Social anxiety disorder, also known as social phobia, is a common and disabling psychiatric illness that is characterized by an excessive fear and/or avoidance of situations in which an individual feels scrutinized by others and is fearful of a negative evaluation by others. Although it is the most common of the DSM-IV anxiety disorders, there is a dearth of clinical neurobiological research on social anxiety disorder and few preclinical models. This review focuses on the generalized subtype, which involves the fear of a wide range of social situations, with the goal of proposing several neurobiological mechanisms that may account for the symptoms of this disorder. We begin with an overview of three nonhuman primate models that are particularly relevant to social anxiety. Next, we review recent literature in the clinical neurobiology of social anxiety disorder, focusing on important findings in developmental neurobiology and genetics. Our findings suggest that social anxiety disorder should be reconceptualized as a chronic neurodevelopmental illness instead of an episodic de novo adult disorder, a semantic distinction with important treatment implications.

Models Relevant to Social Anxiety

Investigating social anxiety disorder with animal models is more problematic than investigating the conditioned-fear paradigm in rodents, which we used to understand panic disorder (1), largely because the interactional nature of the disorder is less amenable to laboratory study. Nevertheless, we review three nonhuman primate models that seem particularly relevant.

Subordination Stress Model

Like man, primates are particularly dependent on social relationships, and laboratory-based behavioral observations can be readily conducted. Shively (2) conducted informative nonhuman primate studies in social subordination and dominance in laboratory-housed female cynomolgus monkeys. Behavioral observations revealed that subordinates spent more time alone, fearfully scanning their social environment, than dominants. Biological studies of these subordinates revealed evidence of hyperactive hypothalamic-pituitary-adrenal (HPA) axis activity, impaired serotonergic functioning, and impaired dopaminergic neurotransmission. In a challenge study with ACTH, social subordinates hypersecreted cortisol, reflecting HPA axis activation. When investigators carried out the fenfluramine challenge test (which causes release of serotonin), laboratory-housed cynomolgus macaques exhibited a blunted prolactin response, which suggests reduced central serotonergic activity. These monkeys were more socially withdrawn and spent less time in passive body contact than those who showed a high prolactin response (3). When investigators carried out a haloperidol challenge test with a dopamine antagonist that enhances prolactin secretion through tubero-infundibular dopamine pathways, reduced prolactin responses were observed in subordinates (2). This result suggested a lowering of the sensitivity of postsynaptic dopamine receptors in this pathway in the subordinates. Consistent with the neuroendocrine data, a positron emission tomography (PET) study (4) of subordinates showed decreased striatal dopamine D2 receptor binding, which suggests abnormal cen-
tral dopaminergic neurotransmission, a finding that mimics the results of a single photon emission computerized tomography (SPECT) study (5) in humans with social anxiety disorder.

Studies of socially subordinate baboons in the wild have revealed other neuroendocrine abnormalities that mimic findings in certain anxious and depressed human subjects. Hypercortisolism, as well as resistance to feedback inhibition by dexamethasone, was reported by Sapolsky et al. (6) in baboons. Another interesting finding is that subordinate male baboons have lower insulin-like growth factor I levels than dominants (7). This finding might explain the observed association between short stature and social anxiety disorder found in one study (8).

There are several important limitations of this model as it applies to patients with social anxiety disorder. First, there is no evidence of an HPA axis disturbance in social anxiety disorder as measured by the degree of dexamethasone nonsuppression (9). Second, the prolactin response to fenfluramine differs in subordinate models versus patients with social anxiety disorder (10). Another important limitation of this and the other animal models is that humans with social anxiety disorder tend to be “hard wired” to act avoidant, submissive, and anxious in social settings, whereas nonhuman primates, because of environmental manipulations in dominance and submission, display a certain plasticity in response to environmental stresses. For example, dominant vervet monkeys have higher blood serotonin levels than subordinates, but their serotonin levels significantly decrease when they are removed from the group (11). Thus, it appears that the major correlative finding in the primate subordination stress model with social anxiety disorder is striatal dopaminergic dysfunction. Whether this dysfunction is a byproduct of social stress or a feature of social subordination per se is not clear.

