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Synaptic Plasticity, Metaplasticity and Depression

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Abstract: The development of a persistent depressive affective state has for some time been thought to result from persistent alterations in neurotransmitter-mediated synaptic transmission. While the identity of those transmitters has changed over the years, the literature has lacked mechanistic connections between the neurophysiological mechanisms they regulate, and how these mechanisms alter neuronal function, and, hence, affective homeostasis. This review will examine recent work that suggests that both long-term activity-dependent changes in synaptic strength ("plasticity"), and shifting set points for the ease of induction of future long-term changes ("metaplasticity"), may be critical to establishing and reversing a depressive behavioral state. Activity-dependent long-term synaptic plasticity involves both strengthening and weakening of synaptic connections associated with a dizzying array of neurochemical alterations that include synaptic insertion and removal of a number of subtypes of AMPA, NMDA and metabotropic glutamate receptors, changes in presynaptic glutamate release, and structural changes in dendritic spines. Cellular mechanisms of metaplasticity are far less well understood. Here, we will review the growing evidence that long-term synaptic changes in glutamatergic transmission, in brain regions that regulate mood, are key determinants of affective homeostasis and therapeutic targets with immense potential for drug development.

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Keywords: Depression, glutamate, metaplasticity, mGluR, NMDAR, synaptic plasticity.

INTRODUCTION

Major depressive disorder is highly prevalent, recurrent, and affects millions of people worldwide. Most clinically available therapeutics consist of selective serotonin reuptake inhibitors (SSRIs) that only improve symptoms in about 55% of patients after weeks of treatment, while 30-40% of depressed patients do not have an adequate response to any available therapeutics. The mechanism of action of these drugs is poorly understood, and it is becoming clear that there are neurotransmitters in addition to serotonin which are important for manifestation of depression. Evidence for the involvement of N-methyl-D-aspartate glutamate receptors (NMDARs) and metabotropic G-protein coupled glutamate receptors (mGluRs) in depression will be discussed herein. This review will also discuss the potential role for activity dependent synaptic plasticity in the development of depression and the resultant metaplasticity that may need to be renormalized for a patient to fully recover from their depressive symptoms.

NMDA RECEPTORS AND LONG-TERM SYNAPTIC PLASTICITY

Long-Term Potentiation of Synaptic Transmission

The phenomenon of long-term potentiation (LTP) of synaptic transmission is an activity-dependent, long-lasting increase in synaptic strength that is hypothesized to play critical roles in cognitive processing and the encoding of long-term memories. While there is evidence for a number of neuronal mechanisms involved in persistently altering neuronal excitability, both at synapses and elsewhere on the neuron, LTP has attracted particular interest because of the isomorphism of its properties with those posited by Donald Hebb [1] to be suitable for a neural network information coding mechanism. In particular, these properties are that persistent increases in synaptic strength should 1) require a minimum threshold for neuronal activity, 2) require temporally coincident presynaptic and postsynaptic activation, and 3) be confined only to the synapses that are so activated.

The NMDAR possesses molecular characteristics that are ideally suited to convey, at the molecular level, these "Hebbian" properties on a single synapse. In particular, the voltage-dependent blockade of NMDARs by Mg^{2+} ensures that presynaptic glutamate release must occur simultaneous with postsynaptic membrane depolarization for NMDAR-gated Ca^{2+} influx to occur [2]. However, NMDARs also possess a number of regulatory sites that bind endogenous modulators of their activity. Essential amongst these is the obligatory co-agonist site on NR1 (or NR3) NMDAR subunits that is stimulated by the full agonists glycine and D-serine. While stimulation of this site alone does not cause channel opening, it must be bound to permit glutamate to trigger channel opening [3]. It remains an open question, but a very appealing idea, whether the NMDAR co-agonist site is a target of endogenous modulators that, either tonically or phasically, control NMDAR activity.

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There is a wealth of literature implicating NMDARs as essential mediators of information storage in long-term memory formation [4], and indicating that excess activation of NMDARs can be neurotoxic [5]. However, activity-dependent synaptic plasticity such as LTP has also been implicated in diseases such as neuropathic pain [6], stroke [7], traumatic brain injury [8], and epilepsy [9]. In principle, NMDAR-dependent persistent alterations in synaptic strength, and the propensity for NMDAR activation to lead to downstream biochemical, gene expression and morphological changes, are likely to be important mediators in shaping neural network function. If these networks are in brain regions associated with affective state and set points, alterations in synaptic strength could underlie depressive disorders.

Long-Term Depression of Synaptic Transmission

While LTP has long been thought to be a key mechanism of storage of long-term memories, it has recently become clear that some mechanism is necessary for long-term depression (LTD) of synaptic transmission for a number of reasons. One is to avoid saturation of synaptic strength at maximum levels. Another is that bi-directional synaptic plasticity that follows some type of covariance rule, *i.e.*, senses the amount of presynaptic input that is temporally coincident with postsynaptic firing versus the amount that is not, maximizes the pattern of strengthened and weakened synapses in a way the optimizes both the development of synaptic networks [10] and the storage of information [11]. These theoretical predictions were confirmed by the discovery that both LTP and LTD can be elicited at individual synapses, depending upon whether high or low levels of paired presynaptic and postsynaptic activation occur [12]. If high levels of paired presynaptic and postsynaptic activity occur, then NMDARs are activated at levels that lead to a large influx of calcium, activation of protein kinases that result in gene transcription, protein synthesis, trophic factor release, synaptic strengthening, and growth of new synapses. If lower levels of paired presynaptic and postsynaptic activity occur, then NMDARs are weakly activated, resulting in smaller influxes of calcium that preferentially activate phosphatases and result in removal of α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) glutamate receptors (AMPAR) from the dendritic spine, loss of trophic factors, synaptic weakening, and eventual retraction or loss of the spine. While both LTP and LTD are now well documented at a variety of synapses, the roles of these distinct forms of plasticity in affective depression remain to be elucidated.

NON-NMDAR FORMS OF SYNAPTIC PLASTICITY

Metabotropic Glutamate Receptors and Synaptic Plasticity

While NMDAR-mediated LTP and LTD are the most studied forms of long-term synaptic plasticity, they are by no means the only biochemical pathways that persistently alter synaptic strength. mGluRs are a large class of glutamate receptors that modulate second messenger levels by activating adenylate cyclase, or generating IP_3-mediated influx of calcium from intracellular stores [13-15]. Activation of mGluRs can elicit both LTP [16] and LTD [17], even when NMDARs are blocked, and shift the threshold for induction of LTP [18, 19] and LTD [20].

