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REVIEW ARTICLE

Plasticity of synapses and reward circuit function in the genesis and treatment of depression

Scott M. Thompson[1] ✉

What changes in brain function cause the debilitating symptoms of depression? Can we use the answers to this question to invent more effective, faster acting antidepressant drug therapies? This review provides an overview and update of the converging human and preclinical evidence supporting the hypothesis that changes in the function of excitatory synapses impair the function of the circuits they are embedded in to give rise to the pathological changes in mood, hedonic state, and thought processes that characterize depression. The review also highlights complementary human and preclinical findings that classical and novel antidepressant drugs relieve the symptoms of depression by restoring the functions of these same synapses and circuits. These findings offer a useful path forward for designing better antidepressant compounds.

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INTRODUCTION

Depression is a leading cause of mortality and morbidity, affecting ~5% of the US population. Its many devastating symptoms, including persistent pathological deficits in mood, responses to rewarding stimuli (i.e., anhedonia), motivation, and cognition, as well as a greatly increased risk of suicide, make it essential to find effective treatments. Most widely used therapeutics, which potentiate monoaminergic neurotransmission, take 3–8 weeks to relieve symptoms, complicating treatment optimization and delaying relief, and are ineffective in one third of patients. Any individual patient may present with a range of possible symptoms, longitudinal time-course, and co-morbidities, as well responsiveness to antidepressants. It is hoped that a better understanding of the underlying neurobiological deficits will allow for a more effective personalized, targeted treatment plan [1, 2].

The etiology of depression involves both genetic and environmental factors [3], with the latter accounting for roughly 60% of risk [4]. Interestingly, pathway analyses from genome wide association studies have implicated many genes involved in synaptic function, axonal projections, and neurogenesis [5], although each contributes only a small amount to overall risk. A common environmental factor that increases the likelihood of depressive episodes is stress. Depressed patients report more stressful life events than non-depressed subjects, including physical illness, troubled family relationships, and financial difficulty [6]. Excessive rumination is common in depression and represents a uniquely human form of psychosocial stress. Early life adversity and traumatic childhood experiences are also a strong predictor of whom is at risk for depression, undoubtedly by triggering life-long lasting reprogramming events during particularly sensitive developmental windows [7], including in cortico-mesolimbic reward circuits [8]. Many of these long-lasting changes are likely to be mediated by epigenetic and transgenerational mechanisms that are beyond the scope of this review [9, 10]. Inflammation, often implicated in the genesis of depression, may also increase the susceptibility of synapses and neurons to the deleterious effects of stress [11].

Although acute stress is adaptive, persistently elevated levels of stress are maladaptive. In this review, I will summarize the abundant evidence that chronic stress damages brain function, to a significant extent, through its deleterious effects on excitatory synapses, thereby impairing the circuits underlying the brain's responses to rewarding and aversive stimuli, cognitive demand, and mood. I will also discuss evidence that a critical mechanism underlying antidepressant efficacy is restoration of the function of stress-damaged synapses, particularly within these same reward circuits. This topic has been reviewed extensively [12–16]. My goal is to provide an up-to-date summary of the evidence of synaptic dysfunction in depression and to discuss the impact of this cellular pathology in the context of circuit-level and systems-level interactions that together regulate mood, hedonic state and other symptom domains characterizing depression.

STRESS, SYMPTOMS OF DEPRESSION, AND THE CIRCUITRY OF REWARD AND EMOTION

The nature of the changes produced in the brain by chronic stress that promote depression in susceptible individuals remains unknown, but one of the most well-defined brain hallmarks of chronic hyperactivation of the HPA axis and chronic elevation of glucocorticoids is damage to excitatory synapses [16]. Glucocorticoids normally regulate neuronal survival, excitability, proliferation, metabolism, and memory but persistently high glucocorticoid levels may promote depression by impairing these processes [17].

The range of behaviors altered in depression suggests that multiple synaptic circuits are adversely affected, with no one synapse or circuit likely to be uniquely responsible for generating

[1]Department of Psychiatry, University of Colorado School of Medicine, Anschutz Medical Campus, Aurora 80045 CO, USA. ✉email: Scott.M.Thompson@CUAnschutz.edu

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the entirety of the depressed phenotype. We can speculate that different phenotypic symptom clusters may reflect anatomical differences in the circuits compromised in these patient groups [18]. The nucleus accumbens (NAc) is a critical link in cortico-mesolimbic reward circuits, integrating information from the prefrontal cortices (PFC), amygdala, and hippocampus to control the release of dopamine from the ventral tegmental area (VTA) back to the telencephalon [19–23]. There are also circuits involving the lateral habenula that display a relatively selective processing of negative valence stimuli and feed forward to the VTA. There is a great deal of evidence of dysfunction in both cortico-mesolimbic and habenular circuits in preclinical stress-based models of anhedonic states, as will be reviewed below, with VTA activation and dopamine release subject to bidirectional regulation by both rewarding and aversive stimuli. Dysregulation of dopamine release in motivating responses to rewarding and aversive stimuli, as well as cognitive demand, is a plausible mechanistic cause that can explain a range of depression symptoms [24–29].

Virtually all preclinical studies of utility for understanding depression involve the production of a depression-like neurobehavioral state by exposure of laboratory animals to various forms of chronic stress. Given the links between human depression and stressful life events, it is generally agreed that such models have a high degree of etiological construct validity, and many researchers consider stress-based models to have the greatest utility for depression research. Chronic stress-based models in rodents come in several varieties, but the common factor is repeated (typically daily) exposure to psychological and physiological stress beyond a period lasting for several weeks [30–32]. Physical stressors include mild unpredictable stressors (a rotating sequence of cage tilting, wet bedding, forced swim, etc) or several hours of physical restraint. One potential challenge is overcoming the habituation to a single stressor after repeated exposure [33]. Psychosocial stressors include social defeat stress and social isolation. Early life stressors include fragmentated maternal care and social isolation [34]. Chronic administration of exogenous corticosteroids (CORT) also mimics many behavioral and physiological aspects of chronic stress paradigms [35, 36].

These chronic stress models induce depressive-like behavioral states, resembling the symptom domains of human depression, and alter the putative underlying brain circuits in parallel with functional imaging findings in depressed humans [18, 37–39]. Importantly, these preclinical changes are reversed by chronic, but not acute, administration of classical monoaminergic antidepressants, such as selective serotonin reuptake inhibitors (SSRIs) [36, 40–44], presumably analogous to the delay for the therapeutic response to SSRIs in humans. They also respond quickly to acute administration of fast-acting antidepressant compounds like ketamine [45]. These models thus demonstrate some degree of predictive validity. Limitations of stress-based models include the induction of several anxiety-related behaviors, perhaps mirroring the co-morbidity and overlap of anxiety disorders and depression and some of their respective symptoms.

