Social Anxiety Disorder and Generalized Anxiety Disorder: Serotonergic and Dopaminergic Neurocircuitry

Dan J. Stein, M.D., Ph.D.; Herman G. M. Westenberg, Ph.D.;
and Michael R. Liebowitz, M.D.

Awareness that an amygdala-based fear circuit plays a crucial role in mediating fear conditioning as well as anxiety symptoms is growing. The efficacy of selective serotonin reuptake inhibitors in certain anxiety disorders has been argued to reflect their ability to modulate this circuit. Whether additional neurocircuits play a differentiating role in specific anxiety disorders, such as social anxiety disorder and generalized anxiety disorder (GAD), is an ongoing subject of investigation. A review of the literature suggests that in social anxiety disorder, dopaminergically mediated striatal circuits may also be important, while in GAD, there may be abnormalities of prefrontal areas. Future work will undoubtedly clarify how genetic and environmental factors interact to fashion the neurocircuitry that mediates anxiety symptoms.

(J Clin Psychiatry 2002;63[suppl 6]:12–19)

Social anxiety disorder and generalized anxiety disorder (GAD) are not only highly prevalent (Table 1) but are characterized by significant chronicity, comorbidity, and disability. Indeed, given the clinical importance of these conditions, their neurobiology has received relatively little attention to date. Future advances in treating these disorders may well require a more detailed understanding of their neuroanatomical and neurochemical underpinnings.

Some work on the neurobiology of social anxiety disorder and GAD has been driven by pharmacotherapeutic findings. Clinical trials demonstrating the efficacy of selective serotonin reuptake inhibitors (SSRIs) in social anxiety disorder and GAD, for example, provide encouragement for investigating the role of the serotonin neurotransmitter system. Nevertheless, therapeutic response per se may only be a rough guide to determining underlying dysfunction; the neurobiology of social anxiety disorder and GAD is likely to involve a complex cascade of factors.

Working from a different starting point, a basic literature on the neurobiology of anxiety has suggested a number of leads for studying social anxiety disorder and GAD. In particular, there have been important advances in clarifying the amygdala-based neuroanatomy of fear conditioning[1,2] and in applying this to understanding anxiety symptoms.[3] The question of whether social anxiety disorder and GAD are differentially mediated by additional circuits is receiving ongoing attention.

In this review, we discuss research relevant to understanding the neurocircuitry of social anxiety disorder and GAD. We focus in particular on the role of the serotonergic and dopaminergic systems in modulating the neurocircuitry thought to underpin these disorders. Although the review will not primarily cover environmental contributors to social anxiety disorder/generalized anxiety disorder or psychosocial interventions, it should be emphasized at the start that these phenomena are also able to modulate the relevant neurocircuitry.

NEUROCIRCUITRY OF FEAR CONDITIONING

An elegant body of animal work has allowed the neurocircuitry of fear conditioning to be specified in detail.[1,2] The amygdala appears to play a crucial role; lesions to the amygdala disrupt the acquisition of conditioned responses but do not affect the learning of relevant declarative facts.

Table 1. Prevalence of Social Anxiety Disorder and
Generalized Anxiety Disorder in Selected Studies

Study	Social Anxiety Disorder (%)	Generalized Anxiety Disorder (%)
Epidemiologic Catchment Area[a]	3.8	4.2
National Comorbidity Survey[b]	13.3	3.8

[a]Data from Davidson et al.[117]
[b]Data from Kessler et al.[118]

The hippocampus is important in processing the context of the fear conditioning; hippocampal lesions disrupt the learning of relevant facts but do not affect the acquisition of conditioned responses.[4]

Afferents from the thalamus to the lateral nucleus of the amygdala allow rapid transmission of fear-relevant sensory information. Efferents from the central nucleus of the amygdala include the lateral nucleus (autonomic arousal and sympathetic discharge) and paraventricular nucleus (increased adrenocorticoid release) of the hypothalamus, locus ceruleus (increased norepinephrine release), parabrachial nucleus (increased respiratory rate), and periaqueductal gray matter (defensive behaviors and postural freezing) in the brain stem.

There are several reasons for suspecting that these circuits may be relevant to a range of anxiety disorders. Panic attacks, which are seen in panic disorder, but also in social anxiety disorder and other conditions, would appear to be analogues of amygdala-mediated fear responses.[3] Furthermore, patients with social anxiety disorder may report that their fears developed or became further entrenched in the aftermath of experiencing unpleasant social situations (conditioned fear).[5]

Panic attacks may, however, emerge spontaneously in the absence of a reported history of fear conditioning. Genetic factors, for example, may contribute to a decreased threshold for triggering fear responses in patients with anxiety disorders. Certainly, the basic literature indicates that fear conditioning occurs more readily in some animal strains than in others.[3] Similarly, the clinical literature has increasingly documented not only that social anxiety disorder and GAD are familial disorders, but also that possibly predisposing traits such as shyness or behavioral inhibition have a heritable component.[5]

In addition, a range of relatively nonspecific factors may lower the threshold for triggering anxiety symptoms. Various agents have been used to provoke symptoms in social anxiety disorder including lactate, CO_2, caffeine, cholecystokinin/pentagastrin, epinephrine, yohimbine, and flumazenil.[6–18] This work has been reviewed in detail elsewhere[19–23]; in general, such panicogens provoke anxiety in social anxiety disorder more than in healthy controls, but less than in panic disorder. It has been suggested that in panic disorder there is nonspecific activation of a general fear circuit. It would seem that the same holds for social

anxiety disorder, albeit to a lesser degree. Some of this work also suggests that patients describe their anxiety after panicogens as differing in nature from social anxiety symptoms, suggesting that additional, more specific circuits may mediate social anxiety disorder.