The role of mGluRs in both synaptic plasticity and regulation of dendritic spine morphology and density has been most strongly associated with Fragile-X syndrome (FXS). FXS is a disease characterized by intellectual disability and autistic traits, which results from the silencing of the FMR1 gene coding for a protein (FMRP) that regulates local synthesis of proteins in individual synapses [21]. The lack of functional FMRP has been proposed to result in excessive signaling of mGluRs [22], enhanced LTD of synaptic transmission [23] and impaired dendritic spine maturation in glutamatergic neurons [24].

Presynaptic Plasticity

In addition to non-NMDAR mGluR-dependent LTP and LTD that are induced and expressed postsynaptically, there are also non-NMDAR forms of long-term plasticity expressed in presynaptic terminals of glutamatergic synapses. Mossy fiber-CA3 synapses in the hippocampus express a presynaptic LTP mediated by calcium influx *via* voltage-dependent calcium channels that trigger production of the second messenger cyclic AMP [25]. At Schaffer collateral-CA1 (SCH-CA1) pyramidal cell synapses that express NMDAR-dependent LTP and LTD, a group II mGluR and A1 adenosine receptor-dependent form of LTD is also expressed as a persistent reduction in presynaptic vesicular release of glutamate [26, 27]. It is evident that long-term increases and decreases in synaptic strength can be induced both presynaptic and postsynaptically without NMDAR activation, but their relevance to the treatment of a number of psychiatric diseases, including depression, is virtually unknown.

It is worth mentioning that there are many forms of "non-Hebbian" plasticity (short- and long-term), both of synaptic transmission and neuronal excitability outside of the synapse. Indeed, the presynaptic form of LTP expressed at mossy fiber-CA3 pyramidal cell synapses, since it does not require postsynaptic firing for its induction, qualifies as "non-Hebbian". Particular patterns of both synaptically-driven and non-synaptic neuronal firing can result in long-term changes downstream of the synapse, in the strength of dendritic excitability that alters coupling between whole populations of synapses on a given dendrite, or even long-term changes in action potential firing at the cell soma that globally regulate output (for review, see [28]). However, because of the distinct information processing and encoding capabilities of each synapse, long-term synaptic plasticity has been the major target of study in cognition, memory storage, and now depression. The potential significance to depression and other neuropsychiatric disorders for these "non-Hebbian" forms of plasticity should not be underestimated simply because of an even more glaring lack of study.

GLUTAMATERGIC SIGNALING AND DEPRESSION

In addition to synaptic plasticity, glutamatergic systems also play important roles in the manifestation of depression. Glutamatergic synapses make up the majority of the excitatory synapses in the brain, and connect many of the regions relevant to depression and stress, including the prefrontal cortex (PFC), hippocampus, and amygdala. It has

become clear that glutamatergic signaling in the brain plays a role in depression, with symptoms likely to result from increased glutamate availability [29, 30]. There are many examples of NMDAR inhibitors that have anxiolytic activity (for review, see 31). There are a few compounds that are particularly interesting since their antidepressant effects last significantly longer than the half-life of the compounds.

Ketamine, an antagonist of open NMDAR channels, shows rapid antidepressant effects in humans and animal models. Humans and animals both exhibit reduced depression within an hour of a single dose, with improvement lasting at least 24 hr and often 1-2 weeks [32-34]. This prolonged efficacy is intriguing since the half-life of ketamine is only 10-15 min. Some studies that used repeated infusions of ketamine reported that some patients retained antidepressant efficacy for 30-80 days after the final infusion [35, 36], suggesting that more aggressive treatments may result in longer lasting effects. Unfortunately, ketamine is frequently associated with psychotomimetic side effects that render the compound impractical for clinical use. Although acute side effects seem to dissipate within 20-30 min of drug infusion [32], repeat dosing can result in addiction [37], and even persistent symptoms of psychosis [38, 39]. Despite the potential side effects, the rapid and strong antidepressant effect of ketamine has prompted the search for other NMDAR-interacting molecules that may prove useful in a clinical setting.

Memantine, though binding to a different site, has similar NMDAR binding kinetics to ketamine and also shows some efficacy in reducing depressive-like behaviors in some animal models. In a rat model of depression caused by unpredictable stress, chronic memantine treatment during the stress was able to prevent anhedonia and protect cognitive flexibility [40]. However, the high dose of memantine used (20 mg/kg) seemed to impair spatial memory in these rats [40]. Another study used a forced swim test to produce depression-like behavior and found no antidepressant effect of memantine at 10 mg/kg [33]. Human studies do not reliably show antidepressant capabilities for memantine [41, 42], although it does remain a useful therapeutic for reducing cognitive impairments associated with a variety of human diseases and animal models [43-45].

One particularly promising new compound is rapastinel (GLYX-13), a partial agonist of NMDAR that functionally modulates the glycine co-agonist binding site [46]. Rodent studies have found significant antidepressant-like effects of rapastinel using several models of depression, including the Porsolt swim test, novelty-induced hypophagia test, and learned helplessness. These effects persisted at least 24 hr after treatment, despite a plasma half-life of only a few minutes [47]. Studies in rat hippocampal slices have shown that rapastinel can acutely both increase LTP and suppress LTD [48], and as shown in Fig. **1**, a single *in vivo* administration can enhance LTP in the hippocampus and medial PFC for 24 hr up to two weeks post-administration, an effect maintained following repeat dosing [47, 49]. Furthermore, rapastinel increases hippocampal NMDAR currents with an inverted U-shaped dose response curve [48], suggesting that the brain could self-regulate drug effects to prevent neurotoxic hyperstimulation. A Phase IIa clinical study recently tested a single dose of rapastinel in patients with major depressive disorder that were non-responsive to antidepressant treatment [50]. Rapastinel treatment showed antidepressant effects within 2 hr of intravenous treatment and improvement persisted for an average of 7 days. Importantly, no psychotomimetic symptoms or other significant side effects were observed. These encouraging results have prompted a Phase IIb study (ClinicalTrials.gov identifier NCT01684163) that will provide patients with multiple doses of rapastinel. Further experimentation is needed to elucidate the molecular pathways involved in both the rapid onset and sustained effect of rapastinel. The prolonged efficacy of a single dose is likely due to changes in synaptic activity such as altered receptor number or spine morphology that persistently shift the threshold for plasticity in critical brain regions.

