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## Synaptic Loss and the Pathophysiology of PTSD: Implications for Ketamine as a Prototype Novel Therapeutic

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### Abstract

**Purpose of Review**—Studies of the neurobiology and treatment of PTSD have highlighted many aspects of the pathophysiology of this disorder that might be relevant to treatment. The purpose of this review is to highlight the potential clinical importance of an often-neglected consequence of stress models in animals that may be relevant to PTSD: the stress-related loss of synaptic connectivity.

**Recent Findings**—Here, we will briefly review evidence that PTSD might be a “synaptic disconnection syndrome” and highlight the importance of this perspective for the emerging

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therapeutic application of ketamine as a potential rapid-acting treatment for this disorder that may work, in part, by restoring synaptic connectivity.

**Summary**—Synaptic disconnection may contribute to the profile of PTSD symptoms that may be targeted by novel pharmacotherapeutics.

### Keywords

PTSD; Synapse; Glutamate; NMDA; Ketamine; Plasticity; Connectivity

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## Introduction

The field of post-traumatic stress disorder (PTSD) research has advanced significantly since the earliest attempts to embed our understanding of this disorder within a modern translational neuroscience context [1, 2]. So far, the greatest progress has been made in studies related to the regulation of fear. PTSD is associated with a bias toward viewing neutral stimuli as threat-related, increased generalization of fear, deficits in fear extinction, and altered processing of threatening contexts that are presumed to contribute to fear-related PTSD symptoms including anxious arousal (startle, hypervigilance), intrusive trauma-like symptoms (intrusive thoughts, nightmares, flashbacks, emotional/ physiologic reactivity), and avoidance of thoughts and reminders of the traumas [3–10, 11•]. These advances have informed the evolution of cognitive and behavioral treatments for PTSD [12, 13], and have led to the testing of pharmacologic approaches that might enhance these processes [14, 15•, 16, 17]. However, even within this area of research, it is not entirely clear why trauma-related fear memories are often so highly resistant to extinction. For example, it is not known whether the persistence of fear-related symptoms in PTSD reflects a deficit in neuroplasticity and whether these neuroplasticity deficits, in turn, have an underlying structural component.

## Toward a Synaptic Deficit Hypothesis

A model of PTSD based entirely on fear conditioning may be too narrow to explain the breadth of associated symptoms. Other PTSD symptoms listed in DSM-5 [18] may not be consequences of dysregulated fear, such as dysphoric arousal (difficulty concentrating, difficulty sleeping), anhedonia (loss of interest, detachment), and externalizing symptoms (irritability/ anger, self-destructive, or reckless behavior) [3], as well as symptoms including guilt, shame, and cognitive impairments [19•]. Some of these symptoms, such as emotional/ behavior disinhibition [20], apathy [21], and impaired attention [22] are also associated with neural lesions that impair the functional connectivity of the brain, as might occur in the context of traumatic brain injury or cerebrovascular disease.

The resemblance of some PTSD symptoms to symptoms associated with impaired synaptic connectivity may be more than coincidence. It is well established that chronic stress causes neural atrophy and decreases the number of synapses within cortical and limbic circuits implicated in the regulation of mood, cognition, and behavior [23•]. Glutamate synapses are the dominant form of synaptic connectivity in these circuits. As reviewed in Fig. 1, stress compromises the integrity of signaling via glutamate synapses in several ways including by

reducing signaling via brain-derived neurotrophic factor (BDNF) and impairing its downstream intracellular signaling. As a consequence, there are reductions in the number of  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) glutamate receptors in the synapse, reductions in the size of dendritic spines, loss of dendritic spines supporting synaptic connectivity, and even loss of larger dendritic elements resulting in decreased dendritic complexity.