Conversely, a range of different interventions may be used to increase the threshold for anxiety. Benzodiazepines, for example, in animal anxiety models and many psychiatric disorders can be shown to decrease symptoms. More unusually, amygdala lesions[24] or genetic abnormalities[25] may lead to loss of fear or hypersociability. *Desensitization* refers to the process whereby conditioned fears are "unlearned"; this is thought to be mediated by medial prefrontal cortex.[1] Slower fronto-amygdala circuits are able to override more rapid thalamo-amygdala ones (although the latter may be prone to reactivation should exposure to fear cues recur).
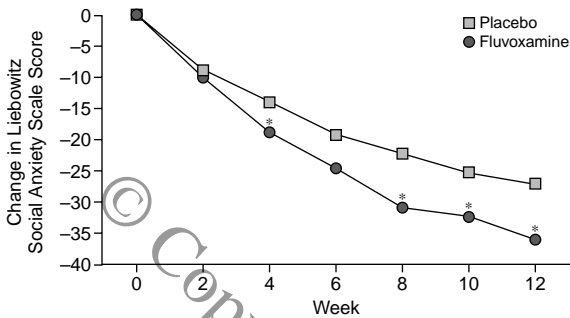
Although imaging studies in social anxiety disorder and GAD remain at a preliminary stage, there is some evidence that patients with social anxiety disorder demonstrate selective activation of the amygdala when exposed to fear-relevant stimuli[26] or tasks,[27] or show abnormal patterns of amygdala activation during aversive conditioning.[28] An early topographic electroencephalogram study indicated differences between GAD and healthy controls in temporal regions,[29] and subsequent positron emission tomographic (PET) studies have also shown temporal abnormalities in this disorder.[30] More recently, amygdala volumes were shown to be significantly larger in pediatric patients with GAD than in controls.[31]

Furthermore, involvement of amygdala-based neurocircuits is consistent with some of what we know about the neurochemistry of these disorders. In the next sections, we focus on the role of the serotonin and dopamine neurotransmitter systems in particular.
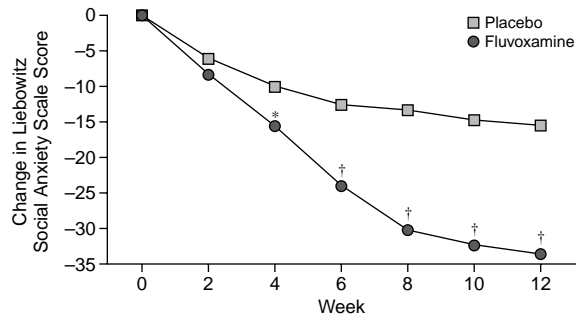
SEROTONIN, SOCIAL ANXIETY DISORDER, AND GAD

A growing database demonstrates that SSRIs are effective and well tolerated in a range of anxiety disorders, including social anxiety disorder[32] and GAD.[33] In some of the most recent work, fluvoxamine controlled release (CR), a slow-release SSRI, was studied in social anxiety disorder in 2 large double-blind, placebo-controlled multisite studies (Figures 1 and 2). In the European and South African study,[34] medication efficacy was apparent on the Liebowitz Social Anxiety Scale (LSAS), with significant separation from placebo as early as week 4 and further improvement in the LSAS until the end of the 12-week study. In the United States study,[35] medication was more effective than placebo on the LSAS and the Clinical Global Impressions-Severity of Illness scale. Interestingly, in both studies, sexual function, as measured by the Arizona Sexual Experience Scale, did not significantly differ

Figure 1. Fluvoxamine Controlled Release (CR) in Social Anxiety Disorder: Intent-to-Treat Analysis of Data From a Multisite, Placebo-Controlled Study in Europe and South Africa[a]

[a]Data from Westenberg.[34]
*p < .05.

Figure 2. Fluvoxamine Controlled Release (CR) in Social Anxiety Disorder: Intent-to-Treat Analysis of Data From a Multisite, Placebo-Controlled Study in the United States[a]

[a]Data from Davidson et al.[35]
*p < .05.
†p < .001.

between fluvoxamine CR and placebo for the entire treatment period.

Buspirone, a 5-HT$_{1A}$ agonist, has also been reported helpful in these disorders, but in social anxiety disorder, controlled data have shown a lack of efficacy.[36] Although response to SSRIs cannot be taken to imply an underlying serotonergic dysfunction in these disorders, it is certainly consistent with the hypothesis that the serotonin system plays an important role in mediating fear conditioning and anxiety symptoms.

Indeed, there is evidence that serotonin plays a crucial role at several points in the amygdala-based fear conditioning pathways.[37] First, serotonergic projections from the dorsal raphe nucleus generally inhibit the locus ceruleus, while projections from the locus ceruleus stimulate the dorsal raphe nucleus serotonergic neurons and inhibit median raphe nucleus neurons. Furthermore, the dorsal raphe nucleus sends projections to prefrontal cortex, amygdala, hypothalamus, and periaqueductal gray matter among other structures. Thus, modulation of the serotonin system can act to decrease noradrenergic activity, diminish the release of corticotropin-releasing factor, and modify defense/escape behaviors.

A number of other reasons exist for believing that the serotonin system plays an important role in social anxiety disorder and GAD. Dominance and submission behaviors may be important to social anxiety disorder, and serotonin plays a role in mediating these behaviors in animal models (increased serotonergic function appears to be associated with increased dominance in primates).[38–40] Although the data are not entirely consistent, administration of SSRIs to healthy humans may result in increased social affiliation.[41] In animal studies more reminiscent of GAD, serotonin hypofunction is associated with hypersensitivity to environmental cues and increased responsiveness to threat.[42] In the social interaction test, which may also be a model of GAD,[43] SSRIs have anxiolytic effects.[44]

Table 2. Serotonergic Challenges in Social Anxiety Disorder

Agent	Observations
Fenfluramine[a]	No difference in prolactin; increased cortisol
m-CPP[b]	No difference in prolactin; increased anxiety

[a]Data from Cheeta et al.[43]
[b]Data from Lightowler et al.[44]