Many mGluR interacting compounds also exhibit anxiolytic activity. Inhibition of postsynaptic Group I mGluRs and activation of Group II mGluRs linked to inhibitory G proteins lead to anxiolytic effects in various rodent models of depression-like behavior [51]. Some mGluR interacting compounds have progressed to clinical trials where they showed significant anxiolytic effects, but trials were discontinued due to severe side effects including psychostimulation [52] and convulsions [53].

The glutamatergic synapse is more complex than the standard model of pre- and post-synaptic interactions has suggested. Most synapses in the brain are tripartite, meaning they involve presynaptic and postsynaptic neurons as well as surrounding astrocytes. Astrocytes are crucial in the removal and recycling of glutamate in the synaptic cleft and are capable of releasing their own neurotransmitters such as excitatory glutamate and D-serine, or adenosine that can inhibit presynaptic release [51]. Both mGluR5 and mGluR3 are found on astrocytes [54] and could be participating in the anxiolytic effects of Group I and II interacting compounds. It has been suggested that glial dysfunction has a role in depression and anxiety [54] and patients with depression show a decreased ratio of glia to neurons [55, 56].

Overall, these findings suggest a complex interaction between pre- and postsynaptic neurons, their associated astrocytes, and the precise levels of glutamatergic transmission required for normal cognition and affect.

OTHER RAPID-ACTING ANTIDEPRESSANT TREATMENTS

While recent studies point to direct modulation of NMDARs as a novel, rapid-acting antidepressant intervention with great potential, there are other rapid-acting antidepressant treatments that may indirectly act by influencing glutamatergic transmission. A single dose of the non-selective muscarinic acetylcholine receptor antagonist scopolamine has been shown to elicit rapid antidepressant-like effects in both rodents [57-59] and humans [60]. Navarria *et al*. [59] recently found that infusion of scopolamine into the medial PFC, and systemic administration of a selective M1 muscarinic receptor antagonist, are antidepressant in rodents. Scopolamine appears to act *via* stimulation of target of rapamycin complex 1 (mTORC1) signaling to enhance glutamatergic transmission

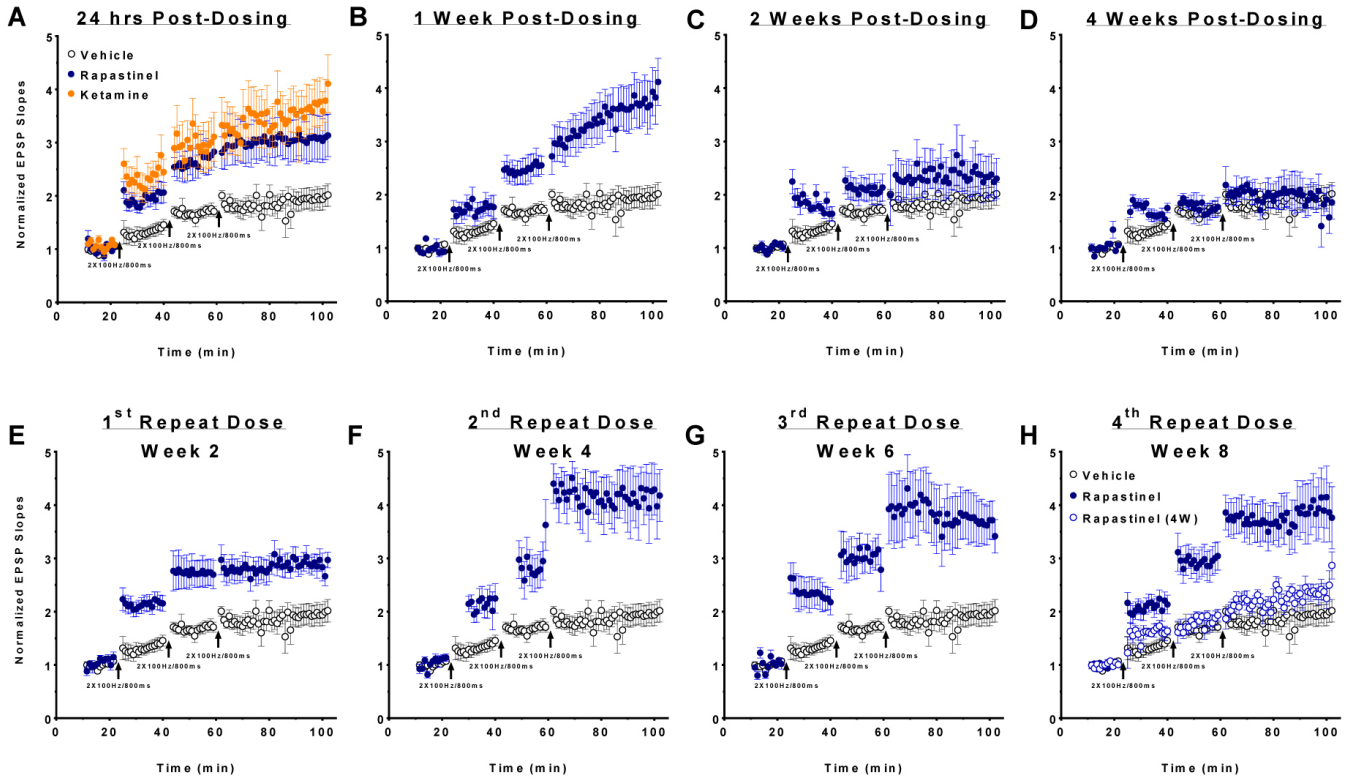

Fig. (1). Rapastinel metaplasticity enhances hippocampal LTP 24 hr and 1 week following a single dose, and persistently enhances LTP following multiple doses every 2 weeks. A single *in vivo* dose of rapastinel (3 mg/kg i.v.; filled blue circles) or ketamine (10 mg/kg iv, filled orange circles; 24 hr timepoint only) in 2-3 month old male Sprague-Dawley rats significantly enhanced the magnitude of long-term potentiation (LTP) of synaptic transmission compared to vehicle treated controls (open black circles), tested *in vitro* (A) 24 hr and (B) 1 week post-dosing at SCH-CA1 synapses after 1, 2 and 3 sub-maximal high-frequency stimulus trains (2x100Hz/800ms, arrows, $P < .05$, Fisher's PLSD post hoc test), but not (C) 2 weeks or (D) 4 weeks post-dosing ($P > .05$). In contrast, short-term potentiation (STP) 5 min after the first high frequency stimulus was significantly increased at all time points from 24 hr to 4 weeks post-dosing ($P < .05$, Fisher's PLSD post hoc test). Repeated dosing once every 2 weeks for up to 8 weeks with rapastinel produced sustained enhancement of both LTP and STP measured 24 hr after the final dose (E-H, filled blue circles, $P < .05$; Fisher's PLSD post hoc test), which reversed by 4 weeks following the final dose (H, open blue circles, $P > 0.05$, Fisher's PLSD post hoc test). N = 5-9 slices per group. Data adapted from references [46, 48].