All chronic stress protocols produce behavioral changes with face validity to the symptom domains of human depression. Diagnosis of major depressive disorder (MDD) in humans requires two cardinal symptoms, persistent depression of mood and persistent anhedonia, or loss of pleasure in all activities that should be pleasurable. In addition, one or more other symptoms may occur, including impaired cognition, concentration, and attention; dysregulation of sleep; changes in appetite; fatigue; feelings of worthlessness; and suicidal thinking. Many of these are impossible to address in laboratory animals, particularly since detection of most human symptoms is traditionally dependent upon self-reporting by the patient. Tests of hedonic state and cognition, however, are readily tested in rodents in a variety of reward related and cognitive tasks. Impairment in these tasks is consistently observed after chronic stress and is clearly maladaptive. Other tests, with less obvious correspondence with human depression symptoms include various measures of 'behavioral despair,' such as the forced swim test (FST) and the tail suspension test. Somewhat easier to interpret are the learned helplessness tasks, in which repeated delivery of an inescapable negative stimulus, such as a foot shock, changes animals' behavior such that they will not escape even when given an opportunity. Although widely used and sensitive to known and novel antidepressants, their utility and interpretation is less clear [46] and their use is discouraged by the National Institute of Mental Health. Because they have been widely used, I will nevertheless discuss them in this review. It is to be hoped that better, more readily translatable, tests of reward behaviors will become more widely used in preclinical studies [47–49] in order to improve the selection of antidepressant compounds to take forward to clinical development.

An advantage of using tests of hedonic state and cognition is that the circuits underlying these behaviors are well known [50–55]. We can thus direct our preclinical search for depression relevant causative mechanisms and antidepressant relevant responses to brain regions in which cellular and molecular descriptions of pathology and treatment can be understood in terms of the behavioral changes they are likely to cause.

A grossly oversimplified overview of these circuits is that the prefrontal cortices and hippocampus are devoted to detecting and decoding specific features of stimuli and the environment, including the social environment, to guide decision-making and ensure adaptive, flexible, and predictive responses to rewarding stimuli, whereas the lateral hypothalamus-lateral habenula circuits predominantly encode features of stimuli with negative emotional valence. Both of these networks are then integrated in the NAc and VTA to regulate the release of dopamine. The feedback release of dopamine in these same regions than helps to reinforce and sculpt subsequent responses to rewarding and aversive stimuli.

THE HIPPOCAMPUS

An impaired ability to think and concentrate, which encompasses deficits in memory, executive function, and attention, is one of the major symptom categories used to diagnose MDD and contributes significantly to the overall disability associated with depression [56, 57]. The hippocampus is well known to be essential in declarative and spatial memory formation from both animal studies and humans. It is also known to be an important regulator of the hypothalamic-pituitary axis, mediating negative feedback of stress hormone secretion.

The role of the hippocampus in reward related behaviors is becoming increasingly apparent [58]. Numerous changes in the electrophysiological responses of hippocampal neurons related to various aspects of reward have been described, including an increase in firing rates as animals approach a reward location [59, 60]. This is thought to result because the learning of reward locations results in the reorganization of place fields so that areas near those locations become overrepresented [61]. Hippocampal ensemble firing patterns also help animals correctly predict which direction they need to move in order to reach a chosen distant goal [62]. Importantly, receipt of a reward triggers an increase in the rate of spike-wave ripples [63], which are known to enhance place field stability, and may thereby promote learning of reward locations [64].

There are also strong, and psychologically impactful, interactions between memory and emotions [65]. Excessive rumination on memories of emotionally significant negative events from the past is positively correlated with incidence of depression and anxiety [66]. Dysfunction of the hippocampal–prefrontal circuits that underlie extinction of emotional memories is postulated to contribute to excessive negative rumination [67]. Proper ventral

hippocampus-to-mPFC signaling is also necessary to recall social memories [68].

McEwen and colleagues first discovered that chronic stress and administration of exogenous corticosteroids lead to neuronal death in the hippocampus in rodents, as well as atrophy of the distal pyramidal cell dendrites and loss of dendritic spines [69–74]. These effects are consistent in all principal cell types and across multiple forms of physical and social stress [75–77].

Hippocampal atrophy is also one of the most consistent anatomical findings in imaging studies of human depression [78–80]. Hippocampal volume loss in depressed patients is correlated with memory dysfunction [81]. As in animal models, human hippocampal atrophy can result solely from elevated corticosteroid levels. Selective atrophy of the hippocampus is observed in patients with Cushing's Syndrome and other diseases with chronically elevated cortisol levels, and these morphological changes are reversed by treatments that lower cortisol levels [82]. These data suggest that chronic stress, either from traumatic life events or psychosocial stressors, like excessive negative rumination, is the cause of the hippocampal atrophy in depression. There is also evidence that early life trauma can cause lifelong decreases in hippocampal volume [83], suggesting that preexisting hippocampal atrophy may predispose some people to the onset of depression later in life. Treatment with conventional antidepressants diminishes the atrophy in human depression [84], including recent longitudinal studies in previously drug naïve patients [85, 86], suggesting that the anatomical changes may underlie functional improvements.

How might stress and elevated corticosteroids produce this hippocampal dendritic atrophy and volume loss? Preclinical studies have shown that chronic stress and exogenous corticosteroid administration decrease the expression of several neurotrophic factors and their receptors, notably brain derived neurotrophic factor (BDNF) and its receptor tropomyosin receptor kinase B (trkB)(for review see: [87]. Furthermore, hippocampal and prefrontal cortical BDNF and trkB levels are decreased in postmortem tissue taken from suicide victims compared to tissue obtained from non-suicidal control brains [88]. The dentate gyrus is a unique source of ongoing neurogenesis in the adult brain, at least in nonhuman animals, and there is preclinical evidence that the birth and maturation of new granule cells may play a role in depression and antidepressant drug actions [89]. Preclinical studies have shown that the genesis of new neurons in the dentate gyrus from stem cells is impaired after chronic stress and exogenous corticosteroid administration [90–92].