There is no evidence for differences in static peripheral measures of serotonin in social anxiety disorder.[45,46] A number of studies[46,47] have, however, used a "pharmacologic challenge" paradigm to investigate serotonin function, and these have suggested possible dynamic dysfunction[4] (Table 2). In GAD, reduced cerebrospinal fluid (CSF) levels of serotonin and reduced platelet paroxetine binding have been observed.[48] Furthermore, administration of the serotonergic agonist m-chlorophenylpiperazine resulted in increased anxiety and hostility.[49]

More recently, a number of studies have investigated serotonin genetic polymorphisms in anxiety disorders. A low-activity polymorphism of the serotonin transporter protein may be associated with anxiety-related traits,[50] although studies in social anxiety disorder have not demonstrated that this particular polymorphism is relevant in this condition.[51]

DOPAMINE, SOCIAL ANXIETY DISORDER, AND GAD

Despite the putative importance of serotonergic modulation of the amygdala-based fear-conditioning neurocircuitry, it is likely that other circuits are also important in mediating social anxiety disorder and GAD. The selective response of social anxiety disorder and atypical depression (with rejection sensitivity) to monoamine oxidase inhibitors rather than tricyclics[52,53] provides some basis for considering the role of the dopamine system in social anxiety.

Table 3. Role of Dopamine in Social Anxiety Disorder[a]

Low dopamine levels in timid mice[54]
Decreased striatal D_2 density in low status monkeys[55]
CSF HVA decreased in introverted depressives[56]
CSF HVA decreased in patients with comorbid social anxiety disorder[57]
10-Repeat allele of dopamine transporter gene associated with social anxiety disorder[63]
D_2 agonist hyporeactivity associated with less positive emotionality[64]
D_2 and dopamine transporter binding lower in more detached subjects[65–67]
D_2 and dopamine transporter polymorphisms associated with schizoid/avoidant behavior[68]
D_4 short allele associated with decreased novelty seeking[69]
Social anxiety is increased in Parkinson's disease[58–60]
Dopamine blockers may increase social anxiety[61,62]
Selective efficacy of monoamine oxidase inhibitors over tricyclic antidepressants in social anxiety disorder/rejection sensitivity[52,53]
Imaging studies of patients with social anxiety disorder suggest dopamine hypofunction[71,72]

[a]Abbreviations: CSF = cerebral spinal fluid, HVA = homovanillic acid.

Several additional reasons exist for thinking that dopamine may be involved in social anxiety disorder (Table 3). First, dopamine levels are reduced in timid mice[54] and striatal dopamine D_2 binding is decreased in lower social status monkeys.[55] Second, in patients with depression, low CSF dopamine correlated with a measure of introversion[56] and CSF homovanillic acid (HVA) tended to be lower in patients with panic disorder with social phobia than in those without.[57] Third, there may be an association between social anxiety disorder and subsequent risk for Parkinson's disease (in which there is decreased striatal dopamine).[58–60] Fourth, patients treated with dopamine-blocking agents may develop an increase in social anxiety symptoms.[61,62] While response to levodopa did not differ in social anxiety disorder and healthy controls,[46] this study may have had methodological limitations.

The crucial question of whether putative dopaminergic dysfunction in social anxiety disorder has a genetic basis has gradually begun to be explored. There appears to be an association between the 10-repeat allele of the dopamine transporter gene and symptoms of social anxiety disorder, GAD, and Tourette's disorder in children.[63] Also, there is an association between decreased dopamine D_2 receptor agonist reactivity and reduced "positive emotionality,"[64] between low striatal dopamine D_2 binding[65,66] or dopamine transporter binding[67] and detachment, between certain dopamine D_2 and dopamine transporter polymorphisms and schizoid/avoidant behavior,[68] and perhaps between short dopamine D_4 alleles and decreased novelty seeking[69] (although findings are not entirely consistent,[69,70] and it is not yet clear to what extent such constructs relate to social anxiety per se).

More recently, functional brain imaging has provided the strongest evidence to date that the dopamine system plays a significant role in mediating social anxiety disorder. A study of the density of dopamine reuptake sites found that striatal dopamine reuptake site densities were markedly lower in patients with social anxiety disorder than in healthy controls.[71] Furthermore, striatal D_2 receptor binding was lower in social anxiety disorder than in controls.[72] Taken together, these findings would suggest that social anxiety disorder is characterized by decreased dopamine function.

In terms of GAD, a long literature indicates that dopamine blockers may be useful for chronic anxiety. However, few controlled trials have been done in this area.[73] Furthermore, few studies have focused specifically on dopaminergic function in this disorder.

OTHER SYSTEMS

Many additional neurochemical systems may play a role in mediating social anxiety disorder and GAD. As indicated earlier, the response of social anxiety disorder to agents from a number of different medication classes would certainly seem to support such a view. Here we briefly review only a few potential candidates.

In terms of other aminergic neurotransmitter systems, there is some evidence for involvement of the noradrenergic system in social anxiety disorder and GAD. Animal work has long demonstrated the involvement of the locus ceruleus-norepinephrine-sympathetic nervous system in fear and arousal.[74] Early work found that healthy volunteers had an increase in epinephrine after public speaking, but an increase in norepinephrine after physical exercise.[75,76] Patients with nongeneralized social anxiety disorder have an increased heart rate response to public speaking, compared with patients with generalized social anxiety disorder[77–79] and healthy controls.[78,79] Patients with social anxiety disorder had higher plasma norepinephrine levels before and after orthostatic challenge compared with patients with panic disorder or healthy controls,[80] but in a subsequent study, this was not replicated.[81] Similarly, β-adrenergic receptor kinetics did not differ in social anxiety disorder and controls,[82] clonidine administration yielded inconsistent results,[46,83] and β-blockers were effective in performance anxiety but not in generalized social anxiety disorder.[53]

In clinical studies of GAD, increased plasma norepinephrine and 3-methoxy-4-hydroxyphenylglycol[84] and reduced platelet $α_2$-adrenergic peripheral receptor binding sites have been reported,[85,86] although not all studies have been consistent. Administration of more dynamic adrenergic probes has, however, indicated reduced adrenergic receptor sensitivity in GAD, perhaps an adaptation to high circulating catecholamines.