Factors contributing to synaptic loss in chronic stress and PTSD may include disturbances in glucocorticoid receptor (GR) signaling, neuroinflammation, and deficits in neurotrophin signaling [24, 25, 26•, 27, 28]. Hypothalamo-pituitary adrenal axis function in PTSD is manifest at many levels including alterations in diurnal cortisol levels [29–31], increased GR numbers [32] or GR function [33], and alterations in GR signaling-related proteins such as the GR chaperone protein, FK506 binding protein 5 (FKBP5) [34•], and serum and glucocorticoid-regulated kinase 1 (SGK1) [35•]. With so many alterations, the impact of hypothalamo-pituitary-adrenal axis (HPA) changes may be complex, contributing to both resilience and vulnerability. This confusion has led to the testing of both GR agonists [36, 37] and antagonists [38] as treatments for PTSD. Elevations in proinflammatory cytokines including interleukin 1 $\beta$ , interleukin 6, tumor necrosis factor  $\alpha$ , and interferon  $\gamma$  are associated with PTSD [39]. One consequence of the combined hypothalamopituitary-adrenal axis dysregulation and pro-inflammatory state may be to compromise the function of glia responsible for maintaining synaptic glutamate homeostasis, resulting in neurotoxic elevations of extrasynaptic glutamate levels [40].

To date, there are limited clinical data that directly support this hypothesis [34•]. One published pilot study of postmortem tissue evaluated 500 dendritic spines from the ventral medial frontal cortex tissue from eight PTSD cases and eight comparison subjects. They reported that the remaining dendritic spines in PTSD tended to be immature (stubby spines as opposed to mature mushroom spines). They also reported that elevated messenger RNA (mRNA) levels for FKBP5, which codes for a chaperone protein for the glucocorticoid receptor, were associated with reduced mushroom spine density.

There are neuroimaging data that indirectly support the hypothesis of deficits in synaptic connectivity in PTSD. These findings include reductions in cortical thickness [41], decreased subcortical volumes on MRI [42–45], reduced integrity of white matter pathways on diffusion-weighted imaging (DTI) [46, 47], and reductions in cortical functional connectivity in some studies [48], but more complex patterns of functional connectivity changes in other studies [49–51]. In these studies, regional reductions in cortical volumes, deficits in structural connectivity, and reduced functional connectivity were associated with PTSD symptoms, cognitive impairments, and overall functional impairment, suggesting their clinical relevance.

Synaptic loss associated with PTSD may aggravate the impact of other pathophysiologic processes. PTSD is often comorbid with conditions that independently may contribute to synaptic pruning including aging [52], traumatic brain injury [53], major depression [23•], high levels of alcohol consumption [54–56], and other medical conditions. The connectivity deficits of PTSD may exacerbate the impact of brain injury contributing to synergy in

cortical network dysregulation, cognitive dysfunction, symptoms, and functional impairment as well as increased PTSD rates the TBI population [57–59, 60•, 61, 62]. Similar concerns apply to comorbid alcohol use disorders [63].

In summary, there are compelling preclinical data and early clinical correlates suggesting that synaptic loss may be an important feature of the neuropathology of PTSD. The MRI findings reviewed above suggest that the structural changes occur in brain regions involved in the executive control of emotion, such as the medial prefrontal cortex; the emotional appraisal of potentially threatening contexts, such as the anterior hippocampus; the generation of emotional states, such as the amygdala and insula; and in the white matter pathways connecting these regions. In computational models of circuit function, adequate integrity of synaptic connectivity is needed to generate and maintain appropriate representations of information [64], to support adaptive neuroplasticity [23•], and to adaptively regulate circuits generating emotional states [65]. These functional roles for normally dense synaptic connectivity support the hypothesis that impairments in these functional domains might emerge from synaptic loss, contributing to PTSD symptoms.

## Synaptic Deficits and Circuit Function

How might synaptic loss impair the regulation of cortical circuits? The nature of synaptic loss described in the preclinical studies is rather subtle. Generally speaking, stress reduces the richness of synaptic connections rather than obliterating the integrity of a brain region or the connections between regions of the brain, as might occur in the context of traumatic brain injury.

