# Social Phobia: Etiology, Neurobiology, and Treatment

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Social phobia is a common and often disabling condition, with an etiology that is not established. There is evidence at several levels for an interplay of biological and psychological processes in social phobia. Genetic studies show that both genetic and environmental factors are important, with evidence pointing to associations with 2 genetic conditions, autism and fragile X syndrome. Behavioral inhibition has emerged as an important precursor to social phobia and possibly to other anxiety disorders. Epidemiologic and clinical studies have suggested that factors within the family environment, such as overprotection, overcontrol, modeling of anxiety, criticism, and in some cases abuse, can play a role in the development of social phobia. During childhood, complex interactions between brain system disturbances that mediate responses to negative social cues and factors in the social setting may lead to the development of a distorted set of internal "blueprints" for social behavior. The impact of severe social anxiety on brain systems that mediate behavioral change may prevent patients from learning better "blueprints." These can be taught through cognitive-behavioral therapies. The effective control of social anxiety with medications enables patients to recover; whether recovery can last after discontinuation of medications may depend on whether a new "blueprint" has been developed and whether stable changes in affected brain systems have occurred. Neuroimaging techniques are at the early stage of identifying abnormalities at the neurotransmitter and systems levels.

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Shyness, social phobia, and avoidant personality disorder (which will be subsumed under the term *social phobia* for the rest of this article) may lie on a continuum, with clinical disorders leading to significant and often severe distress or disability.[1] For social phobia, the complications include educational and occupational underachievement, isolation, substance abuse, depression, and an increased risk of suicide.[2] An analogy might be made with hypertension, which is on a continuous distribution of blood pressure but which also leads to severe complications. Social fears and sociability are interrelated aspects of social behavior. Both affect the formation of affiliations with others. At one extreme end of sociability, patients with schizoid personality disorders can be differentiated from those with social phobia because they are aloof and do not desire relationships, whereas patients with social phobia may want relationships, but fear and avoid social contact. However, social fears and sociability are dimensional, and a less extreme lack of sociability may play a role in social phobia.[3] Genetic as well as environmental factors are implicated in the etiology of social phobia, and biological as well as psychological components are involved in its pathophysiology and treatment.

## FAMILY AND GENETIC STUDIES

First-degree relatives of patients with social phobia have a much greater risk of the disorder, particularly relatives of patients with generalized social phobia.[4,5] Twin and adoption studies have supported genetic and environmental explanations of this familial risk (Table 1).[4–13] A large U.S. study of female twins found concordance rates for generalized social phobia of 24% in monozygotic twins and 15% in dizygotic twins.[6] Twin studies have also found evidence of a genetic factor in shyness, a conclusion supported by the Colorado Adoption Project, which showed that shyness in adopted infants was related to shyness in their biological, but not adoptive, mothers.[10] However, these studies concluded that genetic factors could explain only a proportion of the risk. One genetically influenced trait that may contribute to both social anxiety

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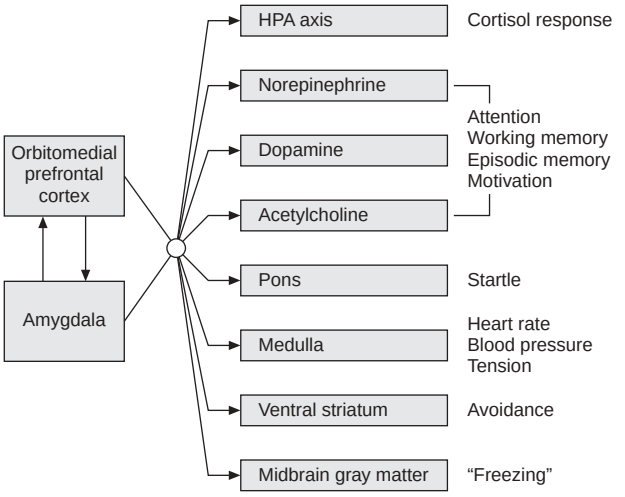
**Table 1. Family and Genetic Findings Related to Social Phobia**

| Finding | Explanation |
|---|---|
| Social phobia | |
| Increased risk in first-degree relatives[4,5] | Genetic and environmental factors |
| Modestly higher concordance in monozygotic twins compared with dizygotic female twins[6] | Genetic and environmental factors |
| Associated with autism[7] | Strongly genetic disorder, but rare |
| Associated with fragile X syndrome[8] | Mutation of specific *FMR1* gene, but rare |
| Shyness | |
| Modestly higher concordance in monozygotic twins[9] | Genetic and environmental factors |
| Linked to shyness in biological, not adoptive, mother[10] | Genetic component |
| Behavioral inhibition | |
| Increased in children of patients with panic disorder/ agoraphobia[11] | Related to anxiety or avoidance |
| Social phobia increased in parents[11] | Related to social phobia |
| Risk factor for social phobia[12] | Related to social phobia |
| Higher concordance in monozygotic twins[13] | Genetic factor |

**Figure 1. Projections of the Orbitomedial Prefrontal Cortex and Amygdala to Multiple Brain Systems That Produce the Physical, Cognitive, and Behavioral Components of an Emotional Response[a]**




