



# Neuroplasticity as a target for the pharmacotherapy of anxiety disorders, mood disorders, and schizophrenia

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**Current treatments for psychiatric disorders were developed with the aim of providing symptomatic relief rather than reversing underlying abnormalities in neuroplasticity or neurodevelopment that might contribute to psychiatric disorders. This review considers the possibility that psychiatric treatments might be developed that target neuroplasticity deficits or that manipulate neuroplasticity in novel ways. These treatments might not provide direct symptomatic relief. However, they might complement or enhance current pharmacotherapies and psychotherapies aimed at the prevention and treatment of psychiatric disorders. In considering neuroplasticity as a target for the treatment of psychiatric disorders, we build on exciting new findings in the areas of anxiety disorders, mood disorders, and schizophrenia.**

Neuroplasticity is at the core of all treatments for psychiatric disorders because symptom reduction is presumed to emerge from a change in the function of neural networks. However, a number of recent reviews indicate that psychiatric disorders are, themselves, disorders of neuroplasticity [1–4], suggesting that the efficacy of current treatments may be limited by neuroplasticity abnormalities. This review will consider briefly the hypothesis that new treatments might be developed to enhance neuroplasticity [5]. Medications that enhance neuroplasticity could increase the rapidity of onset or the extent of clinical improvement and mitigate the need for hospitalization in some cases.

This review will highlight a number of examples that illustrate how neuroplasticity might be productively targeted as a strategy for enhancing the treatment of psychiatric disorders. It will begin by considering the use of drugs that enhance the

stimulation of the glycine<sub>B</sub> coagonist site of *N*-methyl-D-aspartate (NMDA) glutamate receptors to enhance experience-dependent forms of neuroplasticity, as might be associated with extinction of maladaptive fear in patients with anxiety disorders. The implications of the success of this approach for the remediation of cognitive impairments associated with schizophrenia will then be discussed. This review will then present evidence that reductions in cellular resilience and neuroplasticity contribute to mood and stress-related disorders and that these neuroplasticity deficits might be addressed by raising the levels of trophic factors and enhancing related signal transduction mechanisms. Finally, this review will discuss clinical treatments modeled after two well-studied preclinical paradigms for manipulating neuroplasticity, sensitization to the effects of D1 agonists [6] and long-term depression (LTD) [7]. Together, these examples highlight a growing number of novel treatments for psychiatric disorders that are emerging from the effort to design treatments targeting or encompassing neuroplasticity.

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## Combining a generalized increase in NMDA receptor-dependent neuroplasticity with circuit-specific experience-dependent neuroplasticity: the examples of fear extinction for anxiety disorders and cognitive remediation for schizophrenia