Computational neuroscience studies suggest that synaptic loss may impair cortical network function in subtle and, perhaps, paradoxical ways. Stress-related synaptic loss has been best studied in the hippocampus. Clinical studies suggest that anterior hippocampal structural deficits in PTSD are associated to a moderate degree with reduced functional connectivity, profiles of PTSD symptoms [44], and impaired memory [66, 67]. In animals, both chronic stress and chronic glucocorticoid administration produce apical dendrite retraction first in the CA3 region and then in other hippocampal regions [68]. Loss of dendritic connectivity in both conditions is associated with reduced neuroplasticity, as reflected by the capacity to induce long-term potentiation, and impaired memory [69–71]. The learning impairments associated with chronic stress are also associated with altered properties of the place cells within the hippocampus that represent spatial information. These cells become less stable and more cue-dependent in representing spatial information [71]. This reduction in the stability and integrity of the neural representation of information by the hippocampus is consistent with earlier computational models of synaptic loss [72]. Together, these studies suggest that stress-dependent synaptic loss in the hippocampus, and perhaps other regions, may compromise cortical network functions by affecting the integrity of network functions and by undermining neuroplasticity.

However, there are conflicting data about the precise nature of stress-related disturbances in hippocampal network function. While some studies do not report altered neural excitability in association hippocampal dendritic atrophy produced by chronic stress [69, 73], other

studies report increases in neural excitability [74]. The latter have informed a computational hippocampal network model in which dendritic atrophy produces increased excitability that impairs neuroplasticity by saturating long-term potentiation [75]. Another study suggests that chronic stress produces a dysfunctional dyscoordination of heightened excitability and neuroplasticity in some neural compartments, and reduced neuroplasticity in others [76]. This work is at an early stage, and it is hoped that continued progress in computational approaches to network alterations in PTSD will yield deeper insights into brain-behavior relationships.

## Ketamine and Synaptic Therapeutics for PTSD

One of the most important questions raised by a focus on synaptic loss in PTSD is whether the resulting perspective informs the identification of novel therapeutics for this disorder. One might first explore how environmental factors might influence synaptic connectivity. Animals raised in environments without much social, sensory, or activity-related stimulation developed reduced levels of cortical synaptic connectivity, while environmental enrichment has the opposite effect [77–80]. For example, environmental enrichment in animals protects animals against hippocampal dendritic atrophy and the associated memory impairment produced by chronic stress [81]. One form of environmental enrichment that has received particular attention is exercise. In animals, exercise has many effects that enhance neuroplasticity, including promoting neurogenesis, increasing dendritic complexity, and increasing synaptic connectivity ([82–84]; see Fig. 2). These effects appear to be dependent on the level of BDNF [84]. The effects of exercise are sufficient to protect against the detrimental stress-like effects of chronic corticosterone on neurogenesis and synaptic connectivity [85]. Exercise appears to have beneficial effects on symptoms severity in people with PTSD [86]. However, it is not yet clear whether these benefits are mediated by enhancements in synaptic connectivity.

What about exercising the brain? Cognitive remediation therapies might be beneficial for PTSD. This is a relatively new area of research. Some studies suggest that psychotherapy may increase regional cortical volumes or white matter integrity (increased fractional anisotropy in diffusion weighted imaging) in PTSD, but these increases are not universally associated with clinical improvement [87•, 88, 89]. As opposed to cognitive therapies, which aim to address aberrant thought patterns, cognitive remediation therapies are a form of “brain exercise” that aims to engage experience-dependent neuroplasticity in order to restore or enhance functional connectivity [90, 91]. This approach has been studied extensively in the field of schizophrenia research [92], but it has received relatively little attention as a treatment for PTSD symptoms.

The capacity of the brain to protect and restore synaptic connectivity in the context of typical daily activity raises questions as to why synaptic deficits associated with stress persist within the context of PTSD. In fact, most people do recover, at least partly, from severe and repeated traumas. For example, the lifetime prevalence of PTSD among Vietnam veterans was approximately 30% [93]. However, the cross-sectional rate of PTSD declined over time to approximately 15% 10 years after the Vietnam War [93] and approximately 4.5% 40 years after the war [94•]. One possibility is that synaptic deficits persist in PTSD