Involvement of the γ-aminobutyric acid (GABA)/benzodiazepine receptor complex in GAD is supported by a number of studies, including the responsiveness of this disorder to benzodiazepine treatment. Thus, anxious subjects and GAD patients[87] demonstrate reduced benzodiazepine binding capacity, with normalization of findings

after benzodiazepine treatment. GABA is the brain's predominant inhibitory neurotransmitter (whereas glutamate is the predominant excitatory neurotransmitter), and GABAergic pathways are widely distributed; nevertheless, there is a particularly dense distribution of GABA/benzodiazepine receptors in limbic and paralimbic areas. The effectiveness of benzodiazepines and of gabapentin in social anxiety disorder, as well as the high comorbidity with alcohol use disorders, suggests that GABA/glutamate receptors also deserve study in this disorder.

Animal studies suggest that social submissiveness may result in hypercortisolism, leading to the hypothesis that the experience of distress in social anxiety disorder may also be accompanied by endocrine or immunologic abnormalities.[23] Studies of the hypothalamic-pituitary-adrenal axis in social anxiety disorder have not, however, demonstrated dysfunction,[88–90] although in behaviorally inhibited or shy children there may be increased cortisol.[91–93] Thyroid function appears normal in social anxiety disorder, although administration of thyrotropin-releasing hormone may result in greater increases in blood pressure.[94] Despite the predominance of anxiety disorders in women, there has been little specific evidence of a role for sex hormones in mediating these conditions. Uhde[95] has elsewhere reviewed several lines of evidence to suggest an association between social anxiety, growth hormone deficiency, and short stature, a potential link that deserves further inquiry.

Various neuropeptides have been postulated to contribute to mediating social anxiety disorder and GAD symptoms.[96] The finding that oxytocin plays a crucial role in mediating social "space" has led to the suggestion that it may play a role in social anxiety disorder in particular.[97] It is possible that oxytocin acts at dopaminergically mediated pathways that determine whether social stimuli are reinforcing.[23] The observation that blushing is important in social anxiety disorder suggests that further investigation of the neurobiology of this response[98,99] may be relevant to understanding social anxiety disorder.

Finally, given our growing understanding of the complexities of psychoneuroimmunology, additional work to advance our understanding of the immune system in social anxiety disorder and GAD is needed.[100,101]

INTEGRATION

We have emphasized that amygdala-based neurocircuitry is likely to be important in various anxiety disorders, including social anxiety disorder and GAD. Genetic variations in such neurocircuitry may underpin differences in the readiness with which people demonstrate fear conditioning in response to potentially negative situations such as public speaking. Serotonergic modulation of this circuitry may help explain the efficacy of the SSRIs in these disorders. Although baseline functional imaging has not always shown dysfunction in social anxiety disorder,[102] the amyg-

Table 4. Putative Neurocircuits Involved in Social Anxiety Disorder and Generalized Anxiety Disorder[a]

Circuits	Function	Agent
Amygdala-based circuitry	Fear conditioning	Modulated by serotonin
Basal ganglia circuitry	Social reward processing, motoric inhibition	Modulated by dopamine
Prefrontal circuitry	Worry, self-consciousness	Modulated by MAs and CBT

[a]Abbreviations: CBT = cognitive-behavioral therapy, MA = monoamine.

dala and related regions are involved in "social perception"[103] and abnormal activation of the amygdala in social anxiety disorder is apparent in a number of paradigms.[26–28] Furthermore, after treatment with SSRIs, there is a normalization of temporal circuitry.[104] In GAD, there may be abnormal amygdala volume[31] and abnormal benzodiazepine receptor binding in the temporal pole.[105]

Basal ganglia neurocircuits may also play a role in mediating social anxiety disorder. Amygdala-ventral striatal circuitry is important in processing associations between complex stimuli and positive/negative rewards. Also, speculatively, basal ganglia dysfunction could manifest in disturbances such as motoric inhibition; for example, socially anxious children show reduced general facial activity and have a more restricted facial repertoire.[106] Striatal involvement is consistent not only with putative dopamine hypofunction in social anxiety disorder and the functional imaging data reviewed above, but also with reports in social anxiety disorder of a greater reduction in putamen volume with aging,[107] reduced choline and creatinine signal:noise ratios in subcortical, thalamic, and caudate areas,[108] and decreased N-acetyl-aspartate levels and a lower ratio of N-acetyl-aspartate to other metabolites in cortical and subcortical regions.[108,109] Basal ganglia involvement in GAD may also be present, but findings to date are inconsistent.[30,110]

Prefrontal circuits may be speculated to be important in mediating excessive worry and planning about the future in GAD or self-conscious concerns about potential embarrassment in social anxiety disorder, and to be modifiable by cognitive restructuring (Table 4). Increased right precentral frontal gyrus activity has been noted in one study of GAD.[30] In addition, there was increased dorsolateral prefrontal cortex activity during symptom provocation in a PET study of social anxiety disorder[20] and cortical gray matter abnormalities in social anxiety disorder in particular[109] (although not all work is consistent[27]). Anterior cingulate, which is involved in performance monitoring,[111] may play a crucial role in a number of anxiety disorders. Further, imaging studies that have pooled or compared findings across different anxiety disorders also suggest the importance of increased activation of inferior cortex in mediating anxiety symptoms.[112] (In contrast, patients with frontal hypofunction may not worry sufficiently about future consequences and may demonstrate impulsivity.)