Cognitive-behavioral therapy incorporating graded, prolonged exposure to feared stimuli is among the most promising treatments for anxiety disorders [8]. Exposure interventions include *in vivo* exposure (direct confrontation of feared and avoided situations or activities), *imaginal* exposure (prolonged and detailed imagining or remembering of feared and avoided thoughts), and *interoceptive* exposure (exercises designed to elicit feared physical sensations). The purported mechanism of exposure is *extinction*, in which repeated presentations of a conditioned stimulus (CS), outside the presence of an unconditioned stimulus (US), eventually leads to reductions in the conditioned response (CR). Extinction does not imply that the organism forgets the original CS-US association; rather, it is thought to represent the learning of new associations (e.g. the CS becomes associated with stimuli other than the US) that eventually inhibits the original association [9]. However, as new adaptive associations are consolidated and reinforced, the reconsolidation of Classical (Pavlovian) fear conditioning, extinction, and reconsolidation are all NMDA receptor-dependent forms of neuroplasticity involving glutamatergic inputs into the basolateral amygdala [10–13]. Drugs that facilitate NMDA receptor function via glycine site have not been shown to have potent direct anxiolytic effects in animals or humans [14–18]. However, drugs that facilitate NMDA receptor function might promote a variety of NMDA receptor-dependent forms of neuroplasticity, including extinction [19]. The addition of D-cycloserine (DCS) to exposure therapy for anxiety disorders provides the clearest example of the capacity of a medication that increases neuroplasticity diffusely in the brain to enhance the efficacy of a behavioral therapy that produces neuroadaptations in particular circuits. DCS is a partial agonist of the glycine<sub>B</sub> coagonist site of NMDA receptors with relatively more agonist or antagonist effects at NMDA receptor subtypes [20–22]. When surrounding glycine levels are low, DCS facilitates NMDA receptor function. However, when glycine levels are sufficient to saturate glycine<sub>B</sub> sites, DCS may reduce NMDA receptor function [23–25]. Therefore, DCS may improve the efficacy of exposure-based psychotherapies by enhancing NMDA receptor functioning, thereby increasing neuroplasticity, or by reducing NMDA receptor function and interfering with the (re)consolidation of fear memories. Both processes are thought to facilitate fear extinction [5,26,27]. DCS promoted the extinction of fear conditioning in animals, regardless of whether it was present during extinction sessions [28] or immediately after extinction training [29]. These data suggest that DCS facilitates extinction by influencing the consolidation of new learning. In the first study of DCS augmentation of exposure therapy in humans [18], acrophobic patients receiving DCS appeared to benefit more from virtual reality exposure therapy than did patients receiving placebo. These results have now been replicated and extended using DCS in combination with exposure therapy for patients with social anxiety disorder [30,31], panic disorder [32], and obsessive-compulsive disorder [33,34].

Figure 1 presents the results of a recent quantitative review of 15 placebo-controlled studies ( $N = 632$ , 30 independent samples; 5

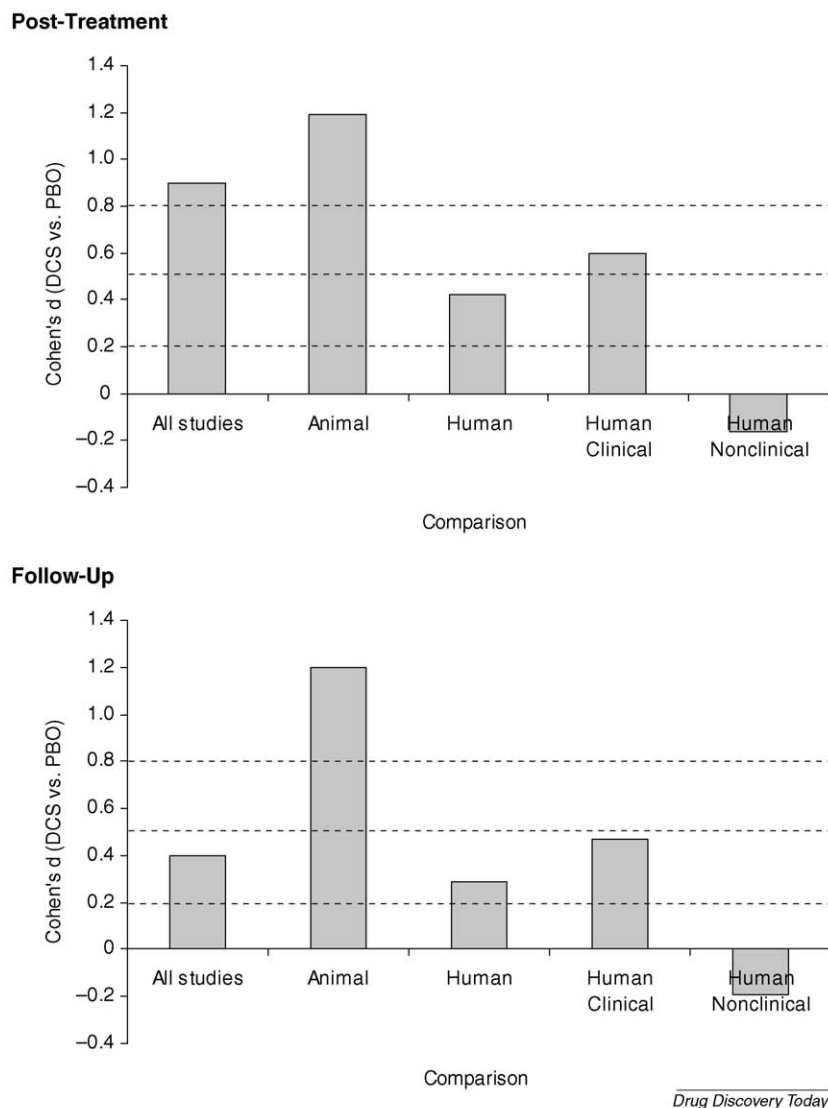
animal studies, 10 human studies [35]) of DCS augmentation of extinction training/exposure therapy. At post-treatment, DCS augmentation was associated with a significant and large effect, indicating that DCS reliably augments the effects of fear extinction/exposure therapy. Animal studies showed a significantly greater effect than did human studies (perhaps not surprising, given the greater experimental control over genetic variation and extraneous variables in animal studies). A secondary analysis revealed that human nonclinical studies showed no significant DCS effect, while human clinical studies showed that DCS produced significant effects with a moderate effect size. A similar pattern was seen at follow-up, suggesting that the effects of DCS augmentation do not disappear upon treatment discontinuation, a potential improvement over other pharmacotherapy augmentation strategies that may actually increase the risk of relapse after discontinuation [36,37].