Variable-Foraging-Demand Model

Another model of potential use is the variable-foraging-demand model in nonhuman primates. Rosenblum and Paully (12) developed this model for social timidity and nonassertiveness by exposing nursing mothers to unpredictable foraging-demand conditions and experimentally inducing unstable attachment patterns to their infants. Grown animals raised under variable-foraging-demand conditions, in comparison to predictably reared comparison subjects, showed stable increases in levels of social timidity—e.g., social subordination, avoidance of antagonistic encounters—and decreased species-typical huddling, in comparison to predictably reared comparison subjects (13). From a biological standpoint, subjects reared under the variable-foraging-demand model exhibited longstanding increases in levels of CSF corticotropin-releasing factor (CRF) (14), the dopamine metabolite homovanillic acid (HVA), and the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA). Only in subjects reared under the variable-foraging-demand model did CRF levels correlate positively with HVA and 5-HIAA levels, which suggests a functional linkage between CRF level and both dopaminergic and serotonergic systems (15). Moreover, within the variable-foraging-demand group, relative increases in CRF levels were correlated with relative reductions in growth hormone (GH) response to the α2 adrenergic agonist clonidine (16), as well as exaggerated anxiety responses to yohimbine, an α2 antagonist (17).

Neurochemically, what appeared to be most relevant for social anxiety disorder is the finding of altered dopaminergic metabolites in CSF in primates reared under the variable-foraging-demand condition, which parallels the numerous dopaminergic abnormalities observed in patients with social anxiety disorder. Behaviorally, the primates reared under the variable-foraging-demand condition resembled what Kagan et al. (18) described in a group of young children who manifested characteristics of “behavioral inhibition to the unfamiliar.” These children exhibited an exaggerated heart rate acceleration to stress, high early-morning salivary cortisol levels, and levels of behavioral inhibition correlated with high total norepinephrine activity. Thus, the variable-foraging-demand model is useful in its suggestion that early environmental stress, particularly of an affective nature, may shift behavior and neurobiology toward a trait-like socially anxious profile. Clinically, however, the neuroendocrine findings of dissociation between increased CRF levels and decreased cortisol levels most closely resembled the profile of patients with posttraumatic stress disorder (PTSD) (19, 20).

Animal Attachment Models

Historically, deficits in attachment behavior have been most closely associated conceptually with autistic disorders and schizoid personality disorders. In fact, an often-noted clinical distinction between patients with social anxiety disorder and those with autism and schizoid personality disorder is in the degree of desire for relatedness and attachment to others. Because patients with social anxiety disorder (and its closely related axis II variant avoidant personality disorder) have been generally regarded as persons who desire connections and attachments with others but are fearful of the negative consequences of such interactions, whereas autistic and schizoid persons generally do not desire these attachments and lack affiliative behaviors, attachment models have not been considered important in understanding social anxiety disorder. However, emerging genetic links between autism and social anxiety disorder suggest a reexamination of attachment neurobiology. For example, Smalley et al. (21) found that the first-degree relatives of autistic probands had an increase in social anxiety disorder relative to comparison subjects. A recent study (22) showed that the parents of autistic probands had significantly higher rates of social phobia than the parents of Down’s syndrome probands, although there was no evidence of an association within individuals between social
TABLE 1. Nonhuman Primate Models Relevant to the Study of Social Anxiety Disorder in Humans

<table>
<thead>
<tr>
<th>Model</th>
<th>Neurobiologic Alterations</th>
<th>Brain Regions</th>
<th>Clinical Correlations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subordination stress</td>
<td>Reduced serotonin activity, decreased striatal dopamine D2 binding</td>
<td>Prefrontal cortex, raphe nuclei, corpus striatum, nucleus accumbens, ventral tegmental area (midbrain)</td>
<td>Blushing, Increased substance abuse</td>
</tr>
<tr>
<td>Variable-foraging demand</td>
<td>Increased CSF levels of corticotropin-releasing factor (CRF), homovanillic acid, and 5-hydroxyindoleacetic acid (5-HIAA); decreased cortisol levels</td>
<td>Hippocampus, amygdala, prefrontal cortex</td>
<td>Comorbid posttraumatic stress disorder, behavioral inhibition in children</td>
</tr>
<tr>
<td>Attachment</td>
<td>Lower 5-HIAA levels in CSF; increased avoidant behaviors, oxytocin system downregulation</td>
<td>Hypothalamic neurons of nucleus arcuatus, paraventricular CRF neurons, prefrontal cortex</td>
<td>Other comorbid anxiety and depressive symptoms, Social incompetence</td>
</tr>
<tr>
<td></td>
<td>Opiate system dysregulation; increased endogenous opiates</td>
<td>Diffusely in prefrontal cortex, limbic areas, postpituitary areas</td>
<td>Autistic or schizoid relational patterns; disruption of affiliation Increased social anxiety in opioid abusers</td>
</tr>
</tbody>
</table>