[a]Abbreviation: HPA = hypothalamic-pituitary-adrenal.

and avoidance is behavioral inhibition, which refers to wariness, fears, decreased social interaction, and withdrawal in novel situations.[14] Direct observations of behavioral inhibition in young twins have shown that it has a strong genetic component.[13]

Two other pieces of genetic research are also relevant to social phobia. First-degree relatives of patients with autism have demonstrated a 10-fold higher risk of social phobia than relatives of children with other neurodevelopmental conditions.[7,15] This might be due to much milder forms of the mechanisms that cause abnormal social behavior in autistic patients, which are not yet fully understood. Another possibly related disorder is fragile X syndrome, which is due to a mutation in the *FMR1* gene that causes a fragile site on the X chromosome.[16] The mutation involves the insertion of a cytosine-guanine-guanine triplet repeat and, as in Huntington's disease, the length of the repeat can expand in successive generations until it interferes with gene function ("genetic anticipation"). Usually, more than 200 repeats are needed to cause the physical features and mental retardation of fragile X syndrome. A premutation consists of a smaller repeat expansion (around 55–200 repeats), which is at high risk of causing the disease in the next generation. Fragile X syndrome is usually less severe in females than males, because one of their X chromosomes is inactivated and the abnormal gene tends to be switched off. Half of affected women do not have mental retardation. Patients with fragile X syndrome often have marked social anxiety but are more sociable than autistic patients.[17] Recently, it was found that women with the fragile X premutation also had significantly higher rates of social phobia and avoidant, schizoid, and schizotypal personality disorders than controls.[8] Both autism and fragile X premutations are too rare to explain the occurrence of social phobia in the general population, but understanding these disorders might cast new light on the neurobiology of social phobia.

## THE NEUROBIOLOGY OF EMOTION AND MEMORY

The amygdala and orbitomedial prefrontal cortex (OMPFC) are involved in assigning emotional value to stimuli. These can be positive or negative reinforcers, such as food or pain.[18] In addition, the amygdala and OMPFC can learn links between primary reinforcers and associated stimuli. These stimuli become secondary reinforcers. In humans, many reinforcers are complex, such as the face of a loved one. Several regions of the cortex process the identity and expression of a face before the amygdala and OMPFC can assign it an accurate emotional value; however, recent studies have demonstrated that the amygdala can generate responses to emotional expressions in the absence of conscious awareness.[19,20] Both brain regions have projections to multiple brain systems that produce the physical, cognitive, and behavioral components of an emotional response (Figure 1). The OMPFC can learn stimulus-reinforcer associations rapidly and reverse old associations, whereas the amygdala appears to form more persistent links and needs to be inhibited by the OMPFC to suppress old associations that are no longer appropriate.[21] Lesions of the OMPFC or the amygdala lead to marked changes in social behavior. Patients with lesions of the amygdala lose social fear and the ability to make negative social judgments. Adolphs and colleagues[22] asked healthy

controls to make ratings of the trustworthiness and approachability of a large number of faces. Patients with amygdaloid lesions were then asked to rate some of the most and least favorable faces. They rated both groups of faces as equally trustworthy and approachable. Lesions of the OMPFC can interfere with the ability to read signs of emotion in others or to respond appropriately to the emotional context of a situation, thereby causing perseveration of social behaviors even when they lead to unpleasant consequences.[23,24]

Human memory can be divided into 3 main systems: working memory, long-term memory, and episodic memory.[25–27] Working memory, which depends on the dorsolateral prefrontal cortex, is highly flexible, evanescent, and of limited capacity, holding on to information only as required for ongoing tasks. Long-term memory includes semantic memory and procedural memory. Semantic memory is our general knowledge about the world and how it works. Procedural memory refers to skills, such as writing, that we acquire and practice to the point where they are automatic. Long-term memory is vast, stable, relatively inflexible, and stored in a distributed manner in the neocortex and in subcortical structures, such as the basal ganglia. Episodic memory is memory for specific facts, events, and experiences. This system has a high capacity, intermediate flexibility and durability, and depends on the hippocampus and closely related structures.

Why do we have multiple types of memory? The advantage of a highly stable long-term memory is that we can understand and approach things in the world that are relatively invariant; we do not continually have to reinvent the wheel. The disadvantage of stability is inflexibility. To compensate for this, if something new or meaningful happens, the hippocampus registers the event as significant. The experiences that the hippocampus registers most strongly are contraventions of norms, novel events, and strong reinforcers.[27] As a result of the temporary storage of memories in the hippocampus, we do not have to incorporate every new experience into our long-term store of knowledge and our behavioral repertoire; rather, we can reflect and have time to reject information that is not useful or to modify our understanding. However, episodic events that are most strongly represented in the hippocampus may exert the most influence on the consolidation of long-term memories. The actions of the prefrontal cortex and amygdala influence the strength with which unexpected, novel, and reinforcing stimuli are registered in the hippocampus. The prefrontal cortex uses working memory to monitor experiences, and its executive control functions to select which experiences must be attended and the appropriate cognitive and motor skills to allocate to deal with them. If events are going as expected and stay within someone's repertoire, the capacities of working memory and executive functions are relatively untaxed. However, if something unexpected happens, if multiple pieces of information have a high priority, or if the situation requires skills that are not well practiced, heavier demand is made on these systems.[28] Unexpected situations also activate the OMPFC and amygdala, which determine their emotional significance. The OMPFC and amygdala have projections to nuclei of the acetylcholine, norepinephrine, and dopamine systems.[29] These systems project back to the prefrontal cortex in order to increase attention and enhance working memory, and to the hippocampus in order to strengthen the early consolidation of memory traces.[27,30] Overall, our memory works efficiently: we have a stable core system so we know our place in the world, and we have attentive and flexible learning systems so we can adapt and change as needed.