Examination of moderator variables found no evidence of a DCS dose-response relationship across studies. However, the timing of the DCS dose significantly predicted effect size, with the greatest effects evident among studies in which DCS was administered either immediately before or after exposure, consistent with the preclinical studies. Smaller DCS effects were also seen for those studies in which the combination of DCS and exposure occurred many times. This decrease in efficacy may reflect the development of tolerance to DCS [38] or the high level of efficacy of repeated exposures in the patients studied to date, that is, a ‘floor effect’ that might reduce the ability to detect the effects of DCS.

Thus, the studies with DCS provide initial support for the hypothesis that a drug that enhanced neuroplasticity by facilitating the activation of NMDA glutamate receptors might promote the efficacy of extinction-based CBT. Future studies with full agonists of the glycine<sub>B</sub> site of the NMDA receptor complex (glycine, D-serine, D-alanine) as well as glycine or D-serine transporter antagonists will help to better evaluate this treatment modality.

In contrast to the glycine-related agents,  $\beta$ -receptor blockade might be a strategy to preferentially disrupt the reconsolidation of fear-related learning. Noradrenergic systems play a number of roles in the neurobiology of memory in animals and humans [39,40]. Recent animal data suggest that  $\beta$ -receptor blockade preferentially disrupts the reconsolidation of fear learning relative to the initial consolidation of learning [41,42]. This finding may be consistent with the ability of  $\beta$ -receptor blockade to reduce reconsolidation of fear learning associated with post-traumatic stress disorder (PTSD) [43,44], while leaving initial fear learning intact [45]. By contrast, preliminary evidence suggests that propranolol may not be effective for the prevention of PTSD [46], despite some initial promise of this strategy [47].