A number of other specific circuits may, however, also be important in social anxiety disorder and GAD; these disorders, and possibly contributing traits (such as shyness and behavioral inhibition) deserve additional study using modern functional and molecular imaging techniques. Some pathways, for example, those governing reward to social stimuli, may be relevant not only in anxiety disorders, but also in a range of other psychiatric disorders. In addition, little work to date has explored the important question of how environmental events or psychotherapeutic interventions modulate the neurocircuitry of these disorders. It is fascinating, for example, that differences in social status in monkeys are associated with variations in striatal dopamine D_2 density. Gene-environment-neurocircuitry interactions are likely to be a fertile area for future investigation.

CONCLUSIONS

Clearly, any models of the neurocircuitry of social anxiety disorder must remain highly tentative. In this article we have not, for example, explored the subtypes of social anxiety disorder and GAD. These are, however, undoubtedly heterogenous disorders; further work will, therefore, be necessary to determine the way in which different neuroanatomical structures and neurochemical systems are differentially involved not only in subtypes of social anxiety disorder and GAD, but also when these disorders are comorbid with a range of other psychiatric conditions.

Also, although serotonin reuptake blockers are currently a first-line option for the treatment of social anxiety disorder/generalized anxiety disorder, the complexity of interaction between serotonergic neurocircuitry, dopaminergic neurocircuitry, and other systems should not be underestimated.[113,114] In obsessive-compulsive disorder, when SSRIs prove ineffective, they are increasingly augmented with dopamine blockers; in social anxiety disorder and GAD, the treatment of refractory patients with combinations of agents (e.g., augmentation of SSRIs with dopaminergic or glutamatergic agents) similarly deserves further study.[115,116]

Drug names: clonidine (Catapres and others), flumazenil (Romazicon), fluvoxamine (Luvox and others), gabapentin (Neurontin), paroxetine (Paxil), yohimbine (Aphrodyne).

Disclosure of off-label usage: The authors of this article have determined that, to the best of their knowledge, fluvoxamine, gabapentin, and buspirone are not approved by the U.S. Food and Drug Administration for the treatment of social anxiety disorder.

REFERENCES

1. LeDoux J. Fear and the brain: where have we been, and where are we going? Biol Psychiatry 1998;44:1229–1238
2. Davis M, Shi C. The extended amygdala: are the central nucleus of the amygdala and the bed nucleus of the stria terminalis differentially involved in fear versus anxiety? Ann N Y Acad Sci 1999;877:281–291
3. Gorman JM, Kent JM, Sullivan GM, et al. Neuroanatomical hypothesis of panic disorder, revised. Am J Psychiatry 2000;157:493–505
4. Bechara A, Tranel D, Damasio H, et al. Double dissociation of conditioning and declarative knowledge relative to the amygdala and hippocampus in humans. Science 1995;269:1115–1118
5. Beidel DC. Social anxiety disorder: etiology and early clinical presentation. J Clin Psychiatry 1998;59(suppl 17):27–31
6. Liebowitz MR, Fyer AJ, Gorman JM, et al. Specificity of lactate infusions in social phobia versus panic disorders. Am J Psychiatry 1985;142:947–950
7. Tancer ME, Stein MB, Uhde TW. Lactate response to caffeine in panic disorder: a replication using an "anxious" control group [abstract]. Biol Psychiatry 1991;29:57A
8. Tancer ME, Stein MB, Uhde TW. Lactic acid response to caffeine in panic disorder: comparison with social phobics and normal controls. Anxiety 1994;1:138–140
9. Gorman J, Fyer M, Goetz R, et al. Ventilatory physiology of patients with panic disorder. Am J Psychiatry 1988;45:31–39
10. Gorman JM, Papp LA, Martinez J, et al. High-dose carbon dioxide challenge test in anxiety disorder patients. Biol Psychiatry 1990;28:743–757
11. Papp LA, Klein DF, Martinez JM, et al. Diagnostic and substance specificity of carbon dioxide-induced panic. Am J Psychiatry 1993;150:250–257
12. Holt PE, Andrews G. Provocation of panic: three elements of the panic reaction in four anxiety disorders. Behav Res Ther 1989;27:253–261
13. Caldirola D, Perna G, Arancio C, et al. The 35% carbon dioxide challenge test in patients with social phobia. Psychiatry Res 1997;71:41–48
14. Papp LA, Gorman JM, Liebowitz MR, et al. Epinephrine infusions in patients with social phobia. Am J Psychiatry 1988;145:733–736
15. McCann UD, Slate SO, Geraci M, et al. A comparison of the effects of intravenous pentagastrin on patients with social phobia, panic disorder and healthy controls. Neuropsychopharmacology 1997;16:229–237
16. McCann UD, Morgan CM, Geraci M, et al. Effects of the 5-HT$_3$ antagonist, ondansetron, on the behavioral and physiological effects of pentagastrin in patients with panic disorder and social phobia. Neuropsychopharmacology 1997;17:360–369
17. van Vliet IM, Westenberg HGM, Slaap BR, et al. Anxiogenic effects of pentagastrin in patients with social phobia and healthy controls. Biol Psychiatry 1997;42:76–78
18. Coupland NJ, Bell C, Potokar JP, et al. Flumazenil challenge in social phobia. Depress Anxiety 2000;11:27–30
19. Potts NL, Book S, Davidson JRT. The neurobiology of social phobia. Int Clin Psychopharmacol 1996;11(suppl 3):43–48
20. Nutt DJ, Bell CJ, Malizia AL. Brain mechanisms of social anxiety disorder. J Clin Psychiatry 1998;59(suppl 17):4–11
21. van Ameringen M, Mancini C, Farvolden P, et al. The neurobiology of social phobia: from pharmacotherapy to brain imaging. Curr Psychiatry Rep 2000;2:358–366
22. Dewar KM, Stravynski A. The quest for biological correlates of social phobia: an interim assessment. Acta Psychiatr Scand 2001;103:244–251
23. Stein MB. Neurobiological perspectives on social phobia: from affiliation to zoology. Biol Psychiatry 1998;44:1277–1285
24. Kluver H, Bucy PC. Preliminary analysis of functions of the temporal lobes in monkeys, 1939. J Neuropsychiatry Clin Neurosci 1997;9:606–620
25. Bellugi U, Adolphs R, Cassady C, et al. Towards the neural basis for hypersociability in a genetic syndrome. Neuroreport 1999;10:1653–1657
26. Birbaumer N, Grodd W, Diedrich O, et al. fMRI reveals amygdala activation to human faces in social phobics. Neuroreport 1998;9:1223–1226
27. Tillfors M, Furmark T, Marteinsdottir I, et al. Cerebral blood flow in subjects with social phobia during stressful speaking tasks: a PET study. Am J Psychiatry 2001;158:1220–1226
28. Schneider F, Weiss U, Kessler C, et al. Subcortical correlates of differential classical conditioning of aversive emotional reactions in social phobia. Biol Psychiatry 1999;45:863–871
29. Buchsbaum MS, Hazlett E, Sicotte N, et al. Topographic EEG changes with benzodiazepine administration in generalized anxiety disorder. Biol Psychiatry 1985;20:832–842
30. Wu JC, Buchsbaum MS, Hershey TG, et al. PET in generalized anxiety disorder. Biol Psychiatry 1991;29:1181–1199
31. De Bellis MD, Casey BJ, Dahl RE, et al. A pilot study of amygdala volumes in pediatric generalized anxiety disorder. Biol Psychiatry 2000;48:51–57
32. van der Linden GJ, Stein DJ, van Balkom AJ. The efficacy of the selective serotonin reuptake inhibitors for social anxiety disorder (social phobia): a meta-analysis of randomized controlled trials. Int Clin Psychopharmacol 2000;15(suppl 2):S15–S23
33. Ballenger JC, Davidson JRT, Lecrubier Y, et al. Consensus statement on