[58], suggesting a convergence on glutamate-mediated synaptic plasticity, perhaps through NMDARs. Similarly, direct stimulation of synaptic activity by either deep brain stimulation (DBS) [61, 62], epidural cortical stimulation [63], or repetitive transcranial magnetic stimulation (rTMS) [64-66] have all been reported to have antidepressant actions. Although it is difficult to delineate the frequency and patterns of synaptic activation evoked by such stimuli, or even the populations of synapses most susceptible, it is a reasonable hypothesis that the parameters that are effective against depression are likely to produce either the type of high-frequency firing that elicits LTP, lower frequency trains that evoke LTD, or complex combinations of the two at differing synapses. There is an important gap in our knowledge of the patterns and loci of synaptic activation, and resulting long-term plasticity, necessary for antidepressant efficacy in brain stimulated patients. However, there has been some success in identifying measurement surrogates for the induction of LTP by non-invasive brain stimulation in humans [67,68], which suggest that theta-burst stimulation patterns, of types that induce synapse-specific LTP in animal and tissue studies, are also effective at eliciting LTP in humans [68]. Such studies have taken advantage of the ability to record motor-evoked potentials in human subjects, making it less clear whether similar measurement surrogates can be found for brain regions that cannot be easily activated by primary sensory or motor stimulation.

EFFECTS OF STRESS ON COGNITION, MEMORY, AND MOOD

Glutamatergic afferents from the PFC control the hypothalamic-pituitary-adrenal (HPA) axis, a key regulator of the stress reaction. Dysregulation of the HPA axis often leads to anxiety and depression. Rodent models of depression-like behavior are induced by severe or chronic stressors. Stress is known to exert complex effects on cognition, learning, and memory that depend on the type, duration, and intensity of the stressor, as well as developmental age. Emotional arousal has been shown to enhance learning and memory by promoting synaptic plasticity at amygdala synapses, a mechanisms that has been suggested to underlie intense, long-lasting memories of traumatic events and post-traumatic stress disorder (PTSD)

[69-71]. However, prolonged stress is more commonly reported to impair learning and memory [72-74, but see 75], and even cause amnesia [76]. These contrasting responses to acute versus prolonged stress may be due to differential sensitivity and expression of corticosteroid receptors throughout the brain. Mineralocorticoid receptors (MRs) have significantly higher affinity for corticosteroids than glucocorticoid receptors (GRs), often keeping MRs saturated under resting conditions, so that GRs provide the brain's responses to circadian rhythms and environmental stressors [77]. MR and GR expression is required for normal affect, memory, and hippocampal morphology in rodents and humans, and an imbalance in the MR:GR ratio has been reported in brains of depressed patients [78, 79]. Repeated psychological stress in rats not only alters the amount of corticosterone and adrenocorticotropic hormone (ACTH) that are released in response to novel stressors, but also alters expression levels and sensitivity of MR and GR in multiple brain regions, including the hippocampus and PFC [80], complicating the brain's acute and chronic responses to stress, including the metaplastic modulation of LTP by chronic unpredictable stress.

There are a variety of stress models that have been developed in rodents to study the mechanisms underlying the pathogenesis of depressive disorders. They range from acute models such as forced swim and tail suspension tests, subchronic models such as learned helplessness, to chronic stress models such as chronic social defeat stress, restraint stress, and chronic unpredictable stress. Alternative rodent models include olfactory bulbectomy or chemical ablation of astrocytes in the PFC, both of which show similar responsiveness to antidepressants as in stress-induced depression [81, 82]. Common depression-like behaviors in rodents include increased immobility in forced swim tests (despair, helplessness), decreased sucrose preference (anhedonia), anxiety-like behavior, and impaired cognitive performance. The forced swim test has become a commonly-used measure of depressive-like behavior because it has good predictive capacity for existing clinically-effective antidepressants [83], but see [84], a somewhat circular reasoning process, to be sure. Chronic stress in rodents causes increased levels of anxiety-like behavior and impairments in spatial and non-spatial memory, and cognitive flexibility [85-88]. Even a single prolonged stress event can increase the latency for rats to escape from a Morris water maze [89].

Human studies concerning the effects of stress usually rely on questionnaires to determine the subjective level of stress experienced by patients. Although seemly biased, this method allows for incorporation of the finding that the biological effects of stressors are dependent upon the subject's interpretation of the event, not necessarily the event severity itself, for both humans and animals [90, 91]. Adolescents were tasked with public speaking for a large virtual audience and later showed impaired decision making and attentional performance [92]. These impairments were worsened for overweight adolescents that likely had increased baseline levels of stress from their daily interactions with peers. Another group of adolescent students reported poor sleep quality when experiencing high stress due to impending examinations [93].

Stressful events do not have to be recent for cognitive changes to be present. Humans who experience multiple depressive episodes show increased levels of sad mood even during remission of their depression [94]. The cumulative effect of stressful life experiences can cause elderly humans to exhibit reduced working memory relative to age matched controls that report lower levels of lifetime stress [95]. This study used questionnaires that had subjects report the number and types of stressors experienced throughout life, ranging from mild ("finding a part-time job") to severe ("death of a spouse/parent"). The group with higher self-reported lifetime stress showed significantly impaired working memory, even after controlling for recent stressors with another questionnaire (including "how often have you felt stressed or nervous in the past month?").

PTSD is a severe example of chronic effects of a stressful experience. PTSD patients often exhibit hypermnesia for the original traumatic event, hypervigilance, irritability, and avoidance of cues that resemble the trauma [96]. Combined inferences from a number of MRI studies of soldiers with PTSD suggest that hippocampal dysfunction may play a role in susceptibility to and/or persistence of severe PTSD [97]. One experiment in which healthy men underwent a fear learning protocol showed that, under stressful conditions, fear learning becomes more dependent on the amygdala than the hippocampus [98]. This is consistent with the finding that disturbed signaling between the hippocampus and PFC may result in impaired ability to remember context [97] resulting in the hallmark symptom of PTSD: severe anxiety during similar but innocuous situations. In addition to soldiers, PTSD can also result from surviving natural disasters or interpersonal conflicts. Large scale destruction due to hurricanes or earthquakes can lead to 20-40% of healthy survivors experiencing some level of anxiety or depression within a year of the disaster [99]. An estimated 90% of children in Iraq in 2007 had learning deficits due, at least in part, to living in a warzone [99]. Healthy survivors of the September 11, 2001 terrorist attack in New York were examined 3 years later and reported normal emotional affect, but had increased amygdala activity (imaged with fMRI) when shown fearful versus calm faces [100], supporting the idea that long term changes in neuronal connectivity can persist years after a sufficiently stressful incident.