## THE DEVELOPMENT OF SOCIAL PHOBIA

Kagan and colleagues[31] postulated that behavioral inhibition is related to elevated amygdala reactivity. From a sample of 462 infants aged 4 months, they selected 20% with high reactivity (e.g., vigorous motor activity and crying in response to sensory stimuli) and 40% with low reactivity. High reactivity is thought to indicate activation of amygdala outputs. At follow-up to 7 years of age, children in the highly reactive group were much more likely to show behavioral inhibition in every category of assessment. They shied away or withdrew from unfamiliar people or events, smiled and spoke less with the researchers, clung more to their mothers, and were slower to play with their peers. When other groups of inhibited and uninhibited children were studied, parents of the inhibited children were found to have much higher rates of social phobia and anxiety disorders.[32] More recently, children who had been assessed as inhibited or uninhibited before the age of 3 years were observed until they were 13 years of age. Behavioral inhibition was found to predict greater social anxiety and social phobia.[12] A substantial minority of the inhibited children reported no social fears at follow-up, showing that the trait can be modified during upbringing. Evidence of amygdala reactivity in children with behavioral inhibition has included higher salivary cortisol release, increased startle responses, and a predominance of sympathetic activity, as shown by heart rate, diastolic blood pressure, pupil diameter, vocal cord tension, and urinary catecholamines.[31,33,34]

In healthy children, fear of strangers is almost universal from the age of 7 to 10 months. This may be related to the development of working memory and to the myelination of inputs to the amygdala at this age.[35] By the third year, most children approach strangers cautiously and make overtures to check out their reactions, monitoring danger by social referencing, which means checking visual and verbal cues from the parent.[36] Social referencing requires joint attention, which is the capacity to observe and follow another person's gaze, orientation, or goal-directed move-

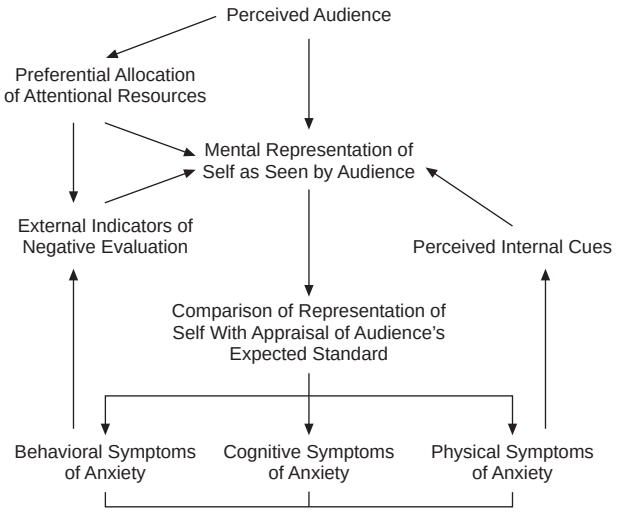
ments in order to be aware of the other person's focus and goals and to modify one's own attention and behavior accordingly.[37] The child's acquisition of social judgment and confidence may be presumed to involve the development of prefrontal and cortical control. If the amygdala is overactive, sufficient inhibitory control may take longer to develop, and negative affect derived from the amygdala may lead to negatively biased encoding of social encounters by the OMPFC.

Social learning may possibly also be affected by problems with joint attention or with synaptic mechanisms of learning. Children with autism have impaired joint attention and poor recognition of facial expressions,[38] and children with fragile X syndrome have marked difficulties with eye contact.[39] Perhaps milder variants of these abnormalities in their relatives may affect the ability to learn social safety cues and contribute to the relatives' increased risk of social phobia. In addition, genetic knockout studies in animals show that the loss of fragile X protein interferes with synaptic processes that may be involved in the formation of new associations.[40,41] In this case, it may be that a failure to learn safety signals occurs at a synaptic level, impairing development of the capacity of the OMPFC to inhibit amygdala activation and perhaps leading to an abnormal persistence of fear or strangers beyond the normal developmental age.