The link between these phenomena and the genesis of depression was considerably strengthened with the finding that conventional antidepressants promote BDNF expression [87, 93] and neurogenesis [94–96]. A neurotrophic hypothesis of depression has been proposed, which posits that a decrease in neurotrophic factor signaling as the root of dysgenesis of dentate granule cells and atrophy of dendrites and synapses in depressed brain [87, 97, 98]. This hypothesis is complementary to the suggestion that stimulation of neurotrophic signaling and neurogenesis by antidepressants explains their therapeutic actions [99–101]. The explanatory power of neurogenesis in depression and antidepressant drug effects is complicated by the fact that neurogenesis is only observed in the dentate gyrus, putting a severe limit on the possible depression symptom domains it can impact, and by recent findings that neurogenesis may be very limited or absent in humans [102]. Nevertheless, it is particularly exciting that several slowly and rapidly acting antidepressant compounds, including fluoxetine and other classical antidepressants, and ketamine and its metabolites, have recently been shown to bind directly to the trkB receptor and thereby promote its activation by BDNF [103].

Beyond dendritic atrophy, there are dramatic alterations in synaptic structure and function in animal models based on chronic stress [104], including altered synaptic currents [105], deficits in synaptic plasticity in CA1 and DG [106], and impaired local circuit function [107]. In the hippocampus, several types of chronic stress cause a loss of distal apical dendritic branches in CA3 and CA1 pyramidal cells and a loss in the size and number of dendritic spines [71, 74, 108]. Nevertheless, the evidence of stress-induced changes in excitatory synaptic transmission in hippocampal pyramidal cells is somewhat mixed. In this regard, it is important to recognize that the effects of acute stress are generally adaptive and very different from the maladaptive consequences of chronic stress [104]. In area CA3, chronic stress enhances synaptic currents mediated by NMDARs but has no effect on AMPARs [109]. In contrast, chronic stress has no effect on basal synaptic strength at Schaffer collateral (SC) synapses in area CA1, although it does impair SC-CA1 long-term potentiation (LTP) [106, 110]. In contrast, at the temporoammonic (TA) synapses formed by entorhinal cortical afferents to the distal dendrites of CA1 pyramidal cells, where atrophy is most apparent, AMPAR-mediated basal synaptic transmission is impaired by chronic stress or exogenous corticosteroid administration, but LTP is unaffected [36, 110]. The functional consequence of stress-weakened TA-CA1 synaptic transmission is an impairment of spatial memory consolidation [36, 110]. Chronic social defeat stress also induces dendritic spine atrophy in CA1 pyramidal cells [111]. There may also be lasting, life-long consequences of early life chronic stress. Chronic adolescent stress in female rats caused a decrease in hippocampal SC-CA1 synaptic strength in adults, accompanied by impaired cognitive flexibility [112].

The mechanisms underlying the ability of chronic stress and exogenous corticosteroid administration to decrease excitatory synaptic function are presumably related to anatomical loss of dendritic spines and decreased expression of AMPARs. For example, GluA1 expression is decreased by 50% in the distal dendrites of area CA1 by chronic stress and glucocorticoid elevation [36, 110]. It is possible that these changes in glutamate expression and function, if occurring at multiple brain regions within reward circuits, are sufficient to cause depression-relevant behavioral phenotypes. Global deletion of the gene for the GluA1 subunit of the AMPAR, for example, results in a depression-like phenotype in the learned helplessness test [113]. Mice in which the GluA1 gene cannot be phosphorylated by calcium/calmodulin-dependent kinase (CaMK), thereby impairing their insertion into synapses, display altered behavior in the sucrose preference and novelty suppressed feeding tests, identical to those produced by chronic stress [44].

It has also been suggested that the ability of allostatic load to affect excitatory synaptic function may influence susceptibility to depression. In the chronic social defeat model, for example, stress susceptible mice had larger decreases in GluA1 expression in area CA1, compared to resilient mice [114]. The authors further examined genetic polymorphisms in genes encoding GluA1 subunits and found a single nucleotide polymorphism that correlated with vulnerability to stress. How this compares to human GluA1 gene SNPs was not described, but this evidence converges with human data implicating AMPARs [115]. Gene clusters associated with excitatory synaptic function are also commonly identified in genetic screens in suicide and depression [116–118] and in preclinical studies [119].

On a network level, chronic stress deceases the spatial tuning of hippocampal cell discharges, as well as the power of gamma oscillations in local field potentials [120]. The power of gamma oscillations contributes to working memory capacity, is reduced in patients with MDD, and is normalized with symptomatic remission [121]. GABAergic inhibition is also affected by chronic stress [122] and may contribute to the altered balance of excitation and inhibition as well as defects in ensemble activity. These results suggest that chronic stress-induced changes in synaptic function impair local network function and thereby impair the neural

computations underlying cognitive processing. Together these data make a strong argument that disruption of hippocampal glutamatergic transmission, specifically AMPAR function, accompanies and may cause the depression-like behavioral state seen in preclinical models.

A common feature of all known antidepressants and many antidepressant treatments under development is their ability to reverse the effects of stress on synaptic structure and function, although they may produce this effect through various mechanisms. Serotonin increases phosphorylation of AMPA receptors and increases their delivery to the cell surface [123], an effect that is mimicked by the tricyclic antidepressant imipramine [124] and by chronic administration of the SSRI fluoxetine [125]. Chronic, but not acute, administration of conventional antidepressants also reverses stress-induced dendritic atrophy in rodents [126].

We have observed that chronic, but not acute, administration of fluoxetine restores the strength of stress-weakened TA-CA1 excitatory synapses, concomitant with the recovery of normal hedonic behavior [44, 120]. We observed that this restoration of synaptic strength and hedonic behavior was absent in mice with genetically modified GluA1 subunits that are incapable of being phosphorylated by calcium/calmodulin-dependent protein kinase (CaMK). We concluded that the antidepressant actions of SSRIs are mediated, in part, by a rapid insertion of AMPARs into synapses, due to $5HT_{1B}$R-dependent activation of CaMK and phosphorylation of GluA1 subunits at serine 831, a mechanism shared with canonical NMDAR-dependent long-term potentiation, as well as a slower restoration in GluA1 expression levels. Similarly, fluoxetine normalizes stress-induced changes in dendritic spine and glutamate receptor expression in the amygdala [127]. Fluoxetine also produces rapid disinhibition in hippocampal brain slices [128], which could also contribute to a net increase in excitation in vivo.