The neurohormone oxytocin is well established in the initiation but not the maintenance of maternal behavior and pair bonding (29), as well as in social interactions in nonhuman primates (30). Recent data from Insel and Winslow (29) demonstrated that a genetically engineered mouse lacking oxytocin emitted few isolation calls and had reduced social interactions. They hypothesized that the neural substrates of attachment are “those pathways which couple social recognition (olfactory, auditory, and visual stimuli) to the neural pathways for reinforcement, such as the [dopaminergic] mesolimbic projections from the ventral tegmental area to the nucleus accumbens and prefrontal cortex” (p. 888). It is known that dopaminergic neurotransmission is implicated in brain reward pathway projections. Social anxiety disorder, as Stein (31) suggested, might therefore be an illness “characterized by dysfunction within the system(s) that evaluate(s) the risks and benefits of social affiliation” (p. 1280) by employment of brain reward pathways. Anatomically, many of these disparate attachment pathways traverse the anterior cingulate, a region recently implicated by functional magnetic resonance imaging (fMRI) in an aspect of the human maternal-infant bond: the response to infant cries (32). In summary, animal attachment models implicate not only oxytocin, but varied serotoninergic, opioid, and dopaminergic pathways.

Although they are incomplete in explaining the varied cognitive misappraisals observed in patients with social anxiety disorder, preclinical attachment models provide a useful construct for understanding the aberrant social affiliativeness seen in subjects with social anxiety disorder and provide guides for future investigations of the clinical neurobiology of the disorder. Unfortunately, the amount of replicated data in primate attachment neurobiology is extremely sparse, particularly in neuroimaging. Thus, the direct applicability of these animal models to social anxiety disorder is necessarily limited at this time. (See Table 1 for a summary of preclinical models of social anxiety disorder.)

anxiety disorder and the broad autism phenotype (defined as milder aspects of autism, including social and communication deficits and stereotypical repetitive behaviors). These studies point to a shared biology of attachment, which makes the neurobiology of animal attachment potentially more relevant to social anxiety disorder than previously acknowledged.

Numerous neurotransmitter systems have been investigated clinically in subjects with autism and preclinically in primate models of attachment and affiliation. Raleigh and colleagues (23) showed that enhancement of serotonergic function resulted in improved social affiliativeness in primates, whereas low serotonin levels promoted avoidance. In separate but related work, free-ranging primates with low levels of CSF 5-HIAA showed less social competence and were more likely to emigrate at a younger age from their social groups than primates with higher levels of CSF 5-HIAA (24).

The brain opioid system was the first neurochemical system to be implicated as a regulator of attachment behaviors in primates and other species. In one study of nonhuman primates (25), 10 juvenile macaques living in a stable social group with their mothers and other group companion subjects were administered naloxone, an opiate antagonist. The primates receiving naloxone made more grooming solicitations and received more grooming and increased their proximity with their mothers. Kalin et al. (26) studied reunions of nonhuman primate infants after separations from their mothers and demonstrated that both infants and mothers who were administered morphine showed a significant reduction in clinging behaviors, whereas those given naltrexone increased their clinging. Finally, there was evidence of complex interrelationships between endogenous opioid activity and other affiliative neurotransmitter systems, as it was suggested that opiate activity was increased by oxytocin injections in the rat (27). Clinically, there is some evidence that opioid abusers have high rates of social avoidance and anxiety (28).
Neurodevelopmental Issues