Drugs, like DCS, that promote neuroplasticity via enhancement of NMDA receptor function might enhance the efficacy of cognitive and behavioral therapies for many psychiatric disorders. It is intriguing to consider the possibility that the efficacy of glycine-related treatments substances for schizophrenia might follow a paradigm similar to the anxiety disorders, that is, they may promote neuroplasticity rather than directly suppressing symptoms and cognitive deficits associated with schizophrenia. A large number of studies that have suggested that

**FIGURE 1**

Effect size (Cohen's *d*) of controlled trials of D-cycloserine (DCS) vs. placebo (PBO). Note: Adapted from [35].

glycine-related substances (glycine, DCS, D-serine, D-alanine, or sarcosine) modestly improve the efficacy of antipsychotic treatment when added to drugs other than clozapine, a drug that has intrinsic glycine transporter activity [16,48–50]. However, there are a number of negative trials, including the largest study of this mechanism [51]. There may be many reasons for the negative findings. One reason may be that it is not clear how glycine should be optimally dose to produce clinical benefit, that is, we have only limited information about the central bioavailability of peripherally administered glycine in humans [52]. Also, on the basis of the data with anxiety disorders [35], one might predict that a limited number of glycine treatments would be more effective than chronic treatment in order to minimize the impact of tolerance to glycine effects. To date, however, all studies of glycine treatments have employed daily or twice-daily administration schedules for several weeks. Also, on the basis of the anxiety studies, glycine might be predicted to augment the

efficacy of a rehabilitative treatment while having limited effects on its own. Cognitive remediation therapy, like fear extinction, would seem to be relatively amenable to this strategy. Cognitive remediation involves the repetitive activation of circuits underlying particular aspects of cognition in order to engage use-dependent forms of neuroplasticity to reduce functional impairments within these circuits [53–55]. Reductions in neuroplasticity intrinsic to schizophrenia would be predicted to constrain the benefits of this type of treatment [3]. Currently, there are no published studies evaluating the interactive effects of glycine-related substances and a cognitive remediation strategy or cognitive-behavioral therapy for schizophrenia. However, there are data that might be consistent with a primary glycine effect on neuroplasticity rather than symptom suppression in schizophrenia. When it works, the benefits of glycine persist for several weeks following its termination, despite its short plasma half-life [52,56,57].

## Restoring neuroplasticity, neurogenesis, and gliogenesis through neurotrophic mechanisms: the case for depression and stress-related disorders

The concept that depression could be related to decreased cellular resiliency and impaired plasticity emerged from a series of ante-mortem and postmortem studies of mood disorders describing significant structural abnormalities [58–60] and histopathological changes, including decreased neuronal and glial density and reduced glial cell numbers [61–64] in multiple brain regions. Parallel findings demonstrated that prolonged stress accelerated the age related decreases in the number of hippocampal neurons in rodents [65] and resulted in changes in dendritic branching in hippocampus, amygdala and prefrontal cortex (PFC) [66–68]. More recent data show that these stress-induced morphological changes have functional correlates, resulting in diminished responses to apically targeted excitatory inputs [69], and deficits in attentional control that are commonly associated with stress-related mental illnesses [70]. Additional studies provide strong evidence of stress-related decreases in the rates of cell proliferation and survival [71,72]. Of special interest to the field of drug development, it was noted that many established antidepressant treatments opposed stress effects on dendritic atrophy [73] and glial cell loss [74], as well as cell proliferation and survival [75–78]. The idea that antidepressant-induced effects on cell proliferation mediated the beneficial cognitive and behavioral effects of the drug was bolstered by evidence that hippocampal neurogenesis was required for the expression of the behavioral effects of antidepressants [79].

A neurotrophic hypothesis suggested that the opposing effects of stress and antidepressant drugs are mediated by modulation of kinase activity, resulting in changes in cyclic AMP (cAMP) levels and altered cAMP response element binding protein (CREB) regulated brain-derived neurotrophic factor (BDNF) gene expression [80,81]. This hypothesis is supported by postmortem human studies of the hippocampus and PFC, and serum studies of depressed patients demonstrating decreased levels of BDNF mRNA and protein in non-medicated depressed patients, but either increased or similar BDNF levels in patients taking antidepressant drugs [82–85]. Although much attention remains directed on the specific role of BDNF in the hippocampus and frontal cortex, there is new evidence of the involvement of several additional neurotrophic factors including fibroblast growth factor (FGF) [86], insulin-like growth factor (IGF-1) [87], and vasoendothelial growth factor (VEGF) [88]. In addition, there are regional differences with regard to the effects of stress and antidepressants on neurotrophic factor regulation [89].