Restoration of stress-impaired excitatory synaptic function also appears to be a fundamental mechanism underlying the actions of known fast acting antidepressant drugs and potential therapeutic compounds. Extensive experience with human patients has established that ketamine exerts rapid, robust antidepressant, antianhedonic, and antisuicidal actions within two hours of administration that are sustained for at least seven days in patients with major depression following a single infusion or intranasal administration [129–133]. Ketamine's antidepressant effects compared to placebo controls are further supported by several thorough meta-analyses [134–136]. Ketamine also exerts strong antidepressant-like actions in preclinical models, including restoration of reward behavior in chronically stressed animals, promotion of dendritic spine formation, restoration of synaptic strength, and promotion of expression of pro-synaptic genes [45]. Three classes of mechanism have been proposed to account for these therapeutic actions on the basis of preclinical work, all of which involve plasticity of excitatory synapses.

The first hypothesis might be called the 'glutamate surge' or 'activity-dependent plasticity' model. Based on early microdialysis measurements of increased extracellular glutamate release after a single administration of a therapeutic dose of ketamine [137], it is now known that ketamine produces increased synchronous neuronal activity in the prefrontal cortex and hippocampus, particularly in the gamma frequency band (30–80 Hz) in preclinical studies and in humans [138–141]. These oscillations are likely to result from disinhibition produced by a selective block of NMDARs on GABAergic interneurons [142, 143]. These high frequency oscillations lead to activation of endogenous activity-dependent synaptic strengthening mechanisms [144], including (paradoxically) NMDA-receptor dependent LTP, increases in dendritic spine number [145], and promotion of BDNF-trkB signaling [146], as we and others have speculated [13, 14, 147, 148].

Indeed, this potential mechanism may be shared by almost all other compounds exerting rapid antidepressant actions in clinical and/or pre-clinical studies, such as AZD6765 [149], $mGluR_{2/3}$ antagonists [150], alpha5 subunit-selective $GABA_A$R-NAMs [151, 152], and the ketamine metabolite (*2 R,6 R*)-HNK [153], all of which enhance EEG power in the gamma frequency band.

The second explanation for ketamine's actions on excitatory synapses is the synaptic scaling hypothesis [154]. This hypothesis posits that ketamine restores stress-impaired excitatory synapses by blocking a subset of NMDARs that are preferentially activated by spontaneous glutamate release. When these receptors are inhibited, postsynaptic Ca^{2+} influx is also inhibited, decreasing the activity of the calcium/calmodulin-dependent protein kinase and eukaryotic elongation factor 2 kinase (eEF2K). Activated eEF2K phosphorylates and inhibits eEF2, an elongation factor that promotes global translation of mRNAs. Reduced eEF2K activity thus de-suppresses eEF2 and thereby promotes protein translation. Among the proteins whose synthesis is promoted are GluA1 receptors and BDNF [155–158]. As a result, synaptic AMPAR expression is increased [154, 159]. As predicted, acute inhibition of eEF2K increases mEPSC amplitude in cultured hippocampal cells and occludes the actions of ketamine on mEPSC amplitude [159]. This hypothesis cannot be readily applied to other fast acting antidepressant compounds that do not target NMDARs. It is also difficult to reconcile with findings that other NMDAR antagonists that do not appear to have antidepressant activity. Finally, it was observed that five days of treatment with the monoaminergic antidepressant citalopram failed to produce antidepressant behavioral effects in mice but did decrease phosphorylation of eEF2 levels [160]. It remains to be determined whether reduced eEF2 phosphorylation is necessary and sufficient for the actions of rapidly acting antidepressants other than ketamine.

Lastly, there is an exciting recent hypothesis that ketamine may exert its antidepressant actions not by blocking NMDARs, but rather by its neuroactive metabolites, particularly the hydroxynorketamines (HNKs). Zanos et al. [153] reported that the behavioral actions of ketamine in mice could be eliminated by deuterating the molecule to greatly reduce its rate of hydrolysis, suggesting that ketamine's inhibition of NMDARs is not sufficient for its antidepressant actions. Direct administration of HNKs mimicked the behavioral actions of ketamine in mice, promoted EEG gamma oscillations, promoted expression of AMPARs and BDNF, and decreased phosphorylation of eEF2 levels in the hippocampus, providing plenty of mechanisms that could be triggered independently from NMDAR inhibition. Acute application of HNKs to hippocampal brain slices also produces a direct potentiation of SC-CA1 synaptic transmission [153], mediated by an increase in the probability of presynaptic glutamate release [161].

Perhaps the most direct evidence of the critical role that plasticity of excitatory synaptic transmission plays in the treatment of depression comes from preclinical studies of positive allosteric AMPAR modulators (i.e., AMPAkines) [162]. Antidepressant relevant effects reported for AMPAkines include decreased immobility in the FST, promotion of BDNF expression, amplification of ketamine effects, and increased neurogenesis in the dentate gyrus [163–166]. One AMPAkine failed to restore sucrose preference in chronically stressed mice, however [165].

THE PREFRONTAL CORTICES

Prefrontal cortical regions act in concert with the hippocampus, to which they are coupled by direct synaptic projections. For simplicity in this review, I will refer to the dorsal and ventral prefrontal cortices, the infralimbic cortex, and the orbitofrontal cortex as prefrontal cortex (PFC), but it is important to recognize that there is strong evidence that their functions are not identical and may display sex differences [167].

An essential adaptive skill of all animals is to learn to associate a rewarding experience with the sensory cues and actions in the environment that can be used to predict their future occurrence.

This learning skill allows us to make optimal decisions and take appropriate approach and consummatory actions. In order to do this, we need an internal representation of the environment and of expected rewards that are based on prior experiences and predictive cues. These cognitive maps of rewards underlie all goal-directed behaviors, providing an adaptive benefit of permitting flexible decision-making optimized for both interoceptive state and environmental availability. Similarly, it is essential to have experience-dependent, up-datable knowledge about where danger lurks or what foods are unpalatable in the environment. There is excellent evidence that these positively and negatively valenced functions take place within the PFC [168–170].

It is becoming increasingly apparent that not only is the physical environment represented within the prefrontal cortices, but also the social environment. Our own experiences tell us that the social environment may be even more dynamic than the physical environment and certainly more arbitrary. Included in the social environment are various features such as cooperativity, competition, and social affiliation that are strongly correlated with the triggers and symptoms of depression. Loneliness, for example, is caused by perceived social isolation and absence of companionship and is associated with increased risk for depression and suicide [171]. On the other hand, social support is one of the strongest predictors of resilience and increasing social support can provide a beneficial component of effective therapeutic approaches [172].