because the symptoms constitute a state of chronic stress. In other words, the persisting symptoms associated with PTSD such as fear, depression, insomnia, guilt, demoralization, shame, and numbing may evoke complex neurobiological responses that undermine synaptic integrity such as dysregulation of the hypothalamo-pituitary-adrenal (HPA) axis [95], induction of a chronic pro-inflammatory state [96], and reductions in neurotrophin signaling [23•]. Supporting this view, as noted earlier, HPA dysregulation [25], elevations of pro-inflammatory cytokines [27], and reductions in plasma BDNF levels [97, 98] have been reported in people diagnosed with PTSD. Further, volume loss on MRI appears to be a predictor of the persistence of PTSD symptoms with treatment [99, 100]. Thus, it is possible that persisting neuroendocrine dysregulation and neuroinflammation may contribute to the chronicity of PTSD via enhancing synaptic connectivity deficits and compromising neuroplasticity (see Fig. 3).

Current pharmacotherapies for PTSD may work, in part, by restoring synaptic connectivity. The most commonly prescribed agents, antidepressant medications, appear to promote synaptic connectivity via raising BDNF levels, enhancing signaling via CREB, and promoting synaptic growth and neurogenesis [102, 103]. Long-term treatment with antidepressant medications appears to increase hippocampal volume and improves memory in individuals with PTSD [104], potentially reversing the deficits described in patients [43, 105, 106]. Interpreting the effects of long-term treatments are complex. Long-term therapeutic effects of antidepressant medications might be mediated by direct neural or anti-inflammatory effects [107, 108] of these drugs. However, they also might reflect the long-term effects of changes in mood or activity, as suggested by the studies of psychotherapy effects on brain function, reviewed earlier.

The emergence of the rapid-acting antidepressants has created the opportunity to study a treatment that might work to reduce PTSD symptoms, in part, by directly restoring synaptic connectivity [109, 110]. The possibility of rapid antidepressant effects produced by N-methyl-D-aspartate (NMDA) glutamate receptor antagonists was suggested by animal models [111]. This area of research was spurred by the observation that a single dose of the NMDA receptor antagonist, ketamine, produced pronounced antidepressant effects in the majority of patients with treatment-resistant symptoms of depression [40, 112]. More recently, there is preliminary evidence that ketamine produces rapid benefits in patients diagnosed with PTSD [113]. In this study, ketamine produced improvement in PTSD symptoms even when controlling for its antidepressant effects and in patients without comorbid symptoms of depression.

As presented in Fig. 4, ketamine may work by rapidly enhancing synaptic connectivity and by rapidly increasing dendritic spines in the apical dendrites of pyramidal neurons in superficial cortical layers, reversing the effects of stress [109, 114]. The clinical evidence supporting this hypothesis is limited currently, but it is being actively studied. In depression, reductions in cortical functional connectivity as measured by functional MRI appear to be ameliorated within 24 h by a single dose of ketamine, in conjunction with clinical improvement [115•, 116]. Similar studies are underway in PTSD patients. In animals, a single dose of ketamine causes a proliferation of functional dendritic spines. There are at least three primary hypotheses as to how ketamine might produce these effects [23•, 40].



One hypothesis suggests that ketamine exerts its effects by stimulating glutamate release. This glutamate release may trigger a chain of neural effects that begins with the stimulation of synaptic AMPA glutamate receptors and involves increased levels and release of BDNF, stimulation of tropomyosin receptor kinase B (TrkB) receptors (the receptor for BDNF), enhanced signaling via the Akt/molecular target of rapamycin (mTORC) signaling pathway, increases in the synthesis of proteins associated with dendritic spines, and the rapid emergence of new spines (see Fig. 5). Another important hypothesis is that ketamine exerts its clinical effects by blocking extrasynaptic NMDA glutamate receptors, reducing the phosphorylation of eukaryotic elongation factor-2 (eELF2), reducing the phosphorylation of the associated kinase, enhancing AMPA signaling, and increasing BDNF levels [117]. A third hypothesis, which might be viewed as a variant of the prior hypothesis, suggests that a ketamine metabolite, 2R,6R-hydroxynorketamine, enhances AMPA signaling through a mechanism that remains to be determined [118]. Other hypotheses include the possibility that antidepressant effects of ketamine are mediated by its anti-inflammatory effects [119, 120], its effects on nitric oxide signaling [121, 122], its modulation of GABA-B receptor signaling [123], and other effects.