Stressful events early in life can alter rodent cognitive development and lead to lasting affective changes in adolescents and adults. During gestation, excessive maternal stress or glucocorticoid treatment causes adult offspring to exhibit increased anxiety-like and depression-like behaviors, as well as impaired learning [101]. Adolescent rats that received maternal separation stress as young pups have excess anxiety and overexpress NR2A, a NMDAR subunit [102]. Adult mice that were deprived of bedding early in life show increased aggression and impaired social recognition [103]. These mice also have altered expression of neuroligin 2, a cell adhesion molecule responsible for stabilizing inhibitory GABAergic synapses in the hippocampus, possibly leading to excess excitatory transmission. Adolescent male rats that experience social defeat stress show decreased cognitive flexibility that lasts into their adulthood [88]. Interestingly, female adolescent rats experiencing social defeat stress

showed temporary cognitive alterations, but normal behavior in adulthood [87], suggesting a role for estrogen and testosterone in modulating long-lasting neuronal plasticity.

Humans can also exhibit lasting cognitive effects from stressful events that occur early in life. Retrospective studies suggest that maternal stress, depression, and glucocorticoid exposure are associated with disturbed childhood behavior, including attention deficit hyperactivity disorder, depression, anxiety, sleep disturbances, and inconsiderate behavior toward peers [101]. Extremely stressful events during early childhood can alter a person's affective state decades after the triggering incident. Women in their early 30s often exhibit phobias and increased anxiety after maltreatment as a child [104]. In a cohort of depressed patients given antidepressant medication for the first time (mean age: 33.6 years), it was found that patients who had experienced childhood maltreatment were less likely to respond to the medication [105], suggesting a significant alteration to their neurochemistry relative to age matched, depressed controls. Interestingly, this study also found that dorsolateral PFC activity measured by fMRI showed significant differences during working memory tasks versus passive letter viewing in depressed patients, but minimal differences between the two tasks in depressed patients with childhood maltreatment, providing further support that early life stress had somehow "rewired" the participants' brains.

EFFECTS OF STRESS ON SYNAPTIC STRUCTURE AND PLASTICITY

Hippocampus

The earliest studies that demonstrated that stress or glucocorticoids could lead to alterations, and even atrophy, of neuronal processes were performed in the hippocampus. These rodent studies consistently reported atrophy of pyramidal neuron dendrites, measured as decreased length and branch number in CA1 [106-108] and CA3 [106, 109, 110] pyramidal neurons. These changes were produced by either chronic stress or glucocorticoid administration, and required both corticotropin-releasing factor (CRF) and CRF receptors, implicating the HPA axis in the effects of stress on remote hippocampal neuronal structure.

While acute stress causes elevations in basal and evoked glutamate release from a number of brain regions including the hippocampus [111], amygdala [112] and PFC [111, 113], chronic stress can also elicit structural changes in presynaptic terminals such as reduced endosome-like structures involved in neurotransmitter processing [114]. However, the functional meaning of these changes to glutamate release in the chronically stressed animal is still largely unknown, and an area in need of examination. Chronic stress causes a significant reduction in dendritic spine number on apical dendrites of CA1 pyramidal neurons [115, 116]. In contrast, studies have reported both reductions [109, 110, 117] and increases [118] in the number of spines on apical and basal dendrites of CA3 pyramidal neurons after chronic stress. Human MRI studies have found reduced volume of hippocampal grey matter in depressed patients, and this reduction was correlated to the duration of untreated depression [119-121]. Variables such as type and length of stress, species, age, and analysis methods could all be involved, but these findings suggest that even closely related neurons may respond differently to stress as a function of their synaptic circuitry and neuronal subtype.

Studies of activity-dependent synaptic plasticity have revealed similarly complex patterns in the effects of stress. At SCH-CA1 synapses in the hippocampus, a variety of acute stressors produce long-term reductions in the expression of LTP, and enhancement of LTD [122]. These effects on plasticity occur following stressors that include shock [123], exposure to a novel environment [124], placement on an elevated platform [125], and exposure to a predator [126]. Significantly, Shors *et al*. [91] found that LTP deficits follow stress only in rats unable to control termination of their exposure to the stress, suggesting that the perceived context of the stress to the organism plays an important role in its physiological impact. In contrast to Schaffer collateral synapses, studies suggest that effects of stress on synaptic plasticity can differ between hippocampal subfields. Exposure to stressors which impair LTP in field CA1 have been associated with both impaired [127] and enhanced [128, 129] LTP in the hippocampal dentate gyrus (DG).

Exposure to chronic stress elicits effects that depend on the nature and severity of the stress, the synapse involved, and the age of the animal. Qiao *et al*. [130] examined the time course of the effects of stress on LTP at SCH-CA1 synapses. Seven days after exposure to chronic unpredictable stress, the magnitude of LTP was not yet altered. However, after 14 days of stress, the beginning of depressive-like behavior was observed, accompanied by reduced brain-derived neurotrophic factor (BDNF) expression and reduced basal synaptic transmission, although the magnitude of LTP was enhanced relative to controls. Moreover, following 21 days of stress, a full range of depressive-like behaviors was associated with marked impairments in the induction of LTP.

Ricon *et al*. [75] studied the interaction between chronic unpredictable stress and early maternal deprivation in young and adult rats. Maternal deprivation produced impaired avoidance learning when rats became adults, but combining maternal deprivation with chronic unpredictable stress reversed this impairment. Moreover, juvenile onset stress did not impair learning in adults the way adult stress did. This study indicates that young animals have a greater resilience to the effects of stress than adults, although the stress of maternal deprivation can produce lasting damage to this resilience. The pattern of developmental effects of stress on LTP, the ability of stimuli such as enriched environments to reverse these effects, and the mechanisms underlying these changes, are all areas in need of further investigation.