The early social environment may also be an important determinant of the development of social phobia. In retrospective studies, patients with social phobia have more commonly reported that their parents are overprotective,[42] and in an epidemiologic sample, parental dysfunction and abuse have also emerged as potential risk factors.[43] Preliminary prospective studies have suggested that some parents with anxiety disorders may be less warm, more controlling, or more critical with their children and less likely to encourage them to take on challenges.[42] Parents with anxiety disorders were shown in one study to be more critical of their inhibited than their uninhibited children and to be more critical of their inhibited children than were nonanxious parents.[44]

An enormous amount of semantic and procedural knowledge is built up during childhood, and self-image, social perception, and social behaviors are part of that knowledge. By about 5 years of age, children become well able to recognize that people have social attitudes and make social judgments.[37] Self-consciousness and social embarrassment normally appear for the first time at this age.[45] The research cited above suggests that this early development could be distorted in behaviorally inhibited children by amygdala overactivity. Inappropriate or exaggerated negative affect might bias evaluations such that others appear displeased or threatening, which, in turn, might adversely affect the development of self-image. Extra efforts to avoid criticism and to obtain strongly positive responses might contribute to the development of perfectionism. Projections from the amygdala to the ventral striatum motivate avoidance responses, which could become habitual procedural "skills" positively reinforced by the reduction of anxiety. The activation of neurotransmitters that strengthen hippocampal encoding of memories would repeatedly ensure that the most negative aspects of social encounters become registered by the hippocampus, increasing the likelihood of subsequent consolidation into long-term memory. Already by the age of 7 years, anxiety disorders have been observed in inhibited children,[11] stressing the potential importance of early intervention.

**Figure 2. Cognitive Model of Social Phobia[a]**




[a]Reprinted from Rapee and Heimberg,[47] with permission.

## COGNITIVE THEORIES OF SOCIAL PHOBIA

I will next discuss psychological and biological mechanisms in established social phobia in adults. Cognitive theories suggest that persons entering a social situation form an internal representation of the setting and participants and generate an image of how they appear to others based on prior knowledge of their general appearance and adjustments for temporary circumstances, such as how they are dressed and their mental state. In patients with social phobia, multiple distortions seem to take place in this process (Figure 2).[46,47] First, they attend much more to their self-perception than to the situation. Second, they focus strongly on perceived negative aspects of their appearance. Third, they distort the perceived effects of their mental state on their appearance (e.g., internal jitteriness may be imagined to look like a gross tremor). Fourth, they attend selectively to feedback, focusing on negative cues from people and ignoring positive ones. Fifth, they perceive feedback more negatively than the reality. Sixth, they may subtly try to control their appearance or avoid feedback, for example, by clasping their hands tightly to suppress tremor

or by averting eye contact. Patients relate their perceived performance to the standard they expect of themselves, which is influenced by schemas that are part of their semantic and procedural memory. These schemas—sets of implicit rules underlying behavior—are often negatively biased in patients with social phobia. Common examples include the belief that they will be disliked if they do not perform perfectly, that if they make a mistake or appear anxious they will be judged as incompetent or stupid, or that they are indeed incompetent or stupid.

## NEUROBIOLOGICAL SUBSTRATES OF COGNITIVE-BEHAVIORAL DYSFUNCTIONS IN SOCIAL PHOBIA

Earlier, I suggested that behavioral inhibition may contribute to the development of negative schemas. However, people have many thousands of social interactions in their lives and, with notable exceptions, do not aim to make these aversive. Therefore, one question that arises is, if patients with social phobia have brain systems for flexibility and adaptation to new events, why don't they register that reality is inconsistent with their fears and change their behavior accordingly? Or, to paraphrase, "Why can't they snap out of it?" One answer might be that anxiety itself interferes with the brain's flexible learning systems.

As noted above, the amygdala and OMPFC influence the focus and intensity of attention by activating the acetylcholine, norepinephrine, and dopamine systems. During phobic anxiety, patients with social phobia focus on bodily symptoms that arise from autonomic arousal, like a pounding heart or jitteriness, and on emotionally salient external stimuli, like critical facial expressions. Intense fear-related activation of these neurotransmitters might mediate excessively focused attention. Furthermore, although moderate activation of these transmitters can improve working memory, their marked activation by stress impairs it, as may occur in anxious patients with social phobia. Finally, executive functions are of limited capacity, which may be consumed by patients monitoring their own performance, trying to avoid showing anxiety, and trying to perform perfectly. Changing schemas or deeply ingrained patterns of learning requires the ability to orient to, monitor, and actively process new information while suppressing conflicting and habitual responses. In the area of social cognition, research has shown that people generally rely on social stereotypes as the context against which individuals are judged. Normally, people more strongly remember the characteristics of an individual that are against the stereotype of the person's social group. However, if executive capacity is taxed experimentally by having to perform another task concurrently with social evaluation, this pattern is reversed and stereotypical characteristics are more strongly recalled.[48] In an analogous fashion, during phobic situations, the other demands on executive capacities may prevent patients from processing information that counters their negative schemas, which can be seen as "self-stereotypes."