Neuroplasticity, Neurogenesis, and Social Dominance

The explosion of research in neurodevelopment has afforded the opportunity of taking a specific animal model of anxiety, such as one concerned with dominance or subordination stress, and investigating its neurobiological correlates by means of in vivo neuroimaging or postmortem tissue sampling. One of the more important findings in human neurobiology in the past decade is accumulating evidence for the remarkable plasticity of the brain and the development of neurogenesis in diverse brain regions, such as the cortex, hippocampus, cerebellum, and olfactory bulb (33). Gould et al. (34) demonstrated altered neuroplasticity in tree shrews in an enduring dominant-subordinate relationship derived from a social dominance paradigm (35). Specifically, her group showed a rapid decrease in the number of new cells produced in the dentate gyrus of subordinate tree shrews compared to those who remained unexposed to a stressful experience (34). This finding was more recently replicated in marmoset monkeys by using a resident intruder paradigm, a psychosocial stress model similar to that of the dominant-subordinate model for the tree shrews (36). At this time, we do not know the nature of neuroplastic changes in the brains of human infants with early signs and symptoms of social anxiety; thus, the translational implications of stress-induced decreases in granule cell production in animal models is unknown. However, a recent study has shown that granule neurons are potentially involved in hippocampal-dependent learning tasks (37) and that consequent decreases in the number of granule neurons are likely to alter adult hippocampal formation (37). Stressful experiences, which increase levels of circulating glucocorticoids and stimulate hippocampal glutamate release (38), might thus inhibit granule cell neurogenesis. In adult social anxiety, we hypothesize that excessive glutamatergic transmission in hippocampal and cortical regions might be a key component of the dysfunctional circuitry, and successful treatments might serve to prevent the inhibition of neurogenesis while modifying glutamatergic neurotransmission.

Although most animal studies have focused on hippocampal formation, there is evidence that stressors affect cortical neurons as well (39). Neuroplastic changes are also dependent on levels of neurotrophins, such as nerve growth factor, which is known to be differentially modulated by experience (40). In fact, drugs such as the selective serotonin reuptake inhibitors (SSRIs), useful in treating social anxiety, are known to increase expression of brain-derived neurotrophic factor in the hippocampus (41, 42).

Course and Neural Circuitry of Precursors

Given the remarkable developmental plasticity of key neural structures, there is considerable interest in delineating the fear and anxiety circuitry across the stages of development (43, 44). Longitudinally, recent work has confirmed that a significant number of children classified as “inhibited” will develop generalized social anxiety by young adulthood (45, 46). Kagan (47) noted that 4-month-old infants who had a low threshold for becoming distressed and motorically aroused to unfamiliar stimuli were likely to become fearful and subdued in early childhood. Similarly, children identified as behaviorally inhibited at 21 months who remained inhibited at subsequent follow-up visits at ages 4, 5.5, and 7.5 years, showed higher rates of anxiety disorders than children who were not behaviorally inhibited (48), although the findings were not specific for social anxiety. However, a more recent prospective study by Pine et al. (43) has suggested a more specific association between childhood and adult social phobia, a finding consistent with those of family studies among adults (49).

The identification of neurobiological correlates to adult social anxiety disorder in children helps validate clinical and epidemiological observations linking behaviorally inhibited children with adult patients (50). The most notable neurobiological correlates of clinical observations have been the brain laterality studies performed in high-reactive and inhibited children (51, 52) and in animals (53). Davidson (52, 54) demonstrated in infants and adults that withdrawal-related emotions, such as anxiety, were associated with activation of the right frontal region, whereas left prefrontal cortex activation was related to approach-related emotions. Adult patients with social anxiety disorder showed a large increase in activations in right anterior temporal and lateral prefrontal scalp regions when anticipating making a speech in relation to comparison subjects (52, 55). In related preclinical work, EEG recordings in fearful rhesus macaques demonstrated relatively higher right frontal lobe activity, elevated cortisol and CSF CRF concentrations, and more intense defensive responses (53, 56). Although these findings are interesting, they might be relatively disorder nonspecific, in that Rauch et al. (57) demonstrated increased activation in the right inferior frontal cortex, among other regions, across three anxiety diagnoses (obsessive-compulsive disorder [OCD], PTSD, and simple phobia) in a PET symptom-provocation paradigm. Thus, although the epidemiological links between behavioral inhibition and adult social anxiety disorder appear to be validated by common regional alterations in brain activity, the biological associations might be disorder nonspecific.