generalized anxiety disorder from the International Consensus Group on Depression and Anxiety. J Clin Psychiatry 2001;62(suppl 11):53–58

34. Westenberg HG. Treatment options of social anxiety disorder. Presented at the 5th International Obsessive-Compulsive Disorder Conference; March 29–April 1, 2001; Sardinia, Italy

35. Davidson J, Yaryura-Tobia J, DuPont R, et al. Presented at the 5th International Obsessive-Compulsive Disorder Conference; March 29–April 1, 2001; Sardinia, Italy

36. van Vliet IM, Boer JA, Westenberg HGM, et al. Clinical effects of buspirone in social phobia: a double-blind placebo-controlled study. J Clin Psychiatry 1997;58:164–168

37. Coplan JD, Lydiard RB. Brain circuits in panic disorder. Biol Psychiatry 1998;44:1264–1276

38. Raleigh MJ, Brammer GL, McGuire MT, et al. Dominant social status facilitates the behavioral effects of serotonergic agonists. Brain Res 1985;348:274–282

39. Raleigh MJ, McGuire MT, Brammer GL, et al. Serotonergic mechanisms promote dominance acquisition in adult male vervet monkeys. Brain Res 1991;559:181–190

40. Higley JD, King ST Jr, Hasert MF, et al. Stability of interindividual differences in serotonin function and its relationship to severe aggression and competent social behavior in rhesus macaque females. Neuropsychopharmacology 1996;14:67–76

41. Knutson B, Wolkowitz OM, Cole SW, et al. Selective alteration of personality and social behavior by serotonergic intervention. Am J Psychiatry 1998;155:373–379

42. Handley SL. 5-Hydroxytryptamine pathways in anxiety and its treatment. Pharmacol Ther 1995;66:103–148

43. Cheeta S, Kenny PJ, File SE. Hippocampal and septal injections of nicotine and 8-OH-DPAT distinguish among different animal tests of anxiety. Prog Neuropsychopharmacol Biol Psychiatry 2000;24:1053–1067

44. Lightowler S, Kennett GA, Wiliamson IJ, et al. Anxiolytic-like effect of paroxetine in a rat social interaction test. Pharmacol Biochem Behav 1994;49:281–285

45. Stein MB, Delaney SM, Chartier MJ, et al. Platelet [³H]-paroxetine binding in social phobia: comparison to patients with panic disorder and health volunteers. Biol Psychiatry 1995;37:224–228

46. Tancer ME, Mailman RB, Stein MB, et al. Neuroendocrine sensitivity to monoaminergic system probes in generalized social phobia. Anxiety 1994/1995;1:216–223

47. Hollander E, Kwon J, Weiller F, et al. Serotonergic dysfunction in social phobia: comparison to normal control and obsessive-compulsive disorder subjects. Psychiatry Res 1998;79:213–217

48. Iny LJ, Pecknold J, Suranyi-Cadotte BE, et al. Studies of a neurochemical link between depression, anxiety, and stress from [³H] imipramine and [³H] paroxetine binding on human platelets. Biol Psychiatry 1994;36:281–291

49. Germine M, Goddard AW, Woods SW, et al. Anger and anxiety responses to m-chlorophenylpiperazine in generalized anxiety disorder. Biol Psychiatry 1992;32:457–467

50. Lesch KP, Bengel D, Heils A, et al. Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region. Science 1996;274:1527–1531

51. Stein MB, Chartier MJ, Kozak MV, et al. Genetic linkage to the serotonin transporter protein and 5HT$_{2A}$ receptor genes excluded in generalized social phobia. Psychiatry Res 1998;81:283–291

52. Liebowitz MR, Quitkin FM, Stewart JW. Phenelzine versus imipramine in atypical depression: a preliminary report. Arch Gen Psychiatry 1984;44:669–677

53. Liebowitz MR, Schneier FR, Campeas R, et al. Phenelzine vs atenolol in social phobia: a placebo-controlled trial. Arch Gen Psychiatry 1992;49:290–300