## BIOLOGICAL FINDINGS IN ESTABLISHED SOCIAL PHOBIA

### Physiologic and Psychological Challenge Tests of Autonomic Function

Social anxiety can trigger prominent autonomic symptoms. Researchers hypothesizing that the autonomic nervous system is generally overactive in patients with social phobia have measured heart rate, blood pressure, and plasma catecholamine responses to standing, deep breathing, and Valsalva's maneuver and also studied skin conductance responses to loud tones. There have been occasional abnormal findings, but they either have not fitted clearly into an overall pattern or have been poorly replicated, such that, on the whole, there is not strong support for this hypothesis.[49] Another approach has been to study autonomic and neuroendocrine reactivity to social stimuli. Several studies have found greater heart rate or blood pressure responses to public speaking or social interaction in patients with social phobia.[50–52] However, plasma catecholamine responses and plasma or salivary cortisol responses did not differ significantly.

Interestingly, the heart rate response has been greater in specific social phobia than in generalized social phobia[50]—a finding that deserves further investigation because it does not fit with the idea of a simple continuum that matches the degree of social fears with the degree of autonomic reactivity. If generalized social phobia is more strongly related to childhood behavioral inhibition than is specific social phobia, perhaps counter-regulatory mechanisms come into play during development that moderate autonomic output despite the continuing emotional dysfunction. The lack of an autonomic component would also explain why β-blockers are not effective in treating generalized social phobia.[53] Studies have found little difference in the cortisol responses of patients with social phobia compared with healthy subjects, but this may be because healthy subjects can have a greater cortisol response when performing a novel task than when performing a familiar one.[54] Greater differences might emerge between patients and healthy controls if habituation to repeated public speaking stress were studied.

### Biochemical Challenge Tests

Biochemical challenge tests have been utilized more extensively in patients with panic disorder, and the impetus for many studies of social phobia patients has been to test whether abnormal responses found in panic disorder are specific or whether they occur in social phobia as well. Multiple agents have provoked panic or anxiety in panic disorder patients, and comparative results, where available

Table 2. Sensitivity of Panic Disorder, Social Phobia, and Healthy Control Subjects to Anxiety-Provoking Agents[a]

| Agent | Panic Disorder | Social Phobia | Controls | Possible Mechanisms[b] |
|---|---|---|---|---|
| Lactate[56] | +++ | + | + | Chemoreceptor sensitivity, interoceptive, cognitive |
| Hypertonic saline[57] | +++ | NS | NS | Chemoreceptor sensitivity, interoceptive, cognitive |
| $CO_2$[58,59] | +++ | +/++ | + | Chemoreceptor sensitivity, interoceptive, cognitive |
| Doxapram[60] | +++ | NS | + | Chemoreceptor sensitivity, interoceptive, cognitive |
| Epinephrine[61,62] | ++ | 0/++ | 0 | Peripheral adrenergic, interoceptive, cognitive |
| Isoproterenol[63] | +++ | NS | + | Peripheral adrenergic, interoceptive, cognitive |
| Yohimbine[64] | +++ | NS | 0/+ | Central $\alpha_2$-adrenergic antagonist |
| CCK[65] | +++ | ++ | + | CCK receptor sensitivity, interoceptive |
| *m*-CPP[66] | +++ | ++ | + | Serotonin receptor sensitivity, interoceptive, cognitive |
| Fenfluramine[67,68] | ++ | NS | 0/+ | Serotonin receptor sensitivity, interoceptive, cognitive |
| Caffeine[69] | ++ | ++ | + | Adenosine receptors, interoceptive, cognitive |
| Flumazenil[70–72] | +++/0 | + | 0 | Benzodiazepine receptors, interoceptive, cognitive |

[a]Abbreviations: CCK = cholecystokinin, *m*-CPP = *m*-chlorophenylpiperazine, NS = not studied. Symbols: +/++/+++ = relative activation, 0 = little activation.
[b]Interoceptive signals may trigger overreactive regions such as the amygdala or orbitofrontal cortex; cognitive mechanism may involve conscious distortion of significance of sensations.

for social phobia patients,[49,55] are shown in Table 2.[56–72] Generally, social phobia patients respond less anxiously than panic disorder patients and slightly more anxiously than do healthy controls. However, social phobia patients seem more sensitive than healthy controls to inhalation of a single breath of high-concentration $CO_2$ and to cholecystokinin tetrapeptide injections. These and some of the other agents produce autonomic activation and strong visceral sensations in healthy volunteers. This makes it hard to be certain if patients have specific changes in chemical sensitivity in response to the agent, nonspecific increases in the reactivity of brain systems that respond to visceral stimuli (such as the OMPFC and amygdala), or excessive attention to visceral symptoms while being watched by experimenters.