The cellular mechanisms underlying the PFC's ability to perform these functions are recently becoming clearer. It appears that the PFC acts as a choice option comparator during reward-guided decision making. Electrophysiological activity in the PFC encodes potential choice options and computes their comparison in the currently relevant environment. PFC output then turns these computations into actual actions [170]. In the human brain, activity increases as cues and stimuli become relevant to decisions, with the magnitude of this increase directly proportional to the outcome and reliability of the decision [173]. Modeling studies suggest that these comparisons are performed by two competing populations of neurons, each representing one option, which compete in a winner-take-all manner for choice via mutual recurrent excitatory synapses and reward-dependent synaptic plasticity [174, 175]. Deficits in PFC synaptic excitation and imbalances between excitation and inhibition would have obvious impact on these calculations.

The PFC is also an important site at which cognitive evaluations, such as the controllability of a stressor [176] or the valence of sensory stimuli [177], can influence affect and reward directly. It also regulates the negative ruminative thinking that can indirectly have an adverse impact on cognition and mood [178]. For example, cognitive control of responses to emotionally laden stimuli activates lateral regions of the PFC in human subjects [179].

Measured with fMRI, the PFC of depressed patients displays evidence of reduced volume, activity, and connectivity. Activity in the human PFC is increased by 'happy' stimuli to a greater extent than it is for 'sad' stimuli and these responses are altered in depressed and anhedonic patients [180–182], consistent with alterations in PFC circuit function. Hypoactivation of these regions is observed in MDD patients when performing tasks that require ignoring negative valence distracters [183]. Similarly, Liston et al. [184] tested heathy subjects in a PFC-dependent attention-shifting task before and one month after exposing them to psychosocial stress. Compared to a group of unstressed control subjects, stress selectively impaired subjects' attention and disrupted functional connectivity within a frontoparietal cortical network. Comparable effects are seen in a decision-making task, in which stress favors habitual choices.

In animal models, chronic stress impairs attentional set-shifting tasks that are mediated by the PFC and decision making in reward-based tasks [185], mimicking the human deficits seen in MDD patients [184]. Chronic stress also results in a ca. 20% reduction in the length of apical dendrites in pyramidal neurons in the PFC and a ca. 30% decrease in the density of axospinous synapses on apical dendrites, along with corresponding decreases in the expression of synaptic genes [186–189]. Longitudinal two-photon microscopic imaging of fluorescently labeled dendritic spines in the PFC revealed that chronic elevation of CORT leads to an increase in dendritic spine turnover and an abnormal loss of stable spines that had been formed early in life [190].

Loss of dendritic spines suggests a loss or dysfunction of excitatory synapses. Indeed, consistent with spine loss, chronic stress decreases the synaptic excitation of pyramidal cells in the PFC [191]. Both AMPAR- and NMDAR- components of the EPSP were equally affected, unlike in the NAc [192, 193] and hippocampus [110]. In parallel to these physiological findings, expression of GluA1 and GluN1 proteins was decreased due to ubiquitination and proteosomal degradation. There was no change in expression of the postsynaptic density protein PSD95, however. Consistent with the decrease in excitation, expression of several immediate early genes and genes associated with synaptic function are decreased in the PFC of depressed humans and in rodent models [194, 195].

There is strong evidence that treatments that reverse the symptoms of depression also reverse deficits in the PFC. Stress induced decision-making deficits in MDD patients are reversible: after one month of reduced stress, subjects were indistinguishable from controls [196]. Treatment of MDD patients with classical monoaminergic antidepressants also restores normal activation of the PFC in attention tasks and restores the volume of the PFC [197–199].

There is also strong preclinical evidence that increases in PFC activity mimic the actions of antidepressants. For example, optogenetic stimulation of the mPFC in a bursting pattern, not unlike that occurring during ketamine-induced gamma oscillations, in mice subjected to chronic social defeat drives changes in immediate early gene expression like those seen in the PFC of human patients medicated with antidepressants and has an antidepressant-like effect in sucrose and social interaction preference tests [194]. These findings are currently being translated into novel clinical therapies in which invasive deep brain stimulation or noninvasive transcranial magnetic stimulation targeted to the PFC or its descending output pathways is used to treat patients with depression [200, 201].

Ketamine and other fast-acting antidepressant candidates all produce a rapid restoration of dendritic spine density in the PFC in stressed and unstressed animals with the same rapid time course as its behavioral actions [145, 187, 202, 203], implying the restoration of synaptic and circuit function, too. Considerable progress has been made in identifying the cellular signaling mechanisms underlying these effects. One strong candidate is the activation of mammalian target of rapamycin (mTOR), a central regulator of cellular growth [202]. Ketamine triggers not only its activation, but also the activation of many of its downstream targets, within minutes-to-hours, in unstressed rats. Furthermore, co-administration of the mTOR inhibitor rapamycin prevented the induction of dendritic spines by ketamine, as well as ketamine's actions in the FST and other behaviors [202]. Use of synaptic vesicle PET ligands has recently revealed that ketamine produces similar synapse-promoting effects in the PFC in human depression [204].

Immunohistochemical analysis of interneurons and transcripts of interneuron-associated proteins are decreased within the PFC and anterior cingulate cortex in human MDD brain tissue and in chronically stressed rats, suggesting that deficits in GABA levels may contribute to the symptoms of depression [205–208]. Somatostatin- and parvalbumin-expressing GABAergic interneurons are particularly affected in chronically stressed rats [209]. There is also evidence that the antidepressant effects of ketamine occur via inhibition of GABA interneurons. As in the hippocampus, ketamine

inhibits the discharge of interneurons in the PFC and reduces spontaneous IPSCs in pyramidal cells acutely [210], while restoring inhibition at later timepoints corresponding to its behavioral actions [211]. Furthermore, knock-down and deletion of critical ketamine-sensitive NMDARs from either somatostatin- or parvalbumin-expressing interneurons alters baseline behaviors in the FST and other tasks and eliminates the ability of ketamine to change these behaviors in unstressed mice [210]. The effects of the deletion on the ability of ketamine to produce electrophysiological disinhibition were not tested, unfortunately. Similarly, chemogenetic inhibition of either somatostatin- and parvalbumin-expressing interneurons in the mPFC mimicked the effects produced by antidepressants in the FST and other tasks, suggesting that transient inhibition of GABAergic interneurons contributes to the actions of rapidly acting antidepressants [212].