54. Mayleben M, Gariepy J, Tancer M, et al. Genetic differences in social behaviour: neurobiological mechanisms in a mouse model [abstract]. Biol Psychiatry 1992;31S:216A

55. Grant KA, Shively CA, Nader MA, et al. Effect of social status on striatal dopamine D$_2$ receptor binding characteristics in cynomolgus monkeys assessed with positron emission tomography. Synapse 1998;29:80–83

56. King R, Mefford IN, Wang C, et al. CSF dopamine levels correlate with extraversion in depressed patients. Psychiatry Res 1986;19:305–310

57. Johnson MR, Lydiard RB, Zealberg JJ, et al. Plasma and CSF HVA levels in panic patients with comorbid social phobia. Biol Psychiatry 1994;36:426–427

58. Lauterbach EC, Duvoisin RC. Anxiety disorders in familial Parkinsonism [letter]. Am J Psychiatry 1987;148:1274

59. Stein MB, Heuser IJ, Juncos JL, et al. Anxiety disorders in patients with Parkinson's disease. Am J Psychiatry 1990;147:217–220

60. Richard IH, Schiffer RB, Kurlan R. Anxiety and Parkinson's disease. J Neuropsychiatry Clin Neurosci 1996;8:383–392

61. Pallanti S, Quercioli L, Rossi A, et al. The emergence of social phobia during clozapine treatment and its response to fluoxetine augmentation. J Clin Psychiatry 1999;60:819–823

62. Mikkelsen EJ, Deltor J, Cohen DJ. School avoidance and social phobia triggered by haloperidol in patients with Tourette's syndrome. Am J Psychiatry 1981;138:1572–1576

63. Rowe DC, Stever C, Gard JM, et al. The relation of the dopamine transporter gene (DAT1) to symptoms of internalizing disorders in children. Behav Genet 1998;28:215–225

64. Depue RA, Luciana M, Arbisi P, et al. Dopamine and the structure of personality: relation of agonist-induced dopamine activity to positive emotionality. J Pers Soc Psychol 1994;67:485–498

65. Farde L, Gustavsson JP, Jonsson E. D$_2$ dopamine receptors and personality traits [letter]. Nature 1997;385:590

66. Breier A, Kestler L, Adler C, et al. Dopamine D$_2$ receptor density and personal detachment in healthy subjects. Am J Psychiatry 1998;155:1440–1442

67. Laakso A, Vilkman H, Kajander J, et al. Prediction of detached personality in healthy subjects by low dopamine transporter binding. Am J Psychiatry 2000;157:290–292

68. Blum K, Braverman ER, Wu S, et al. Association of polymorphisms of dopamine D$_2$ receptor (DRD2), and dopamine transporter (DAT1) genes with schizoid/avoidant behaviors (SAB). Mol Psychiatry 1997;2:239–246

69. Strobel A, Wehr A, Michel A, et al. Association between the dopamine D$_4$ receptor (DRD4) exon III polymorphism and measures of novelty seeking in a German population. Mol Psychiatry 1999;4:378–384

70. Kestler LP, Malhotra AK, Finch C, et al. The relation between dopamine D$_2$ receptor density and personality: preliminary evidence from the NEO personality inventory-revised. Neuropsychiatry Neuropsychol Behav Neurol 2000;13:48–52

71. Tiihonen J, Kuikka J, Bergstrom K, et al. Dopamine reuptake site densities in patients with social phobia. Am J Psychiatry 1997;154:239–242

72. Schneier FR, Liebowitz MR, Abi-Dargham A, et al. Low dopamine D$_2$ receptor binding potential in social phobia. Am J Psychiatry 2000;157:457–459

73. Gale C, Oakley-Browne M. Anxiety disorder. BMJ 2000;321:1204–1207

74. Grant SJ, Redmond DE Jr. The neuroanatomy and pharmacology of the nucleus locus coeruleus. Prog Clin Biol Res 1981;75:5–27

75. Dimsdale JE, Moss J. Short-term catecholamine response to psychological stress. Psychosom Med 1980;42:493–497

76. Dimsdale JE, Moss J. Plasma catecholamines in stress and exercise. JAMA 1980;243:340–342

77. Heimberg RG, Hope DA, Dodge CS, et al. DSM-III-R subtypes of social phobia: comparison of generalized social phobics and public speaking phobics. J Nerv Ment Dis 1990;173:172–179

78. Levin AP, Saoud JB, Gorman JM, et al. Responses of generalized and discrete social phobias during public speaking challenge. J Anxiety Disord 1993;7:207–221

79. Hofmann SG, Newman MG, Ehlers A, et al. Psychophysiological differences between subgroups of social phobia. J Abnorm Psychol 1995;104:224–231

80. Stein MB, Tancer ME, Uhde TW. Physiologic and plasma norepinephrine responses to orthostasis in patients with panic disorder and social phobia. Arch Gen Psychiatry 1992;49:311–317

81. Stein MB, Asmundson GJG, Chartier M. Autonomic responsivity in generalized social phobia. J Affect Disord 1994;31:211–221

82. Stein MB, Huzel LL, Delaney SM. Lymphocyte beta-adrenoceptors in social phobia. Biol Psychiatry 1993;34:45–50

83. Tancer ME, Stein MB, Uhde TW. Growth hormone response to IV clonidine in social phobia: comparison to patients with panic disorder and healthy controls. Biol Psychiatry 1994;34:252–256

84. Sevy S, Papadimitriou GN, Surmont DW, et al. Noradrenergic function in generalized anxiety disorder, major depressive disorder, and healthy subjects. Biol Psychiatry 1989;25:141–152

85. Cameron OG, Smith CB, Lee MA. Adrenergic status in anxiety disorders: platelet alpha two-adrenergic receptor binding, blood pressure, pulse, and plasma catecholamines in panic and generalized anxiety disorder. Biol Psychiatry 1990;28:3–20