Amygdala

In rodents subjected to chronic stress or glucocorticoids, the response of amygdala neurons is quite opposite from hippocampal neurons. In rats subjected to chronic immobilization stress, LTP and NMDAR currents are enhanced in basolateral amygdala neurons, and associated with conditioned fear memory [71]. Moreover, chronic stress also produces elongation of dendrites and increases in

dendritic spine density in the basolateral amygdala [131]. This persistent enhancement of synaptic strength, and associated morphological alterations favoring stronger synapses, has been suggested to underlie the central role of the amygdala in fear conditioning and persistent fear memories in PTSD. In contrast, stress has been shown to have different effects on the central amygdala, producing a much more delayed enhancement of LTP and spine density which appears to be necessary for the reversal of stress effects on the basolateral amygdala and hippocampus [132], suggesting that LTP in the central amygdala may mediate the reversal of stress effects on other brain regions.

Prefrontal Cortex

The effects of chronic stress on the PFC are more similar to the hippocampus. Acute and chronic stress impair the induction of LTP within the PFC [133] and causes dendritic atrophy [134], though it is not known whether it also enhances LTD. However, the effects of stress on reciprocal connections between amygdala and PFC are more complex. Stress impairs induction of LTP in basolateral amygdala-PFC [135] and hippocampal-PFC [136] synapses. However, a reciprocal pathway from PFC to the basolateral amygdala, normally resistant to induction of LTP, exhibits a stress-induced upregulation of the induction of LTP [137].

Metaplasticity in the PFC is also affected by stress in interesting ways. Richter-Levin and Maroun [138] found that either stress or stimulation of the basolateral amygdala inputs to PFC induces a form of heterosynaptic metaplasticity which prevents a second episode of stress from suppressing the induction of LTP at hippocampal-PFC synapses. While the significance of these findings is far from clear, one appealing hypothesis is that repeated bouts of stress, while suppressing LTP within the PFC in ways that contribute to depression, simultaneously strengthen the contextual and fear components of stress through LTP at hippocampal-PFC and intra-amygdala synapses. It seems likely that metaplasticity in the PFC, a region critical to affective homeostasis, has the potential to greatly alter response of the PFC to stress, and offers the potential to promote renormalization of synaptic strengths in the PFC away from set points that promote or underlie depression.

As shown in Fig. **2**, a depressogenic regimen of chronic unpredictable stress markedly suppressed synaptic plasticity and metaplasticity, as measured by the nearly complete inability to elicit LTP in rat medial PFC slice preparations. This impairment was reversed when rats exposed to chronic unpredictable stress were administered rapastinel and tested 24 hr later [139].

The mTORC1 pathway is critically involved in expression of negative symptoms of stress, including anxiety, depression-like behavior, and neuronal atrophy. Overexpression of a kinase downstream of mTORC1, ribosomal S6 kinase (rS6K), can prevent depression-like behavior in stressed rats while increasing neural complexity in the PFC [140]. Expression of an inhibitory protein upstream of mTORC, REDD1 (regulated in development and DNA damage response 1), is increased by chronic unpredictable stress or dexamethasone treatment, while knocking out the protein makes rats resilient to stress [141]. Interestingly, humans with depression have increased REDD1 expression in their PFC relative to controls [141]. Genetic inhibition of the mTORC pathway, by knocking down rS6K or overexpressing REDD1, can cause anxiety, depression-like behavior, anhedonia, and neuronal atrophy even in the absence of stress. These findings are consistent with the antidepressant effects of scopolamine described earlier.

DENDRITIC SPINES AND SYNAPTIC PLASTICITY

If chronic affective impairments such as depression and anxiety are maintained by loss of dendritic spines and shifts in their morphology, a question of paramount importance to treating these afflictions is whether modulating activity-dependent synaptic plasticity has the potential to reverse

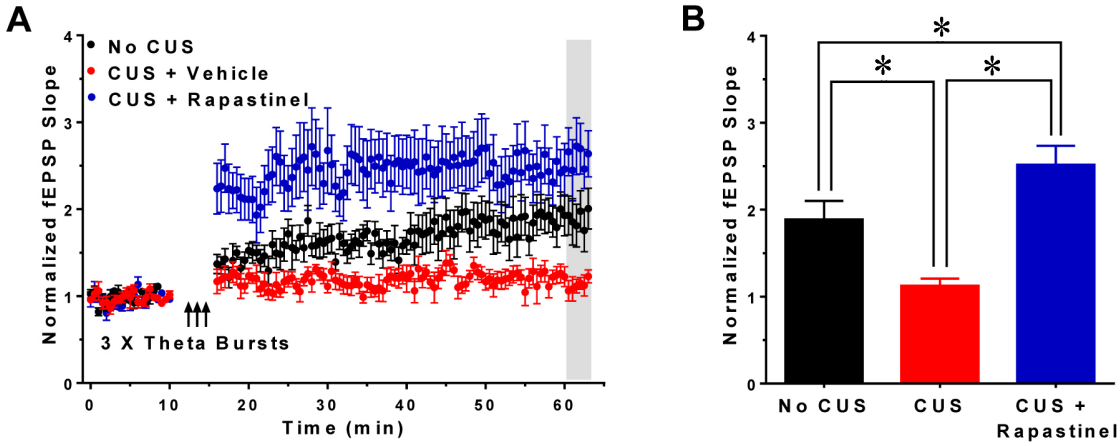

Fig. (2). Rapastinel (3 mg/kg i.v.) rescues chronic unpredictable stress-induced deficits in LTP in the medial PFC 24 hrs post-dosing. (**A**) Time course, and (**B**) Mean ± SEM normalized field excitatory postsynaptic potential slopes evoked in layer II/III and recorded in layer IV of rat medial PFC slices from 2-3 month old adult male SD rats exposed to a depressogenic regimen of 21 days of chronic unpredictable stress (CUS; 2 stressors / day for 21 consecutive days; red circles and bar), versus control animals (No CUS; black circles and bar). CUS-exposed animals were treated with rapastinel (3 mg/kg i.v.; blue circles and bar) or 0.9% sterile saline vehicle (1 ml/kg i.v.; red circles and bar) 24 hr before *ex-vivo* LTP testing. LTP was measured 60-62 min post-tetanus (shaded). N = 8-10 slices per group. * P < .05 Fisher's PLSD post hoc test. Data adapted from reference [139].

these anatomical changes. Neurotrophic factors and the neurotransmitter pathways that stimulate their synthesis and release are a key, perhaps obligatory, step in the formation and stabilization of new synapses. Exposing rodents to an enriched environment consisting of housing with horizontal and inclined boards and activity-stimulating items such as swing boards, wooden blocks and balls, has been shown to increase spine density, and to do so in normal [142, 143], and post-ischemic brain [144]. A critical pathway in the activity-dependent preservation of synaptic connections and dendritic spines during development is NMDAR-activated, calcium-dependent transcription, translation and release of BDNF [145-147]. NMDARs and BDNF both appear to be necessary for synaptic competition during neuronal network development, for increases in dendritic spine number driven by environmental enrichment [148, 149], and for induction of some forms of LTP [150, 151]. Chronic unpredictable stress has been shown to decrease BDNF synthesis and release [130], and transgenic mice where BDNF production was inducibly knocked out in adulthood exhibited reduced dendritic spine density and depressive behaviors [152]. Given its importance for synapse growth and preservation, BDNF is an important product of NMDAR activation that is critical to maintaining normal patterns and levels of synaptic strength throughout the forebrain.