As discussed above, inhibition of interneurons may promote the kinds of high frequency oscillatory activity in pyramidal cells that underlies gamma oscillations, as seen in human and rodent EEGs, and, in turn, promotes endogenous activity-dependent mechanisms that strengthen stress-impaired excitatory synapses, such as LTP and BDNF-trkB signaling. Indeed, ketamine and $GABA_A$ receptor negative allosteric modulators share an ability to promote gamma oscillations in the PFC at doses that reverse the behavioral consequences of chronic stress [152, 153]. Many of these forms of activity-dependent plasticity are likely to be NMDAR-dependent, as supported by the antidepressant-like actions of the NMDAR positive allosteric modulator GLYX-13 (rapastinel) in preclinical models [213]. Ketamine's disinhibitory action in dendrites also promotes dendritic Ca^{2+} influx [214], providing an additional mechanism to drive endogenous activity-dependent synaptic strengthening mechanisms.

THE NUCLEUS ACCUMBENS

The nucleus accumbens in the ventral striatum is an essential integrator of input pathways from the prefrontal cortex, hippocampus, and amygdala and is critical for determining motivating and reinforcing responses to rewarding stimuli and avoidance responses to aversive stimuli [215–217]. The NAc is divided into two histologically distinct subregions, the core and the shell, which have unique patterns of inputs and outputs [218, 219] and are thought to serve distinct, but similar functions [177]. The NAc consists primarily of GABAergic medium spiny neurons (MSNs), which can be distinguished into two primary populations based on their largely non-overlapping expression of dopamine receptors. As originally described in the dorsal striatum, MSNs expressing D1-type dopamine receptors, canonically considered the 'direct' pathway, project to and inhibit GABAergic interneurons within the VTA that, in turn, inhibit VTA dopamine releasing cells. Activation of D1-expressing MSNs thereby promotes activation of dopamine projections back to the forebrain by disinhibiting them [220]. In contrast, MSNs expressing D2-type dopamine receptors, canonically considered the 'indirect' pathway, project to GABAergic cells within the ventral pallidum, that then project to the interneurons within the VTA. Activation of D2-expressing MSNs thereby inhibits activation of dopamine projections back to the forebrain by disinhibiting the interneurons that silence them. More recent findings have established that these neat divisions do not apply as simplistically to the ventral striatum [221, 222]. Nevertheless, activity in D1 MSNs is more likely to be associated with motivation, reward, and positive responses [193, 223–225] and resilience to stress [226]. Conversely, a decrease in the ability of D1 MSNs to drive dopamine release from the VTA, due to decreased excitation and/or increased activity of D2 MSNs, may contribute to the loss of the rewarding properties of normally rewarding stimuli characterizing anhedonia and lack of motivation in the depressed state.

Activation of inputs to the NAc from the hippocampus and PFC is rewarding and reinforcing of rewarding stimuli [227, 228]. Excitatory synapses in the NAc in these pathways display activity-dependent plasticity. Much like canonical hippocampal LTP, high frequency stimulation of hippocampal afferents to the NAc elicits a rapid and persistent NMDAR-triggered, Ca^{2+}- and CaMK-dependent increase in postsynaptic AMPAR responses in D1 and D2 MSNs [193]. Dopamine receptor activation is not required for this potentiation but may be modulatory under physiological conditions [229]. Activity-dependent LTP in vivo was both necessary and sufficient to induce a conditioned place preference lasting for at least 24hrs [193]. Silencing hippocampal inputs to the NAc prevented formation of a place preference following social interactions, as assayed one day later, but did not prevent the rewarding properties of the social interaction itself. Similarly, establishment of cocaine place preferences is accompanied by a potentiation of hippocampal-NAc synaptic excitation [230]. Conversely, weakening inputs to the NAc can reverse previously established reward responses to addictive drugs [231, 232].

In response to chronic stress, rodent NAc MSNs display an array of plastic changes that act in concert to alter forebrain dopaminergic release from the VTA and, thereby, alter the responses to rewarding and aversive stimuli [233]. As such they are heavily implicated as central players in the genesis of depression. Susceptibility to chronic social defeat stress is accompanied by atrophy of MSN dendrites, specifically in D1 MSNs and not D2 MSNs, and a corresponding loss of dendritic spines [226, 234, 235]. Consistent with the anatomical findings, the frequency of miniature EPSCs is decreased without a change in amplitude. Similarly, evoked AMPA receptor-mediated excitatory synaptic currents are reduced by chronic stress in D1, but not D2, MSNs [236], including in response to afferents from the hippocampus [193]. These decreases in the excitation of D1 MSNs may be sufficient, in and of themselves, to mediate an anhedonic loss of reward behavior. Lim et al. [236] demonstrated that preventing stress-induced AMPA receptor loss in D1 MSNs was sufficient to prevent stress-induced loss of hedonic responses in sucrose preference and cocaine-induced place preference (although not the FST).

Chronic stress also impairs hippocampal – NAc LTP in D1 MSNs, but not D2 MSNs. This differential effect suggests a possible stress-induced biasing of NAc responses from D1 MSN towards D2 MSN activation, hence favoring negative valence responses over positive valence. Neuromodulators, including dopamine itself, serotonin, and enkephalins are also likely to play a significant role in gating synaptic strength and the balance between D1 and D2 MSN activity [217, 233, 237]. The intrinsic excitability of NAc MSNs is also affected by stress. Susceptibility to social defeat stress is accompanied by an increase in input resistance and firing in response to depolarizing currents pulses in D1 MSNs, but not D2 MSNs [226, 234].

Although receiving less attention than cortical plasticity, there is evidence that known and novel potential antidepressant compounds exert some of their therapeutic benefits via actions within the NAc. Chronic, but not acute, administration of fluoxetine to stressed mice restores the strength of hippocampal excitatory synapses in D1 MSNs and their ability to undergo LTP, concomitant with restoration of sucrose preference [193]. Consistent with these synaptic findings, the probability of action potential firing of neurons in the NAc in response to stimulation of hippocampal afferents is increased by escitalopram administration [238]. The net effect of these synaptic changes is to restore the function of the NAc- VTA circuit. Chronic treatment with escitalopram restores the ability of rewarding stimuli to trigger DA release within the NAc in chronically stressed rats [239]. Almost nothing is known about the mechanisms underlying the restorative actions of SSRIs in the NAc.