Beyond the neurotrophins, other mechanisms crucial to the regulation of plasticity may contribute to the pathophysiology of mood disorders and to antidepressant efficacy. For example, there is growing evidence of stress and antidepressant drugs on chromatin remodeling [90], with recent evidence suggesting that early epigenetic processes produce long-standing effects on neuroplasticity and cellular resiliency that may persist into adulthood. Furthermore, the ability of drugs such as valproic acid that modulate histone deacetylase (HDAC) proteins [91,92] and enhance long-term memory for both acquisition and extinction may provide the mechanism of action to some mood stabilizing medications, and suggest a role for the drugs as adjuncts to behavior therapy [93,94].

Recent studies now suggest that activity-dependent plasticity may be impaired in depressed patients and that antidepressant drugs may reverse or attenuate this deficit [95,96]. For example, stimulus induced plasticity is impaired in the visual system of depressed individuals and that chronic administration of sertraline to healthy subjects increased the amplitude and plasticity of the evoked potentials [97]. In addition, fluoxetine administration enhances the plasticity of ocular dominance columns in adult rats [98]. Together these studies provide strong evidence that antidepressant medications promote activity-dependent plasticity in visual cortex, and raise the possibility that similar plasticizing effects can be seen in brain circuits more closely related to mood regulation and cognition. Future studies might target these mechanisms more directly via actions on glutamate and GABA receptors [99,100].

The notion that antidepressants may work by increasing activity-dependent plasticity parallels the prior studies of DCS in anxiety disorders. In this case, again, providing the medication alone may not be sufficient, or at least not the optimal strategy, for reversing the pathophysiological state of depression. Selective activation of specific brain circuits and synapses may synergize with drug therapies to reinforce and strengthen desirable behaviors and cognitive schemata that are useful in reversing and preventing depressive episodes. This may contribute to the interesting finding demonstrating that the combined use of an antidepressant medication with cognitive-behavioral therapy for chronic depression was much more effective than either treatment alone [101]. In an attempt to explore this hypothesis, a recent pilot study found that CBT augmentation of ECT might enhance the antidepressant effectiveness of the treatment and delay the time to relapse [102]. Obviously, this area of investigation now requires much more rigorous studies before any firm conclusions can be made related to clinical practice. Also, it would be interesting to determine whether a drug that enhances neuroplasticity generally, like DCS, promotes the clinical efficacy of traditional antidepressant treatments.

## Using a sensitizing administration regimen to achieve lasting benefits from dopamine D1 receptor agonists in schizophrenia

It would be elegant to design a treatment regimen that turned a pathophysiologic process into a treatment mechanism and, in so doing, solved an obstacle in drug development, the problem of the development of tolerance to agonists. There has been substantial interest in the potential value of dopamine D1 receptor agonists for treating cognitive impairments in schizophrenia [103]. The benefits of D1 receptor agonist treatment might, however, be limited by the emergence of tolerance [104–106]. Thus, there has been interest in strategies that might circumvent this limitation.

One potential strategy emerged from studies of the sensitization to the psychotogenic effects of psychostimulants [107]. Although there is recent evidence of psychostimulant sensitization in humans [108], it has been demonstrated more clearly and robustly in animals. In rodents, psychostimulant administration produces glutamate release in multiple brain regions that produces an NMDA receptor-dependent form of synaptic neuroplasticity that contributes to the behavioral features of stimulant sensitization

[109–111]. Amphetamine sensitization in the nonhuman primate induces a disorder characterized by long-lasting alterations in behavior, profound working memory impairments, and a deterioration in the integrity of prefrontal neuronal circuitry [112–114].