If ketamine proves to produce lasting improvement in PTSD, it may serve as a prototype for other putative rapid-acting antidepressants. For example, preclinical studies suggest that muscarinic cholinergic receptor antagonists [124], metabotropic glutamate receptor-2 antagonists [125], and AMPA antagonists [126] might produce rapid antidepressant effects by directly or indirectly enhancing AMPA receptor signaling. Only the first of these mechanisms has been tested as an antidepressant in humans, with promising early results [127].

However, the persisting potentiation of neuroplasticity by ketamine suggests a novel role in the treatment of PTSD: the enhancement of fear extinction among patients who have failed to respond to exposure-based treatments. Deficits in fear extinction in PTSD are a central challenge in treatment and modifications to traditional cognitive and behavioral therapies are a major focus of treatment development [128, 129]. There has long been an interest in developing medications that might enhance this process [130]. One strategy that of enhancing NMDA receptor signaling using D-cycloserine has not proven effective in PTSD [131]. Ketamine, perhaps by increasing synaptic connectivity, appears to increase neuroplasticity and to enhance fear extinction in animals [132]. This raises the possibility that the therapeutic effects of ketamine in PTSD might be potentiated by using it to enhance the efficacy of progressive exposure, cognitive processing therapy, eye movement desensitization and reprocessing (EMDR), or other exposure-based therapies.

## Summary and Implications

Synaptic deficits associated with PTSD may contribute to the complex profile of symptoms and functional impairments associated with this disorder. These deficits may arise in part from the neurobiology of chronic stress associated with persisting symptoms of PTSD. In turn, synaptic deficits may compromise neuroplasticity and impair resilience among individuals with PTSD, contributing to symptom chronicity and compromising clinical responses to current treatments. A wide range of interventions could be viewed as targeting

impaired synaptic connectivity, such as stimulating life activities, including exercise. However, the ability to respond to these forms of self-healing may be compromised by PTSD-related neuroplasticity deficits. Long-term antidepressant treatment may contribute to clinical recovery by promoting synaptic plasticity. However, recent rapid-acting antidepressants may more directly target synaptic deficits associated with PTSD and there is now preliminary evidence of the rapid efficacy of ketamine. Further, ketamine may open a window of increased neuroplasticity where cognitive and behavioral therapies might be more effective in treating PTSD symptoms.

This review relies heavily on many sources of data that are quite preliminary, and so some of its key assertions may be vulnerable to being disproved by future research. For example, postmortem studies of brain tissue from individuals with PTSD are in their infancy. Results from studies employing PET radiotracers that might serve to quantify cortical synaptic density in vivo in PTSD before and after treatment have yet to be reported. Inferences about synaptic connectivity based on MRI-based imaging methods are likely to be risky. Further, our limited knowledge of the neurobiology of PTSD limits our ability to rigorously evaluate the applicability of findings from animal models of stress to the pathophysiology and treatment of this disorder. Thus, the purpose of this review is to draw attention to the importance of synaptic loss for PTSD, balancing the focus on fear acquisition in considerations of the pathophysiology, and treatment of PTSD, with the aim of stimulating more research in this area.