Ketamine also has effects on NAc synaptic function, including a direct potentiation of PFC-NAc synapses. Ketamine also restores the ability to induce LTP in the hippocampus-accumbens pathway in stressed animals [240]. Restoration of synaptic function is accompanied by restoration of circuit function. Ketamine restores a stress-induced decrease in VTA dopaminergic cell firing [240] and increases extracellular levels of dopamine in the nucleus accumbens [241]. The mechanisms underlying these effects remain unknown. Like the effects of ketamine in the cortex, ketamine increases the power of high-frequency oscillations of local field potentials in the NAc in unanesthetized mice [242], suggesting a potential role for activity-dependent synapse strengthening mechanisms. Given the lack of local excitatory interactions within the NAc, it is likely that this high frequency synchronized activity is projected onto the NAc via afferents from the PFC and hippocampus. As elsewhere in the brain, elevated BDNF – trkB signaling may be crucial within these mesolimbic circuits [243]. Finally, local infusion of ketamine into the NAc reversed stress-induced decreases in the phosphorylation of GluA1 AMPARs at serines 831 and 845, which is known to promote their insertion into synapses, suggesting a direct mechanism for the potentiation of NAc synapses [244].

Increases in resolution and increased use of reward-based tasks that correlate with preclinical studies have enhanced the ability to resolve the NAc in human functional imaging studies and allowed for new insights into the role its plasticity plays in reward deficits in human depression. There is evidence that the NAc is activated by reward anticipation and both motivational and hedonic aspects of reward processing [245]. Defects in hippocampal – NAc coupling have been observed to correlate with reward processing deficits [246]. Unmedicated MDD patients show deficits in reward learning, reduced responses in the ventral striatum for positive prediction errors in a reward task, and reduced NAc- VTA connectivity [247, 248]. There is limited evidence of the effect of antidepressants on these measures of reward circuit function, but it has been shown that improvements in self-reported depression severity and negative affective bias are improved with chronic SSRI administration in depressed patients and are strongly correlated with increases in NAc activity and NAc- PFC connectivity [249]. Similar increases in NAc-PFC connectivity correlate with reduced symptom severity and quality-of-life measurements in SSRI-responsive patients compared to unresponsive controls [250]. More studies are clearly needed. In particular, direct before-and-after comparisons of patients receiving fast-acting antidepressants would be of great interest. For example, Sterpinich et al. [251] observed that ketamine increased responses in a reward task and caused an accompanying increase in activity in the orbitofrontal cortex, ventral striatum, and the ventral tegmental area. Importantly, these effects persisted for up to a week after a single ketamine administration, strongly supporting an important role for plasticity in the cortico-mesolimbic circuitry in the genesis and treatment of depression.

THE LATERAL HABENULA

The habenula is an epithalamic nucleus comprised of medial and lateral subregions. The lateral habenula (LHb) is another key node in regulation of reward behaviors that has been implicated in the genesis of depressive symptoms and reward dysregulation [252]. It integrates glutamatergic inputs from the lateral hypothalamus [253] and from the anterior cingulate and medial prefrontal cortices [254]. Excitatory synapses onto LHb cells are characterized by a high ratio of AMPAR- to NMDAR-mediated synaptic responses [255], indicative of low levels of NMDAR expression. LHb neurons also receive feed-forward and feedback GABAergic inhibition [253, 255]. The glutamatergic neurons of the LHb have three primary targets, the dopaminergic cells of the VTA, the serotonergic neurons of the nucleus raphe, and the GABAergic neurons of the rostromedial tegmental nucleus (RMTg). RMTg neurons, in turn, project to the VTA and are largely responsible for the predominantly inhibitory action of LHb projections onto VTA dopaminergic neurons [256].

Activity of LHb neurons is generally correlated with aversive and negative affective behaviors. LHb neurons fire in response to both aversive stimuli and the absence of an expected reward [257–260]. Conversely, reward delivery decreases LHb discharge [257]. Optogenetic activation of LHb neurons via projections from the lateral hypothalamic nucleus (LH) triggers avoidance and escape behaviors, whereas optogenetic or pharmacological inhibition of LHb cell discharge impairs avoidance and escape in response to aversive stimuli [258–260]. With regard to behaviors typically used to study depression and antidepressant drugs, acute physical restraint, foot shock, tail suspension, forced swimming, and social defeat are all accompanied by strong LHb activation [258, 260]. The consequences of LHb activity are largely mediated by its output to the RMTg [261]. Importantly, activation of LHb inputs to the RMTg reduced motivation to work for a rewarding sucrose solution in an operant task, without reducing its rewarding hedonic properties [262].

There have now been several demonstrations that chronic stress results in changes in LHb discharge and synaptic function. Mechanisms include both changes in the intrinsic excitability of LHb neurons and plasticity of their synapses. Stress-induced increases in firing are attributed to decreased function of G-protein coupled K^+ channels in LHb neurons [263]. Increased burst discharges [264] are attributed to dysregulation of the astrocytic K^+ channels that regulate extracellular K^+ concentrations, thereby promoting hyperpolarization of LHb neurons [265], although this hyperpolarization was not shown. Increased numbers of burst-firing LHb neurons were observed in vitro and in vivo in both a rat strain with congenital learned helplessness and in wild type rats after chronic restraint stress, although no overall change in membrane potential was reported [266]. Bursting in LHb cells is mediated by T-type voltage-dependent Ca^{2+} channels and NMDA receptors. Surprisingly, bursting was largely unaffected by AMPAR antagonists, suggesting that synaptic activity does not drive bursting. Optogenetically induced increases in burst firing in LHb neurons increased mobility in the FST and decreased sucrose preference [266], like the effects of chronic stress.

Chronic stress potentiates excitatory transmission onto LHb cells in parallel with altered excitability. An increased probability of presynaptic glutamate release in the LHb accompanies learned helplessness and chronic restraint stress [255, 260]. Some forms of chronic stress also increase the amplitude of spontaneous excitatory synaptic responses [260]. Selective activity-dependent potentiation of synapses formed by axons of LH neurons with LHb neurons promoted LHb discharge and was sufficient to induce mimic the behavioral effects of chronic stress in the forced swim and sucrose preference tests [260, 267].

These behavioral results, although demanding to demonstrate, can be predicted from previous evidence that LHb firing is aversive. So, does the increase in LHb bursting drive behavioral changes in response to chronic stress? Lesioning or pharmacologically silencing the LHb can normalize learned helplessness responses [266, 268], including inhibition of NMDAR-mediated LHb bursting [264]. Evidence that chemo- or optogenetic silencing of LHb neurons can prevent pathological behaviors in a chronic stress paradigm is lacking. Viral knockdown of beta-CaMK, the enzyme underlying the stress-induced presynaptic potentiation of LHb excitatory synapses, prevented forced swim and learned helplessness behaviors in congenitally learned helpless rats [267]. Whether prevention of activity-dependent potentiation of LH-LHb synapses would block behavioral changes in response to chronic stress remains to be demonstrated. Nevertheless, the evidence is plentiful and strong that the LHb is an important mediator of

aversive behavioral responses via its outputs to the VTA and that its behavior is profoundly increased in a variety of chronic stress conditions used to model depression relevant behaviors in rodents (for excellent further reviews, see: [252, 269, 270]).