The process of sensitization, however, also might be exploited for the treatment of cognitive impairments associated with schizophrenia [115]. Thus, long-term administration of neuroleptics downregulates D1 receptor function, leading to working memory deficits that can be reversed by repeated intermittent treatment with a full D1 agonist [6]. In this case primates received multiple sessions involving the administration of very low doses D1 agonists that were interleaved with washouts. Under these conditions primates began to respond to doses that were previously too low to produce behavioral effects. They also showed progressive improvements in working memory that persisted long after cessation of treatment. Together, these findings were suggestive of an underlying process of sensitization. This hypothesis was tested in another dopamine/D1 deficient state, namely natural aging, and it was found that this same sensitizing regime of D1 agonist treatment profoundly enhanced working memory performance in elderly, but not young-adult, nonhuman primates and again this benefit persisted long after treatment [116]. Thus, by administering low doses of D1 receptor agonists intermittently, it is conceivable that one could surmount the problem of tolerance development to these agents, producing long-lasting or even irreversible improvement of some of the cognitive impairments associated with schizophrenia.

### **Delivering low frequency transcranial magnetic stimulation to depotentiate cortical synapses: treating antipsychotic-resistant auditory hallucinations**

In approximately 25% of patients diagnosed with schizophrenia, auditory hallucinations (AHs) respond poorly or not at all to currently available antipsychotic medication [117]. One important feature of AHs is that they generally are experienced as spoken speech with discernable loudness, timbre and other ‘percept-like’ features. These characteristics suggest direct involvement of speech perception neurocircuitry.

An early O-15 positron emission tomography study found that activation in left temporoparietal regions accompanied AHs [118]. These brain regions are adjacent to the Wernicke’s area and active during speech perception [119]. Numerous studies have found that 1-Hz repetitive transcranial magnetic stimulation (1-Hz rTMS) reduces cortical excitability [120–125]. These effects appear analogous to long-term depression (LTD) elicited by 1-Hz direct electrical stimulation of gray matter in animal studies, which can endure for many weeks [7,126]. We consequently predicted that ‘suppressive’ 1-Hz rTMS delivered to the temporoparietal cortex might reduce AHs. Clinical trials comparing this intervention strategy with sham stimulation in patients experiencing AHs have been undertaken at Yale [127,128] and elsewhere. A meta-analysis considering 10 sham-controlled double-masked studies found robust evidence of efficacy relative to sham stimulation based on a combined total N of 212 (effect size = 0.76 95% CI 0.36–1.17 [129]). Most recently, functional magnetic resonance imaging (fMRI) maps of abnormal activation and functional connectivity have been used to position rTMS in patients with especially severe

AHs [130]. Delivering rTMS to temporoparietal sites in Wernicke’s area and the adjacent supramarginal gyrus was accompanied by a greater rate of AH improvement compared to sham stimulation. Repetitive TMS delivered to other sites did not consistently improve AHs. These findings suggest that targeted brain stimulation designed to induce neuroplastic alterations in neurocircuitry responsible for positive symptoms can produce clinical improvement in patients with schizophrenia.

### **Commentary**

Traditional treatments for psychiatric disorders emerged from the convergence of happy accident and acute clinical observation, that is, when administration of a substance suppressed symptoms. However, the treatment strategies reviewed above diverge from this approach, emerging from mechanistic foundations in basic research that may translate to novel treatments. As a result, this review identified some promising new treatment approaches as well as emerging conceptual approaches to medications development for psychiatry.

*A treatment that works by increasing neuroplasticity may require combination with another treatment, perhaps a cognitive-behavioral therapy, to exhibit efficacy*

Traditional medication development strategies assume that medications, by themselves, produce the necessary adaptations in synaptic function to demonstrate efficacy in animal models. However, a drug that increases neuroplasticity might require testing in animal models involving behavioral change, for example extinction, to exhibit efficacy. Similarly, these drugs may only show clinical efficacy in humans in combination with these cognitive or behavioral manipulations, as was the case for glycine-related treatments for anxiety disorders and perhaps schizophrenia.