Some of these uncertainties can be reduced if patients also respond abnormally to nonanxiogenic agents that act through the same system. For example, panic disorder patients show abnormal responses to the calming central $\alpha_2$-adrenergic agonist clonidine, as well as anxiety responses to the $\alpha_2$-antagonist yohimbine.[73] Similar data are not available for social phobia patients. One study[74] in social phobia found decreased growth hormone responses to clonidine, but this was not shown in a second study[67] with a different dose. Levodopa has been given as a test of dopamine activity, but the eye-blink response was not different from that in controls.[67] Other evidence for dopamine dysfunction has been found using neuroimaging, as discussed below. Depression is a frequent complication of social phobia,[75] and serotonergic abnormalities have been found repeatedly in depression. However, few studies of serotonergic function have been performed in social phobia, and the only positive finding was an increased cortisol response to fenfluramine that may indicate greater postsynaptic receptor sensitivity.[67] Basal levels of urinary or plasma cortisol and cortisol suppression by dexamethasone have not been found to differ between social phobia patients and controls, in contrast to the cortisol hypersecretion and reduced dexamethasone suppression found in depressed patients.[76,77]

## Electroencephalography

Electroencephalographic (EEG) measures show abnormalities both in childhood behavioral inhibition and in adult social phobia. Behaviorally inhibited children show abnormal hemispheric EEG asymmetry, in that the power of the low-frequency alpha rhythm is greater in right frontal than in left frontal regions. This is the reverse of the pattern in uninhibited children.[14] In a series of studies,[78] it has been shown that these patterns are associated with affect. Greater right-sided power is associated with negative affect, whereas greater left-sided power correlates with positive affect. Recently, social phobia patients and controls were compared in anticipation of and immediately after a public speaking test. Results indicate that the patients had a marked, selective activation of right frontal alpha power, which was highly correlated with their change in subjective anxiety.[79] This may represent stimulation by the amygdala and OMPFC of acetylcholine and serotonin release, which can activate the cortical EEG.

## Neuroimaging

There is only 1 published structural imaging study, which shows no differences in cortical, basal ganglia, and thalamic volumes between social phobia patients and controls.[80] However, the same group of researchers has published 2 studies showing that patients have a reduced ratio of *N*-acetylaspartate (NAA) to other brain metabolites in anterior cortical gray matter.[81,82] The functional roles of NAA are not fully understood at the present time, but reduced NAA concentrations are generally regarded as indicating reduced neuronal function. It will be interesting to see if this abnormality can be localized further and if it is related to impaired OMPFC function.

In the one study that used single photon positron emission computed tomography (SPECT) to measure resting

regional brain blood flow, there were no differences between social phobia patients and controls.[83] Two studies have reported interesting preliminary results using socially relevant tasks, however. In the first study,[84] 7 patients with generalized social phobia and 5 healthy controls were presented both with images of emotionally neutral faces and with an aversive foul odor, in a randomized order, during functional magnetic resonance imaging. The odor activated a similar proportion of the amygdala in both groups, but the proportion activated by the faces was much larger in the patients. The patients did not differ from controls in their self-rated levels of anxiety during the tasks.

In the second study,[55] generalized social phobia patients produced scripts describing their most fearful social encounters and neutral experiences for comparison. These were read back to them in the positron emission tomography (PET) scanner, and they were asked to imagine themselves in the situations. Subtraction of the blood flow images was used to produce maps of the regions that responded differently to the script of the feared situation. The researchers observed relative activation in the left anterior cingulate, right dorsolateral prefrontal cortex, bilateral orbitofrontal cortex, and cerebellum, with relative deactivation in the right medial prefrontal cortex, left amygdala, right parahippocampal gyrus, and polymodal and visual association cortices.

In both studies, therefore, regions were activated that are known to be involved in emotional processing. Despite the greater amygdala activation in patients with social phobia in the first study, it was notable that there was no difference in subjective anxiety. This might represent the involvement of an evaluative circuit that includes the amygdala, without the information reaching circuits that mediate the subjective component of fear. Physiologic responses were not measured in this study. In the future, however, it will be important to do so, because recent research into the learning of fear in healthy subjects shows that amygdala activation and physiologic changes in skin conductance can occur without the subjects' awareness of the relevant facial stimuli.[20] This has implications for our understanding of how the biases in attention and information processing highlighted in cognitive theories can occur in an "automatic" fashion.

Functional magnetic resonance imaging has better time resolution than PET, and amygdaloid activity has been transient in relation to the time course of behavioral and physiologic fear responses in other studies.[85,86] PET might therefore fail to detect amygdala activations. In the second study,[55] the orbitofrontal cortex was activated with fear, but the amygdala was deactivated. In this case, a transient amygdala activation might have been masked by a subsequent inhibition of the amygdala by the orbitofrontal cortex. It is also possible that the episodic memory recall involved in the second paradigm preferentially activates circuits involving the OMPFC and dorsolateral prefrontal cortex rather than the amygdala, whereas the converse may be true for the external stimuli used in the first paradigm. Finally, information processing in the brain may achieve selectivity through a narrowing of the area of neurons that are activated, via a suppression of surrounding neurons. Because the spatial resolution of brain images is limited, this may mean that only the surrounding suppression is visualized. Although substantial further research will be needed, these studies show that the neurobiological foundations of the cognitive and affective psychology of social phobia can now be studied at the level of brain regions.