EFFECTS OF STRESS ON DENDRITIC SPINES

Chronic stress, both prenatal and postnatal, has been shown to increase risk of depression and to alter neuronal structure in a number of ways. Chronic stress reduces dendritic spine density and branch number in the hippocampus [115, 118, 153] and medial PFC [115, 154, 155]. Interestingly, the same chronic stress increases dendritic spine density and branching in the basolateral amygdala, and enhances anxiety-like behavior, alterations that are extremely persistent even once the stressors are removed [131, 156, 157]. Depending upon the brain region, terminating the stressors can result in reversal of some of the changes observed [155], although many can be quite persistent [157, 158]. The persistence of damage to dendritic spines is a likely substrate of the persistence of stress-triggered depression and anxiety. Since NMDAR-triggered synaptic plasticity is associated with increases in dendritic spine density and shifts in spine morphology towards mature synaptic forms, it is reasonable to hypothesize that upregulating NMDAR-dependent synaptic plasticity has the potential to rescue persistent stress-induced alterations in dendritic spines that are associated with depression-like and anxiety-like behaviors.

DENDRITIC SPINE PLASTICITY AND DEPRESSION

Spine morphology and function are intimately connected, and proper actin dynamics are crucial to normal physiology of excitatory synapses [159]. The levels of proteins involved in actin stabilization and remodeling are altered in mice and humans with depressive behavior [160], and their activity can be directly altered by GR activation [161]. A number of proteins that regulate the density, number, and shape of spines are altered in rodents with depressive-like behavior [162-164]. Postmortem studies of depressed humans showed decreased hippocampal expression of spinophilin, a dendritic protein that regulates glutamatergic transmission and spine morphology [165]. Microarray studies of depressed patients identified increased expression of a transcriptional repressor that, when overexpressed in rodents, led to reduced expression of multiple synaptic proteins, as well as depressive-like behavior [166].

GRs can directly modulate NMDAR conductance [167], leading to modification of synaptic architecture. This supports the use of a cell culture model of depression for drug screening that involves monitoring actin dynamics in response to NMDA exposure [168]. The mood stabilizer lithium, or direct inhibition of its target glycogen synthase kinase 3β (GSK3β), can prevent drastic alterations in actin organization in response to NMDA [168]. GSK3β was been reported to be hyperactive in a cohort of depressed patients [169], and mouse studies found that deleting GSK3β in hippocampal neurons attenuated excitatory transmission by reducing spine stability [170].

A rodent depression model produced by olfactory bulbectomy also shows significantly modified activity of multiple synaptic proteins important for normal plasticity, including NMDAR and AMPAR, as well as downstream calcium/calmodulin-dependent protein kinase II (CaMKII) and cyclic AMP response element-binding protein (CREB) [82]. Although a single traumatic event can result in long lasting symptoms of depression [89, 96], moderate levels of stress may take time to produce lasting changes in brain architecture. Daily exposure of male rats to chronic unpredictable mild stress does not affect neuronal morphology or signaling for the first week, but significant reductions in spine density and LTP can be seen after 3 weeks of mild stress [130]. Sex hormones also play a role in the severity of spine retraction after stressful events. In ovariectomized rats, estrogen treatment can prevent spine retraction during stress and expedite recovery of spines after stress [171, 172].

METAPLASTICITY

Developmental

In addition to abundant evidence that most synapses exhibit the ability to persistently increase (LTP) and decrease (LTD) their strength, there is now clear evidence that the threshold and sensitivity of these mechanisms are themselves subject to activity-dependent regulation. The ability of neurons to adjust the requirements for induction of synaptic plasticity based on their prior history of activity has been broadly termed “metaplasticity”. Metaplasticity can be thought of as dynamic shifts in the set point for the amount of synaptic activation needed to produce the neurochemical events that induce either LTP or LTD, much like a climate set point determines the mean temperature fluctuations day-to-day. There are a number of forms that such metaplastic mechanisms can take, and both their importance for cognitive function and disease, and their potential as therapeutic targets, are largely unknown. Here, we will focus on metaplasticity of homosynaptic LTP and LTD, though it should be pointed out that heterosynaptic alterations where activation of one synaptic population alters the strength of another population of synapses on the same neuron have also been shown to occur.

The importance of metaplasticity to stabilization of synaptic strength and prevention of saturation of LTP or LTD was suggested by Bienenstock *et al*. [10]. In theoretical analyses, they found that, to prevent runaway LTP and LTD of synapses leading to enhanced likelihood of future LTP or LTD until synaptic strengths are saturated, the threshold for induction of long-term plasticity should be regulated such that a previous history of LTP would make it harder to evoke LTP and easier to elicit LTD, while the reverse would occur following recent LTD of synaptic strength. However, there are a number of forms of metaplasticity that occur both during the course of development, and in mature synapses. We will discuss these forms of metaplasticity at SCH-CA1 synapses in the hippocampus, as the synapses where plasticity and metaplasticity have been most studied, but it is likely that other synapses, including cortical synapses, exhibit many of these features.

Three forms of metaplasticity exist at SCH-CA1 synapses during development. First, electrophysiological recordings have shown there are multiple phases in development of presynaptic transmitter release probability in rodents. In the first postnatal week, release probability is high and declines with increasing age to the end of the second postnatal week [173]. Release probability then increases again during the third week, arriving at adult levels by the first month of life [174]. Conversely, LTP is hard to induce in slices from neonates, largest in amplitude at approximately 2 weeks of age, and declines thereafter to stable adult levels [175, 176]. Quantal analysis [177] and direct presynaptic imaging of release [178] indicate that LTP in the 2 week old hippocampus is more strongly associated with presynaptic alterations, while postsynaptic alterations increase into adulthood. Although much less is known about LTD, it appears to be easier to induce in slices from very young animals [179], declining to lower levels in adults [176].