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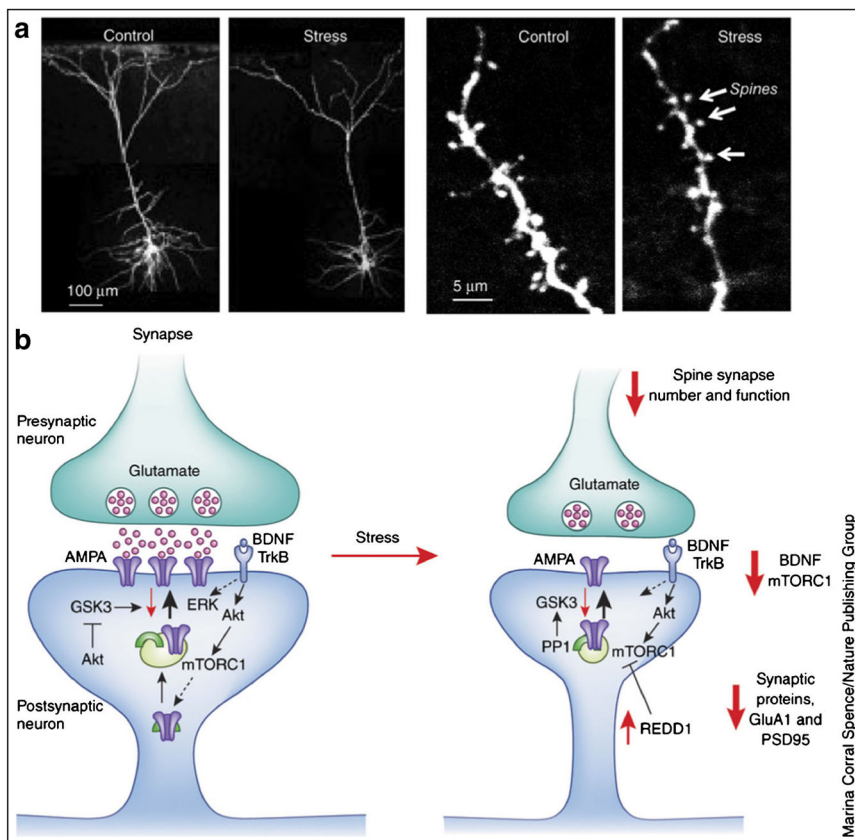
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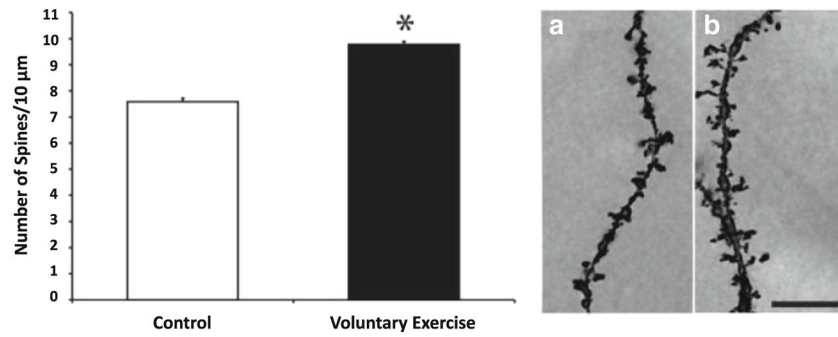
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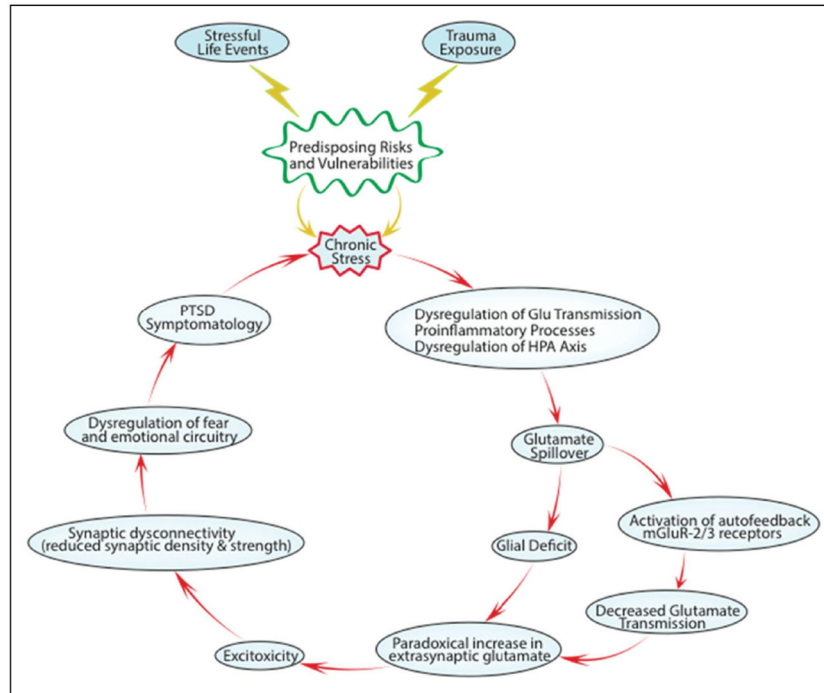
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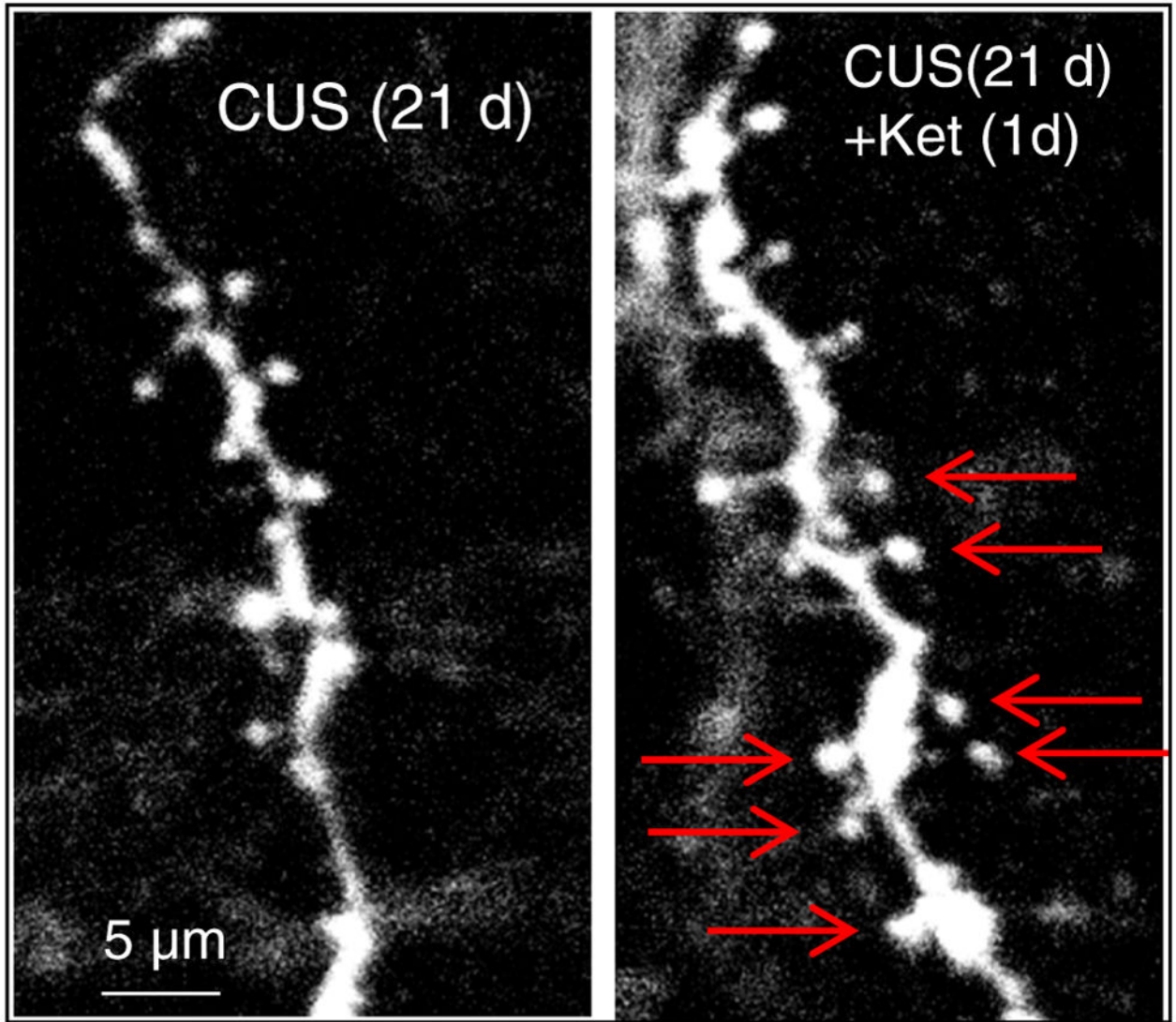
**Fig. 1.** Stress causes neural atrophy and synapse loss. **a** The influence of repeated-restraint stress (7 d) on pyramidal neurons (layer V) in the medial prefrontal cortex (mPFC) of rat. The left-hand set of images shows that stress reduces the number and length of apical dendrites. The right-hand set of images shows a magnified segment of dendrite, with its spines at the point of synaptic contacts with neuronal inputs to the mPFC; repeated stress significantly decreases the number of spine synapses. **b** Under normal conditions, stimulation of the presynaptic neuron releases glutamate, resulting in the activation of postsynaptic glutamate AMPA receptors and depolarization; this causes activation of multiple intracellular pathways, including the BDNF-TrkB signaling pathway (and the downstream kinases Akt and ERK) and the mTORC1 pathway. These pathways are essential for regulation of synaptic plasticity, a fundamental adaptive learning mechanism that includes maturation (increased spine-head diameter) and an increase in the number of synapses. This process requires mTORC1-mediated de novo protein synthesis of synaptic proteins, including glutamate GluA1 AMPA receptors and PSD95. Repeated stress decreases BDNF and mTORC1 signaling in part via upregulation of the negative regulator REDD1 (regulated in DNA damage and repair), which decreases the synthesis of synaptic proteins and thereby contributes to a decreased number of spine synapses. Other proteins that are involved in the regulation of synaptic plasticity include GSK3 and protein phosphatase 1 (PP1) (from [23•])