86. Weizman R, Tanne Z, Granek M, et al. Peripheral benzodiazepine binding sites on platelet membranes are increased during diazepam treatment of anxious patients. Eur J Pharmacol 1987;138:289–292

87. Rocca P, Ferrero P, Gualerzi A, et al. Peripheral-type benzodiazepine receptors in anxiety disorders. Acta Psychiatr Scand 1991;84:537–544

88. Uhde TW, Tancer ME. Normal urinary free cortisol and post dexamethasone cortisol in social phobia. J Affect Disord 1994;30:155–161

89. Potts NLS, Davidson JRT, Krishnan KRR, et al. Levels of urinary free cortisol in social phobia. J Clin Psychiatry 1991;52(11, suppl):41–42

90. Tancer ME, Stein MB, Gelernter CS, et al. The hypothalamic-pituitary-thyroid axis in social phobia. Am J Psychiatry 1990;147:929–933

91. Kagan J, Reznick JS, Gibbons J. Biological basis of childhood shyness. Science 1988;240:167–171

92. Martel FL, Hayward C, Lydons DM, et al. Salivary cortisol levels in socially phobic adolescent girls. Depress Anxiety 1999;10:25–27

93. Schmidt LA, Fox NA, Rubin KH, et al. Behavioral and neuroendocrine responses in shy children. Dev Psychobiol 1997;30:127–140

94. Tancer ME, Stein MB, Uhde TW. Effects of thyrotropin releasing hormone on blood pressure and heart rate in social phobia patients, panic disorder patients, and normal controls: results of a pilot study. Biol Psychiatry 1990;27:781–783

95. Uhde T. Anxiety and growth disturbance; is there a connection? a review of biological studies in social phobia. J Clin Psychiatry 1994;55(6, suppl):17–27

96. Stein MB, Hauger RL, Dhalla KS, et al. Plasma neuropeptide Y in anxiety disorders: findings in panic disorder and social phobia. Psychiatry Res 1996;59:183–188

97. Insel TR. A neurobiological basis of social attachment. Am J Psychiatry 1997;154:726–735

98. Stein DJ, Bouwer C. Blushing and social phobia: a neuroethological speculation. Med Hypotheses 1997;49:101–108

99. Bouwer CJ, Stein DJ. Hyper-responsivity to nicotinic acid challenge in generalized social phobia: a pilot study. Eur Neuropsychopharmacol 1998;8:311–313

100. Rapoport MH, Stein MB. Serum interleukin-2 and soluble interleukin-2 receptor levels in generalized social phobia. Anxiety 1994/1995;1:22–25

101. Rapoport MH. Circulating lymphocyte phenotypic surface markers in anxiety disorder patients and normal volunteers. Biol Psychiatry 1998;43:458–463

102. Stein MB, Leslie WD. A brain single photon-emission computed tomography (SPECT) study of generalized social phobia. Biol Psychiatry 1996;39:825–828

103. Allison T, Puce A, McCarthy G. Social perception from visual cues: role of the STS region. Trends Cogn Sci 2000;4:267–277

104. van der Linden G, van Heerden B, Warwick J, et al. Functional brain imaging and pharmacotherapy in social phobia: single photon emission computed tomography before and after treatment with the selective serotonin reuptake inhibitor citalopram. Prog Neuropsychopharmacol Biol Psychiatry 2000;24:419–438

105. Tiihonen JF, Kuikka J, Rasanen P, et al. Cerebral benzodiazepine receptor binding and distribution in generalized anxiety disorder: a fractal analysis. Mol Psychiatry 1997;2:463–471

106. Melfsen S, Osterlow J, Florin I. Deliberate emotional expressions of socially anxious children and their mothers. J Anxiety Disord 2000;14:249–261

107. Potts NL, Davidson JR, Krishnan KR, et al. Magnetic resonance imaging in social phobia. Psychiatry Res 1994;52:35–42

108. Davidson JRT, Boyko O, Charles HC, et al. Magnetic resonance spectroscopy in social phobia: preliminary findings. J Clin Psychiatry 1993;54(suppl 12):19–25

109. Tupler LA, Davidson JRT, Smith RD, et al. A repeat proton magnetic resonance spectroscopy study in social phobia. Biol Psychiatry 1997;42:419–424

110. Buchsbaum MS, Wu J, Haier R, et al. Positron emission tomography assessment of effects of benzodiazepines on regional glucose metabolic rate in patients with anxiety disorder. Life Sci 1987;40:2393–2400

111. MacDonald AW III, Cohen JD, Stenger VA, et al. Dissociating the role of the dorsolateral prefrontal and anterior cingulate cortex in cognitive control. Science 2000;288:1835–1838

112. Rauch SL, Savage CR, Alpert NM, et al. The functional neuroanatomy of anxiety: a study of three disorders using positron emission tomography and symptom provocation. Biol Psychiatry 1997;42:446–452

113. Kapur S, Remington G. Serotonin-dopamine interaction and its relevance to schizophrenia. Am J Psychiatry 1996;153:466–476

114. Klimke A, Larisch R, Janz A, et al. Dopamine D_2 receptor binding before and after treatment of major depression measured by [^{123}I]IBZM SPECT. Psychiatry Res 1999;90:91–101

115. Emmanuel NP, Brawman-Mintzer O, Morton WA, et al. Bupropion-SR in treatment of social phobia. Depress Anxiety 2000;12:111–113

116. Villareal G, Johnson MR, Rubey R, et al. Treatment of social phobia with the dopamine agonist pergolide. Depress Anxiety 2000;11:45–47

117. Davidson JRT, Hughes DL, George LK, et al. The epidemiology of social phobia: findings from the Duke Epidemiologic Catchment Area Study. Psychol Med 1993;23:709–718

118. Kessler RC, McGonagle KA, Zhao S, et al. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States: results from the National Comorbidity Survey. Arch Gen Psychiatry 1994;51:8–19