*Cellular resilience, that is, neuronal and glial structural integrity may be targeted by treatments for psychiatric disorders*

Treatments for psychiatric disorders have traditionally used behavioral rather than biological endpoints. However, strategies involving raising neurotrophin levels to restore synaptic connectivity or to stimulate neurogenesis might have structural endpoints that precede behavioral change.

*Agonist administration schedules may be designed to produce sensitization rather than tolerance*

The model of D1 receptor agonist sensitization suggests that doses that are too low to produce initial behavioral effects might become effective doses with repeated but intermittent administration. Equally intriguing is the possibility that sensitization strategies might produce long-lasting or even irreversible improvement mitigating the need for further drug administration.

*TMS, deep brain stimulation [131] and other focal neurostimulation treatments may be administered to shape the function of cortical networks, that is, to potentiate or depotentiate synaptic function*

TMS may serve to produce specific forms, for example resembling LTD or LTP, in particular circuits. In producing a specific form of use-dependent neuroplasticity in a circumscribed circuitry, TMS shares some features of cognitive and behavioral therapy. From

this perspective, future research might explore ways that TMS might be combined with drugs that affect neuroplasticity diffusely in the brain, such as the glycine-related agents.

In considering neuroplasticity as a treatment, many questions emerge. For example, one might expect that new strategies would be needed to identify drugs that would act to modulate neuroplasticity in therapeutic ways, but might be behaviorally inactive by themselves. Major challenges for this field of research may be economic or regulatory rather than scientific. For example, would a pharmacologic treatment for a psychiatric disorder that involved the administration of a limited number of doses be sufficiently profitable to justify the investment of the pharmaceutical industry? If not, what other type of company, research foundation, governmental organization, or academic institution would have the capacity to test these drugs? Also, how does one develop and obtain FDA approval for a medication that must be administered in combination with a specific form of cognitive behavioral therapy? In particular, how important will it be to validate and standardize the psychotherapeutic component of the medication–therapy combination? These and other challenges will accompany the enormous apparent opportunities associated with the development of agents that attempt to facilitate the treatment of psychiatric disorders through the modulation of neuroplasticity.

## Disclosure

*Declaration of financial interests:* During the period of 2007–2009, Dr. Krystal has served as a scientific consultant to the following companies: AstraZeneca Pharmaceuticals, Cypress Bioscience, Forest Laboratories, Glaxo SmithKline, Lohocla Research Corporation,

HoustonPharma, Eli Lilly and Company, Pfizer Pharmaceuticals, Schering–Plough Research Institute, SK Life Sciences, Takeda Industries, and Transcept Pharmaceuticals. He holds less than \$10 000 in exercisable warrant options with Transcept Pharmaceuticals. He is the principal investigator of a multicenter study in which Janssen Research Foundation has provided drug and some support to the Department of Veterans Affairs. He is a co-sponsor for two patents under review for glutamatergic agents targeting the treatment of depression. During the period of 2007–2009, Dr. Tolin received research funding from Organon/Schering–Plough, Pfizer, and Indevus Pharmaceuticals. During the period of 2007–2009, Dr. Sanacora has served as a scientific consultant to or accepted honoraria from the following companies: AstraZeneca Pharmaceuticals, Bristol–Myers Squibb, Cenestra, Eli Lilly and Company, Lundbeck, Pfizer Pharmaceuticals, Hoffmann-La Roche Ltd., Ruxton Inc. and Sepracor. He is or has been the principal investigator of studies funded by AstraZeneca Pharmaceuticals, Bristol–Myers Squibb, Pfizer Pharmaceuticals, Hoffmann-La Roche Ltd., Ruxton Inc., and Sepracor since 2007. He is a co-sponsor on a patent under review for glutamatergic agents targeting the treatment of depression.

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