Functional neuroimaging can investigate how brain regions interact to process stimuli or execute responses, but studies of signaling systems are needed to understand the control of these processes. Recent important investigations have shown abnormalities of the dopamine system in generalized social phobia. The first study[87] showed a reduction by 20% in striatal dopamine transporter sites, and the second,[88] a similar magnitude of reduction in dopamine-2 ($D_2$)-receptor binding. This reduction of both presynaptic and postsynaptic binding strongly implicates changes involving the dopamine system in the disorder. Additional indirect evidence for this involvement has come from 3 studies in which the levels of striatal $D_2$ receptor[89,90] and dopamine transporter[91] binding in healthy controls were inversely correlated with measures of social detachment on the Karolinska Scales of Personality. Normal variations of this social trait might, therefore, also be related to dopamine function.

Conceptually, detachment relates to sociability rather than social anxiety. In practice, however, many items on the Karolinska scales used to measure social detachment are the same as those used as indicators of social anxiety; measures of detachment derived from 2 other scales, the Tridimensional Personality Questionnaire[89] and the NEO Personality Inventory-revised,[92] have not shown significant correlations with dopaminergic indices. An important limitation of cross-sectional studies is that they do not indicate whether dopaminergic deficits might cause social anxiety or be an attempt to compensate for it. Animal studies show that dopamine in the ventral part of the striatum is important in motivation and energizing behavior, as is evidenced by the effects of psychostimulant drugs on this brain region.[93] Psychostimulant intoxication releases dopamine and is associated with increased social confidence, whereas chronic use can impair dopamine function. Reports of social phobia in chronic users of psychostimulants make it seem plausible that dopaminergic deficits are a cause, rather than a consequence, of social phobia.[94] Ongoing studies are examining genetic influences on $D_2$ receptor binding in healthy volunteers, with the finding that some alleles are associated with lower binding.[95] Further study will tell if these variations are also related to social behavior.

## THE NEUROBIOLOGY OF THE TREATMENT OF SOCIAL PHOBIA

### Cognitive-Behavioral Treatment

Not surprisingly, given the few biological studies that have been conducted in social phobia, there are no published studies on the neurobiological effects of pharmacologic or cognitive treatments. Cognitive-behavioral treatments help patients to recognize and alter distorted thinking; focus on the interaction at hand, rather than on internal or external distractors; learn social skills, such as assertiveness, if they are deficient; and reduce avoidance behavior. Cognitive theorists often refer to "cold" cognitions outside the phobic situation and "hot" cognitions within it. In order to achieve long-term benefits, patients have to put skills into practice in real social situations (exposure homework).[96] However, during treatment, patients first work out plans with their therapist for cognitive and behavioral change before entering into anxiety-provoking situations. In this therapeutic setting, the patient is able to take in new information and practice new strategies through mental rehearsal and role-play. The patient then works at implementing the strategies in a hierarchy of situations that range from the least to the most anxiety provoking.

An important biological component of this cognitive-behavioral therapeutic process may be that the generation of new behavioral plans in episodic memory is at first isolated from the disruptive effects of marked phobic anxiety on prefrontal executive processing and the processing of information that does not conform to preexisting schemas. When patients go back into phobic situations during homework, they have a new episodic memory "blueprint" to try to implement. However, for the new plans to produce lasting therapeutic change, they may also have to be incorporated into procedural and semantic memory, setting up new social schemas in "hot" real-life settings. Working up through a graded hierarchy may help to protect this process from marked disruption, and modest levels of anxiety may actually facilitate the new learning.

### Pharmacologic Treatment

The main pharmacologic treatments that have been shown to be effective for social phobia are selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs),[97] and benzodiazepines.[98] β-Blockade with propranolol or atenolol can be effective for performance anxiety, a specific type of social phobia.[99] There is preliminary evidence that the antiepileptic drug gabapentin[100] and a related investigational compound called pregabalin[101] may have therapeutic benefits. In contrast to major depression and panic disorder, there is little evidence that tricyclic antidepressants are effective in social phobia,[102] although why SSRIs should be superior to tricyclics is not established. How might effective treatments work?

Often when multiple treatments work in a disorder, we look for common biochemical actions. Although a case has been made for the beneficial effect of enhancing dopamine transmission in social phobia, which might fit nicely with the dopaminergic deficits revealed in neuroimaging studies, this would not explain the effects of SSRIs, the benzodiazepine clonazepam, or gabapentin.[103] The MAOI that has been best studied for social phobia is phenelzine. Although it is not widely known to clinicians, phenelzine enhances brain levels of γ-aminobutyric acid (GABA), which is the main inhibitory neurotransmitter of the brain, as well as levels of monoamines.[104] This is a property shared by gabapentin in animals.[105] Benzodiazepines reduce anxiety by boosting the sensitivity of GABA receptors to GABA.[106] It would not be possible at this stage to fit SSRIs into this framework as a group, but it has been noted that fluoxetine and fluvoxamine can both increase levels of allopregnenolone in the cerebrospinal fluid of depressed patients.[107] Allopregnenolone is a neurosteroid metabolite of progesterone, which also has the property of increasing the sensitivity of GABA receptors to GABA.[108]