Genetics of Social Anxiety Disorder

Although there is increasing evidence that social anxiety disorder and its childhood variants, including behavioral inhibition and shyness, have a strong familial basis, the genetics of the disorder have not been adequately studied. Several early studies (58, 59) established a familial link, but
only for the generalized subtype (59). It was reported that if a proband has a diagnosis of social anxiety disorder, the percentage of first-degree relatives with the illness was 15%, which was greater than the 10% finding in subjects with agoraphobia and less than the 31% seen in subjects with simple phobia (49). Subsequently, a larger study (60) showed that the generalized subtype was markedly increased in frequency (approximately 10 times greater) among first-degree relatives of generalized social phobic probands. Another study (61) demonstrated that the children of patients with social anxiety disorder were at an increased risk of developing this disorder and other anxiety disorders.

The low genetic concordance rates for social anxiety disorder in monozygotic twins (62) have suggested that genetics plays a limited role in its development. As we suggested for panic disorder (1), what appears to be inherited is a susceptibility to social anxiety, not the disorder itself. Although no systematic genetic linkage studies employing a genomic scan or search among candidate genes have been conducted for social anxiety disorder so far, such studies are underway for panic disorder (63) and OCD (64). Likewise, molecular genetic studies of candidate genes for the several neurotransmitter systems implicated in social anxiety, notably the serotonin transporter and dopamine receptor and their various subtypes, have allowed for associations between specific genes and behavioral traits, such as harm avoidance and novelty seeking (65, 66)—characteristics relevant to the social anxiety disorder phenotype. Thus, genetic and family studies in social anxiety disorder are still in their infancy but support longitudinal clinical data that are suggestive of links between childhood and adult variants of the disorder.

Clinical Neurobiology of Social Phobia

The two primary tools for the neurobiologist investigating social anxiety disorder have been pharmacological probes and, more recently, neuroimaging. In examining the clinical neurobiological literature, we attempt to highlight data that replicate preclinical experiments, if possible, although few such studies have been performed.

Pharmacological Probes

Challenge studies have shown abnormalities in monoamine (dopamine, norepinephrine) and indoleamine (serotonin) neurotransmission. Of the serotonergic studies, Tancer et al. (10) reported an augmented cortisol response to fenfluramine in patients with social anxiety relative to comparison subjects, a finding similar to that observed in subjects with panic disorder. Hollander et al. (67) reported increased anxiety responses to the serotonergic probe mCPP but there were no notable neuroendocrine alterations. In studying dopamine function, Tancer’s group (10) did not find any abnormality of dopaminergic function when using L-dopa as the pharmacological probe (see Appendix 1 for a summary of dopaminergic abnormalities observed in social anxiety disorder [68–72]). Other probes commonly used in studies of panic disorder, such as CO2, lactate, pentagastrin, and epinephrine, generally have produced an intermediate response, between those of patients with panic disorder and comparison subjects, in patients with social anxiety disorder (73, 74). A recent report by Pine et al. (75) revealed a lack of association between CO2 sensitivity and childhood social phobia, which is consistent with studies finding no association between childhood social phobia and adult panic disorder (76). We conclude from these limited studies that there exists an overlapping but distinct neurobiology of social anxiety disorder and panic disorder.

Norepinephrine in Social Phobia

Since autonomic hyperarousal (manifested by flushing, tachycardia, and tremulousness) is a common symptom of patients with panic anxiety and social anxiety in performance situations, understanding autonomic nervous system function in these patients might shed light on the dysfunctional circuitry involved in social anxiety disorder. Stein et al. (77) performed an orthostatic challenge test in patients with social anxiety disorder, panic disorder, and healthy comparison subjects and found that the first group had higher plasma levels of norepinephrine before and after the challenge. This finding was not replicated in a subsequent study comparing subjects with social phobia with normal comparison subjects, and in fact there was a suggestion of impaired parasympathetic (not sympathetic) activity in the group with generalized social anxiety disorder in relation to comparison subjects (78).

Limited data have suggested that the α2 adrenergic antagonist yohimbine increases social anxiety in patients with social anxiety disorder and is associated with increased plasma 3-methoxy-4-hydroxyphenylglycol concentrations (79). In contrast, Papp et al. (80) infused intravenous epinephrine in patients with social anxiety disorder and observed that only one out of 11 patients experienced observable anxiety, which suggests that an increase in plasma epinephrine levels alone is inadequate to cause social anxiety. Notably, Tancer et al. (81) observed a reduced GH response to intravenous, but not oral, clonidine, an α2 adrenergic agonist. The blunted GH response to clonidine is also observed in subjects with panic disorder, major depressive disorder, and generalized anxiety disorder and is thought to possibly reflect reduced postsynaptic adrenergic-2 receptor functioning owing to norepinephrine overactivity. Alternatively, Coplan et al. (16) hypothesized that the blunted GH response to clonidine or other GH secretagogues may reflect an increased central activity of the fear-inducing neuropeptide CRF. In summary, although there are limited data on the role of autonomic nervous system dysfunction in social anxiety, the autonomic hyperarousal
observed clinically in some patients bespeaks an underlying dysregulation of the autonomic nervous system.