FUTURE RESEARCH DIRECTIONS: PUTTING IT ALL TOGETHER

The work cited above, describing results from both preclinical and human studies, provides compelling evidence, first, that prolonged stress, both physical and psychosocial, affects the structure, protein composition, and function of excitatory synapses in every area of the brain devoted to the processing of reward related stimuli and cognitive, learning, and memory processes. These plastic changes appear maladaptive. Excitatory synapses generally become reduced in number and weaker in areas devoted to directing attention and making decisions about cues and stimuli and stronger in the pathways processing negative valence stimuli. These synapses are the working elements of the circuits they are embedded in and hence are could be the cause of significant changes in the function of those circuits. In general, the synaptic changes result in a weakening of pathways that promote dopamine release by activating cells in the VTA, such as the direct and indirect weakening of excitatory drive of D1 MSNs in the NAc, and potentiation of pathways inhibiting dopamine secretion, such as those within the LH-LHb-RMTg.

These concerted changes in synapses in response to chronic stress have been found in essentially every circuit in every reward pathway, providing a mechanistic explanation for the wide range of symptoms that together constitute the clinical definition of depression. As summarized above, there is strong evidence from imaging and functional connectivity studies of human patients to suggest that analogous changes occur in human MDD. Of course, not all patients display the same combination of symptoms. Perhaps the relative prevalence of individual symptoms in a given MDD patient arises from the relative degree to which any particular synapses and circuits are affected in that patient. Considering emotional dysregulation [271], for example, an overactive LHb circuit may favor an increase in negative affect. In contrast, hypoactive PFC circuits might be more heavily affected in patients with more prevalent cognitive and decision-making symptoms. A better understanding of the function of these reward circuits in preclinical models and human subjects and their dysfunction in depression may thus help to distinguish between subtypes of depression [2]. Because not all circuits and symptoms may respond in the same manner to all antidepressants, a better understanding may also guide the choice of antidepressant therapies to employ. For example, increased negative affective bias in depressed subjects was shown to respond rapidly to a norepinephrine reuptake inhibitor, even though patients reported no overall improvement in their overall depression [272]. The distributed nature of these changes also complicates experimental efforts to identify a single synapse or circuit as the unique 'cause' of a given behavioral deficit, given their highly interconnected nature. Driving the LHb may overpower counterbalancing NAc inputs to the VTA, for example, regardless of whether they are fully functional or dysfunctional.

An underlying assumption of all preclinical models is that the forms of chronic stress we produce experimentally in our animals provides a realistic model of human depression. On the one hand, the evidence of the etiological relevance of stressful life events to human depression, either acutely or during critical developmental windows, is very strong. On the other hand, environmental factors are believed to account for only 60% of risk for MDD. Preclinical studies are largely done on experimental animals with a relatively homogenous genetic background, obscuring the important contributions of genetics to susceptibility and resilience. Given the likelihood that overall genetic risk results from small differences in large numbers of genes, each with small contributions to overall risk, this blind spot represents a particular short coming in our current understanding and significant experimental challenge for future progress.

Supporting the hypothesis that synaptic and circuit dysfunction is a major cause of depression, there is increasing evidence that restoration of the function of synapses and circuits is a common mechanism of action underlying a wide range of known and novel antidepressants. Those antidepressants that restore synaptic strength slowly, such as SSRIs, restore synaptic strength slowly, whereas fast acting antidepressants do so rapidly. Further supporting this hypothesis of antidepressant action, these substances do not necessarily share the same mechanisms of action. Although there is overlap, some favor activity-dependent synaptic strengthening mechanisms, such as ketamine and ketamine metabolites, whereas others, such as SSRIs, favor neurotrophic growth factor signaling. Nevertheless, all strengthen synapse function. The search for novel antidepressants should be focused on a search for compounds that share this mechanism of action. For example, we hypothesized that negative allosteric modulators of $GABA_A$ receptors containing alpha5 subunits would promote a transient, ketamine-like increase in high frequency, synchronized oscillations in the PFC and hippocampus and would therefore produce a ketamine-like rapid antidepressant response. Subsequent preclinical experiments supported this hypothesis [152, 273].

One of the most exciting developments in the treatment of depression and other psychiatric disorders has been the recent findings that a single administration of psilocybin produces a rapid and persistent improvement in self-reported depression symptoms in patients resistant to conventional antidepressants (e.g., [274]). There is also robust preclinical evidence that psilocybin can restore both reward behaviors and synapse structure and function. In the hippocampus, stress-impaired reward behaviors are restored to baseline levels 24 h after a single administration of psilocybin [275], exactly as seen with other fast-acting antidepressants. Taking hippocampal brain slices from these same mice revealed that psilocybin also restored the strength of the stress-sensitive TA-CA1 synapses, concurrent with the restoration of reward behavior, again much like other fast-acting antidepressants. Similarly, in the PFC, psilocybin administration to unstressed mice leads to an increase in the net formation of new dendritic spines in pyramidal cells, persisting for over one month, which is accompanied by an increase in the frequency of spontaneous mEPSCs [276]. These preclinical findings are paralleled by human functional imaging findings that psychedelics change connectivity in reward- and emotion-relevant brain regions in a persistent manner [277]. Surprisingly, both studies suggested that the actions of psilocybin were independent of the serotonin 2 A receptor that mediates the mind-altering properties of psychedelics, raising the possibility of dissociating the 'trip' from the antidepressant benefits of psychedelics. Because of the expense and time-consuming nature of current psychedelic therapies, involving multiple clinic visits and a full day with one or more therapists, this could considerably lower barriers to widespread use. An active current area of research is to define the expression mechanisms underlying the persistent increases in synaptic strength. Many of the same processes described above are likely to be involved, including neurotrophin signaling and enzymatic cascades promoting receptor trafficking and process outgrowth [278]. It will be of great interest to further identify and refine the beneficial properties of these powerful compounds and determine whether their promise is mediated by promoting plasticity of synapses and reward circuits.

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COMPETING INTERESTS

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ADDITIONAL INFORMATION

Correspondence and requests for materials should be addressed to Scott M. Thompson.