A second form of metaplasticity during development is the shift over the first three weeks from AMPARs containing GluA1 subunits to those containing GluA3 subunits, resulting in a reduction in the frequency threshold for the induction of LTP. Early in development, there are a larger number of so-called "silent" synapses that contain only NMDARs [180, 181]. During the first three postnatal weeks, AMPARs are inserted into synapses in an activity-dependent manner [182], the number of silent synapses is reduced [175, 183], and population synaptic strength increases [184]. Postsynaptic LTP is induced by insertion of GluA1-containing AMPARs into synapses, where they are then replaced during constitutive cycling by GluA3-containing AMPARs that exhibit more prolonged responses that lower the frequency threshold for LTP induction [185-187]. This developmental switch to GluA3-AMPARs results in a metaplastic upregulation of postsynaptic LTP that matches the time course of reduction in the contribution of presynaptic LTP.

A third form of metaplasticity during development is the appearance, at about 3 weeks of age, of the ability of low frequency stimulation that does not itself induce LTD, but raises the threshold for the subsequent induction of LTP [176]. A similar effect has been observed following a weak tetanus insufficient to elicit LTP, but sufficient to raise the threshold for LTP [188]. Evidence suggests that this metaplastic suppression of LTP also requires NMDAR activation [189]. At the same time, mGluRs have also been found to metaplasticly shift the threshold for LTP in the opposite direction, that is, toward larger LTP. Trains of stimuli in the 10-20Hz range can prime synapses to exhibit larger theta-burst induced LTP [190], a priming that studies suggest might involve activation of either mGluR1 [18, 191] or mGluR5 [192]. Thus, particular patterns of synaptic activity that do not, themselves, persistently alter synaptic strength, can either suppress or enhance the propensity of a synapse to exhibit LTP or LTD.

Adult

Once basal adult levels of LTP and LTD have been reached, evidence indicates that metaplasticity of the threshold for induction of LTP and LTD continues to be a property of adult synapses. Huang *et al*. [188] first showed, at SCH-CA1 synapses in hippocampal slices, that a weak high-frequency stimulation that was incapable of inducing LTP could, nevertheless, suppress the induction of future LTP for a number of hours. This suppression itself required NMDAR activation, was synapse-specific, and could be elicited by focal application of NMDA itself. Wexler and Stanton [193] showed the converse at these same synapses, that similar bursts of high-frequency stimulation that did not induce LTP could, in a synapse-specific way, enhance the ability of a low-frequency stimulus train (1Hz/15min) to induce LTD for hours afterwards. Surprisingly, activation of NMDAR alone was not sufficient to shift threshold in favor of LTD, but this may be explained by the observation that induction of LTD required activation of both NMDAR and mGluR. These experimental data confirm the presence of the computational mechanisms postulated by Bienenstock *et al*. [10] as necessary for long-term homeostasis of synaptic strength, and optimization of patterns of stronger and weaker synapses by extracting information from covarying input streams [11, 12]. They also point to both NMDAR and mGluR as potential therapeutic targets in depression, and likely other mental illnesses, for renormalizing synaptic strengths through metaplastic regulation of the thresholds for LTP and LTD.

While evidence is strong that metaplasticity in the threshold for induction of both LTP and LTD of glutamatergic transmission can be induced and expressed in the same postsynaptic target, there are also polysynaptic mechanisms that can result in similar metaplastic regulation of the excitatory synapse. Xu *et al*. [192] has demonstrated that the involvement of mGluR5 activation in priming synapses for greater LTP results from mGluR5-mediated mobilization of endocannabinoids that spread intercellularly to elicit LTD of inhibitory transmission in the circuit, allowing for greater excitation leading to greater LTP.

The fact that NMDAR activation is necessary for induction of both LTP and LTD, and for metaplastic regulation of the thresholds for future plasticity, offers important computational and homeostatic benefits, and the possibility that dysfunction of metaplasticity may be a

contributor to CNS illnesses characterized by cognitive, memory and affective impairments.

Significance of NMDAR activation versus blockade to antidepressant activity

While both ketamine and rapastinel have been shown, in rodents and humans, to have rapid and long-lasting antidepressant activity, ketamine is an NMDAR open channel blocker [194], while rapastinel is a glycine-site allosteric modulator that can enhance (at low dose) induction of LTP by enhancing NR2B-containing NMDAR activation [47-49, 195]. This leads to speculation about the role of antagonist versus selective agonist properties in antidepressant actions of these agents. Long-lasting antidepressant actions are likely to result from altered expression of many genes including, but not limited to, particular NMDAR subunits such as NR2B [196, 197]. However, the rapid onset of antidepressant actions suggests that the insertion, removal, and phosphorylation of NMDARs are all likely to result from both antagonists like ketamine [46], and more complex modulators with partial agonist properties such as rapastinel [46], and to precede and trigger transcription-dependent changes. Though we know that late-phase LTP requires transcription and translation, we are far from a full understanding of the coupling between rapid, receptor-mediated changes in NMDAR activation, and the consequences of these changes for either long-lasting shifts in the threshold for induction of LTP/LTD, or for the morphological alterations in dendritic spine density that would appear to be critical for persistent antidepressant, and even cognitive-enhancing, actions of NMDAR modulators.

CONCLUSION

The understanding of activity-dependent regulation of long-term synaptic plasticity that is emerging now has extraordinary implications for our understanding and treatment of a broad range of mental illnesses. It is becoming clear that there are set points for the amount of temporally coincident presynaptic and postsynaptic activity necessary to induce LTP and LTD of synaptic strength, and that these set points are themselves regulated by biochemical mechanisms that sense previous mean synaptic activation *at each synapse.* This realization leads to the hypothesis that malfunctions in these mechanisms of metaplasticity can lead to synapses that are either too strong or too weak. If such mechanisms malfunction in brain regions, such as the medial PFC, that are essential for mood homeostasis, the result could manifest as depression. In other regions, impairments in cognition, learning and memory (hippocampus), or anxiety (amygdala) might result. The discovery that the NMDAR open channel blocker ketamine, and the NMDAR modulator with glycine-site partial agonist properties rapastinel, can elicit long-term antidepressant effects, point to NMDAR-mediated metaplasticity as an important new target mechanism for treatment of the range of mental illnesses that require activity-dependent synaptic plasticity.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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