**Neuroimaging**

Neuroimaging studies to date have primarily focused on basal ganglia or striatal pathology and have shown preliminary evidence of impaired dopaminergic functioning in these regions. The interest in these specific brain regions followed accumulating clinically based evidence of dopaminergic deficits in social anxiety disorder (Appendix 1). Neuroanatomically, of the four major dopamine pathways in the CNS, dysfunctions of the mesocortical and mesolimbic (ventral striatal, including the nucleus accumbens) pathways appear most relevant to social anxiety, with a presumed lesser importance of tuberoinfundibular and nigrostriatal (dorsomstriatal) pathways, although published imaging studies do not provide sufficient spatial resolution to make this determination.

A study by Tiihonen et al. (82) reported a decrease in striatal dopamine reuptake sites on SPECT in patients with social anxiety disorder compared to normal volunteers, which suggests a deficit of dopaminergic innervation into the striatum. The authors suggested that the lowered dopamine reuptake site density reflects an overall smaller number of dopaminergic synapses and neurons in the striatum of patients with social anxiety disorder. The recent [123I]-iodobenzamide ([123I]IBZM) SPECT study of Schneier et al. (5), which showed reduced mean D2 receptor binding in the striatum, implicate dopaminergic hypofunction in the striatum. However, the interpretation of this report is difficult to reconcile with the report by Tiihonen et al. of decreased dopamine transporter binding, in that decreased binding potentials of the SPECT radiotracer [123I]IBMZ could also reflect increased levels of free dopamine in the vicinity of D2 receptors, altered affinity of D2 receptors for dopamine, or some combination of these factors. It was recently argued that SPECT or PET studies measuring dopamine binding after changes in synaptic dopamine levels are probably more complex than accounted for by simple binding occupancy models and might involve changes in the subcellular distribution of receptors (83). Indeed, most of the variance in D2 receptor binding appears to be due to alterations in receptor expression, whereas endogenous dopamine levels contribute to only about 10%–20% of the variance (personal communication, Marc Laruelle, M.D., 2001).

Most neuroimaging studies not specifically focusing on dopamine systems have detected basal ganglia and cortical abnormalities, and one study suggested amygdala involvement. Using magnetic resonance spectroscopy (MRS), Davidson et al. (84) reported a decrease in choline and creatine signal-to-noise ratios in the subcortical, thalamic, and caudate areas, as well as lowered N-acetylaspartate signal-to-noise ratios in cortical and subcortical regions, which was interpreted as possible neuronal atrophy and degeneration. The use of signal-to-noise ratios and limited spatial resolution were notable limitations of this study, as more recent MRS studies have analyzed the ratios of metabolites (85). Potts et al. (86) showed in another MRS study that patients with social anxiety disorder had a greater decrease in putaminal volumes during aging than normal comparison subjects. In studies of cerebral blood flow (CBF), Stein and Leslie (87) found no basal metabolic cerebral differences between patients and comparison subjects on SPECT, which indicated that any posited subcortical abnormality might not affect resting metabolism. Bell et al. (88), in a symptom-provocation study measured by means of H215O-labeled PET, reported an array of anxiety-related changes but stated that the changes specific to social anxiety disorder included increased regional CSF in the right dorsolateral prefrontal cortex and left parietal cortex. Finally, a recent fMRI study (89) implicated the amygdala in the pathophysiology of social anxiety, suggesting the generation of a hypersensitive amygdala when patients are exposed to potentially fear-relevant stimuli. In this study, neutral face stimuli elicited greater amygdala activity bilaterally in patients versus comparison subjects, despite knowledge that the neutral faces were not harmful, as shown by subjective ratings of anxiety. The causal relationship between fear elicitation and amygdaloid activation is unclear; however, this preliminary study is the first direct evidence for a role of the amygdala in social anxiety disorder.

