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

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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.
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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.

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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-amgygdala ones (although the latter may be prone to reactivation should exposure to fear cues recur).

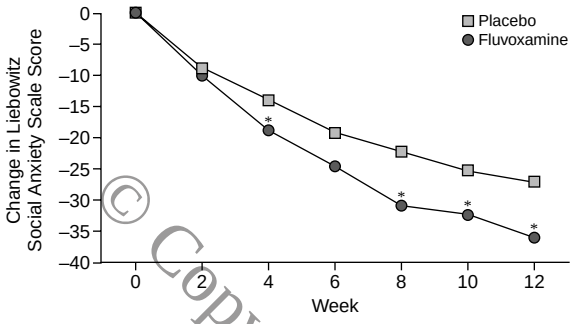
Although imaging studies in social anxiety disorder and GAD remain at a preliminary stage, there is some evidence that patients with social anxiety disorder demonstrate selective activation of the amygdala when exposed to fear-relevant stimuli[26] or tasks,[27] or show abnormal patterns of amygdala activation 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

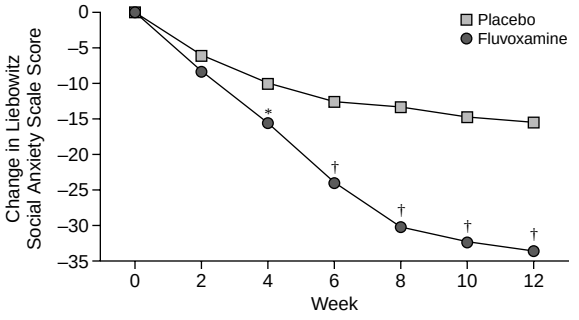
A growing database demonstrates that SSRIs are effective and well tolerated in a range of anxiety disorders, including social anxiety disorder[32] and GAD.[33] In some of the most recent work, fluvoxamine controlled release (CR), a slow-release SSRI, was studied in social anxiety disorder in 2 large 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 amygdala 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]

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.

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.

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