SP. Because of the variability and nonspecificity of results, however, NA may not play a primary role in the etiology of SP, but its dysfunction could be related to a common anxiety circuit that is shared with other anxiety disorders. Although there is no doubt as to the efficacy of GABAergic agents, research into the role of GABA in SP is still in early stages, and further research is required to determine its precise role in the disorder.

Family and twin studies have established that generalized SP is heritable, with a significant genetic component, and molecular and behavioural genetic studies hold promise in further defining the nature of the trait that is actually transmitted — with possible candidates being behavioural inhibition, schizoid–avoidant traits, specific SP symptoms and novelty seeking.

Research into the neurobiology of SP has been exciting, and by integrating results from neurotransmitter and neuroimaging data, a hypothetical neural circuit involving the cortex, basal ganglia, thalamus and amygdala has emerged that can guide research and serve as a relevant model for understanding SP.

References

6. Burke KC, Burke JD, Regier DA, Rae DS. Age at onset of selected mental disorders in five community populations. *Arch Gen Psychiatry* 1990;47:511-8.
20. Tiihonen J, Kuikka J, Bergstrom K, Lepola U, Koponen H,


57. Gorman JM, Fyer MR, Goetz R, Askaran J, Liebowitz MR,


60. Kennet GA. 5-HT_1C receptor antagonists have anxiolytic-like actions in the rat social interaction model. *Psychopharmacology (Berl)* 1992;107:379-84.