In summary, there are few replicated neuroimaging studies to date regarding social anxiety disorder, but the convergence of data thus far implicates basal ganglia structures, the amygdala, and varied cortical regions. SPECT studies of the dopamine transporter and D2 receptor in the striatum thus far are inconclusive in confirming a hypothesis of low dopamine innervation. Recent initiatives, such as the development of a PET D2 receptor agonist ligand (90), which allows for direct determinations of neurotransmitter-D2 receptor interactions, will potentially provide valuable information on the role of this receptor in social anxiety disorder.

**Conclusions**

There are many unanswered questions regarding the neurobiology of social anxiety disorder. Given our assertion that social anxiety disorder should be conceptualized as a chronic neurodevelopmental illness beginning in childhood, several issues require further inquiry. First, we have no knowledge of studies examining the use of early identification and treatment of social anxiety disorder and its comorbid disorders and childhood precursors. Childhood social anxiety disorder is often comorbid with generalized anxiety disorder or separation anxiety disorder (91), and these comorbid forms of the illness have a greater association with panic disorder (92). Comparisons of laboratory neurobiological and neuroimaging measures of suc-
cessfully treated patients with early intervention and successfully treated patients who were managed only in adulthood would be of interest, as would analyses of treatment responsivity across comorbid subgroups. Such secondary prevention studies might be the natural extension of longitudinal studies of behaviorally inhibited children.

Second, a better understanding of the developmental neurobiology of the brain regions important in social anxiety, such as the amygdala and striatum, and their interactions with the cortex, ascending monoaminergic systems, and hippocampus, clearly is necessary. Related to this objective neurodevelopmental genetic research, we should attempt to target susceptibility genes for the broad social anxiety phenotype. We have a limited understanding of the interaction between genetic vulnerability and stress exposure in socially anxious individuals. Cross-fostering paradigms in which primates raised under the variable-foraging-demand condition are randomly assigned to the offspring of either socially withdrawn or socially competent mothers might help answer the question of whether stress exposure has a more pernicious effect on genetically susceptible individuals.

Third, MRS imaging can be used to study neurotransmitter systems that have not received extensive attention in social anxiety, such as the glutamatergic system. Preclinical rodent models contend that prefrontal cortical efferents, either directly or by means of thalamic nuclei efferents, use the glutamatergic system as a primary source of neuronal stimulation of the “fear” neurocircuitry, which originates from the central nucleus of the amygdala and bed nucleus of the stria terminalis (93, 94). Stressful situations faced by a person with social anxiety disorder might stimulate glutamate release in hippocampal (38) and other brain regions. In this light, agents that attenuate glutamatergic neurotransmission should reduce anxiety levels, as well as the concomitant biochemical alterations associated with stress. Clinical investigations of glutamatergic antagonists might be warranted, since the SSRIs have been only partially successful in the treatment of this disorder. MRS also allows investigators to explore neurotransmitter interactions in vivo, such as the interaction between serotonin and glutamate, elegantly recently explored by Rosenberg et al. (95) in pediatric OCD.

Finally, an important limitation of our understanding of the neurobiology of social anxiety is the difficulty in discriminating what findings are a response to anxiety or stress and what are true risk factors for the development of anxiety. It is of importance that the clinical neuroendocrinology of social anxiety suggests a fully compensated state in adulthood, in that no peripheral (i.e., HPA axis) pathology is evident. In this light it would be of interest to study patients with a recent onset of social anxiety disorder versus patients with distant onset in order to gauge which neuroendocrine findings persist and which ones change over the course of the illness. Another important contrast would be to study patients with active social anxiety disorder versus patients in remission. A more refined understanding of this compensatory phenomenon might offer valuable insights not only into social anxiety disorder but into other psychiatric disorders with prominent neuroendocrine abnormalities as well.

APPENDIX 1. Preclinical and Clinical Evidence for Dopaminergic Dysregulation in Social Anxiety

- Low striatal dopamine D2 binding in primate subordinates (shown by PET) (4) and in humans with generalized social anxiety disorder (shown by SPECT) (5)
- Decreased dopamine reuptake site density in the striatum (82)
- Lower CSF levels of HVA in patients with panic disorder and comorbid social anxiety disorder (68)
- High association with Parkinson’s disease (69)
- Increased phobic symptoms during haloperidol treatment in patients with Tourette’s disorder (70)
- Response to MAOIs (71) but not to tricyclic antidepressants (72)

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