It is more likely, however, that an explanation of why multiple treatments can be effective will come from a systems approach. To return to the earlier analogy of hypertension, even if we do not know the cause of essential hypertension, we know that it can be treated by modifying one or more of a number of systems that normally contribute to blood pressure control. In the case of psychiatric disorders, we have perhaps tended to look for a single biochemical explanation as a "magic bullet" because of our relative ignorance of the underlying systems that we are treating. Effective therapies for social phobia may have beneficial effects at a number of levels in brain systems that mediate social anxiety. For example, GABA is inhibitory at various sites, including the amygdala itself, the hypothalamic paraventricular nucleus that controls corticotropin and thereby cortisol release, the midbrain nuclei that coordinate fight and flight responses, and also at acetylcholine, dopamine, and norepinephrine nuclei. Agents that boost GABA function may therefore damp down excessive responses at several levels of the system. Serotonin, which is boosted by SSRIs and MAOIs, is inhibitory to acetylcholine and dopamine release and also inhibits midbrain fight and flight nuclei. These actions of benzodiazepines and SSRIs to reduce dopamine function stand in contrast to the idea that dopaminergic deficits are causal in social phobia. An abstract published after the preparation of this article has provided preliminary evidence that treatment with an SSRI may act to prevent the deactivation by social anxiety of brain regions that mediate executive functions.[109] This finding suggests the hypothesis that a common mechanism of both cognitive-behavioral therapy and pharmacotherapy might be to reduce the disruptive effects of social anxiety on systems that mediate behavioral change. However, considerably more work needs to be done to establish what the

critical therapeutic actions of these treatments are on brain systems relevant to social phobia.

### Combined Treatment

Current evidence shows that for patients who enter a treatment program, phenelzine and cognitive-behavioral therapy are both effective, with some advantages in terms of speed and degree of recovery for phenelzine. However, the gains achieved with cognitive-behavioral therapy appear to be better maintained after the end of the treatment period.[110] One possible explanation for this is that for cognitive-behavioral therapy to be fully effective, changes may have to become part of semantic and procedural memory. As noted earlier, this process takes time, and it is not clear whether it would take place in the same way with drug treatment. For example, although medications may reduce fear, some patients may not modify their habitual behaviors. They feel better with drug treatment, but their old schemas may still be active when they stop medication. In some patients, new schemas may become established while they feel calm, but may not be present at the procedural level when they feel anxious, so that any return of anxiety after discontinuing medication triggers a relapse. In other cases, the use of a drug can itself become part of a schema. With "as required" benzodiazepines, for example, the patient may learn that coping in social encounters is conditional on swallowing a pill. In some instances, medications may interfere pharmacologically with new learning. For example, benzodiazepines can impair episodic memory. Adding medication to cognitive-behavioral therapy might turn out to mean 1 + ½1.1, or even only 0.8, rather than 2.

## CONCLUSION

The etiology of social phobia is not yet established, but evidence has been provided for both genetic and environmental factors. Behavioral inhibition has emerged as an important precursor of social phobia and possibly of other anxiety disorders. Several effective pharmacologic treatments have been identified. It has been established that cognitive-behavioral disturbances play a central mediating role in the disorder and that targeting these in treatment is clinically effective. Neuroimaging studies have started to investigate brain systems and neurotransmitter abnormalities in the disorder. These abnormalities may include dopamine dysfunction. There have been major strides in preclinical understanding of the neurobiology of fear and learning systems in recent years. The advent of neuroimaging techniques should allow further integration of our understanding of neurobiological and cognitive processes in this common and disabling disorder.

*Drug names:* atenolol (Tenormin and others), clonazepam (Klonopin and others), clonidine (Catapres and others), dexamethasone (Decadron and others), flumazenil (Romazicon), fluoxetine (Prozac), fluvoxamine (Luvox), gabapentin (Neurontin), phenelzine (Nardil), propranolol (Inderal and others), yohimbine (Yocon and others).

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# Question and Answer Session

**Question:** Given the purported contribution of neurotransmitters to the symptoms of social phobia, has dopamine been considered as a potential target for treatment in social phobia?

**Dr. Coupland:** Early work from Dr. Michael R. Liebowitz suggested that one of the mechanisms of nonselective monoamine oxidase inhibitors (MAOIs) is to increase dopamine availability. In this scenario, however, one would expect selegiline, a selective monoamine oxidase B inhibitor, to block symptoms, but the same group found only modest response with this drug. Because the trial was small and uncontrolled, however, we cannot draw any firm conclusions yet.

Another possible explanation for the efficacy of phenelzine in social phobia has been linked to its ability to block γ-aminobutyric acid (GABA) transaminase. It is actually a stronger blocker of GABA transaminase than is vigabatrin, an anticonvulsant.* Phenelzine has been shown to raise GABA levels in rat brains at concentrations equivalent to therapeutic levels in humans.[1] Furthermore, Baker and colleagues[2] carried out a study showing that plasma GABA levels increase during phenelzine therapy in patients with various psychiatric disorders. This has implications for gabapentin, which also increases brain GABA levels. However, in the end it is very difficult to separate out the individual effects of a single neurotransmitter in a system in which multiple neurotransmitters have influence and may interact.

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*Note: In October 1998, vigabatrin was denied approval by the U.S. Food and Drug Administration, primarily because of concern about visual field defects.