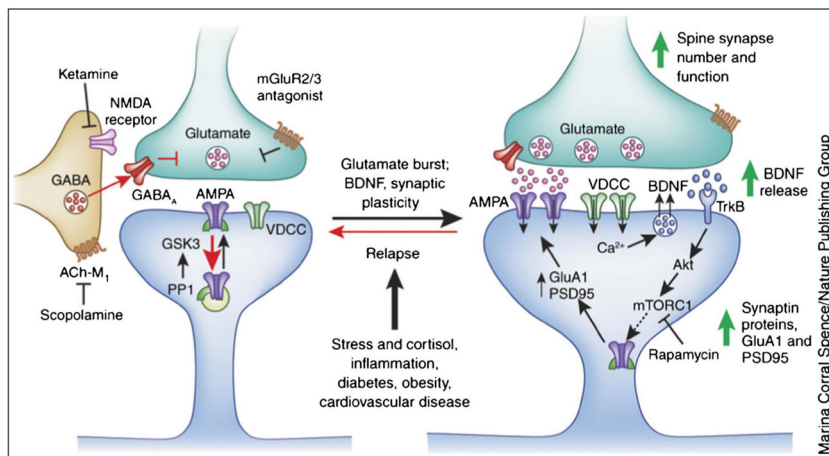
**Fig. 2.** Evidence that voluntary exercise increases dendritic spine density in the dentate gyrus of the hippocampus in rats. The left figure presents the number of dendritic spines per 10 μm for dentate granule cells. The asterisk symbol indicates  $p < .05$ . The right figure presents results from Golgi-impregnated dentate granule cells at  $\times 100$  magnification from control (A) and exercised (B) animals. Scale bar = 10 μm [82]



**Fig. 3.** This figure illustrates a “vicious cycle” through which neuroinflammation, HPA activation, and stress-related alterations in circuit function interact to contribute to synaptic loss and how synaptic loss then contributes to the chronicity of PTSD by compromising the regulation and neuroplasticity of emotion-related neural networks (modified from [101])



**Fig. 4.** Confocal photomicrographs of labeled layer V pyramidal neurons in the medial prefrontal cortex. The left figure shows the low numbers of dendritic spines present in the dendrites of layer V pyramidal neurons after 21 days of chronic uncontrollable stress (CUS). The right figure illustrates the reversal by a single dose of ketamine 1 day later. Red arrows highlight dendritic spines present after ketamine



**Fig. 5.** Ketamine causes a burst of glutamate that is thought to occur via disinhibition of GABA interneurons; the tonic firing of these GABA interneurons is driven by NMDA receptors, and the active, open-channel state allows ketamine to enter and block channel activity. The resulting glutamate burst stimulates AMPA receptors, which causes depolarization and activation of voltage-dependent  $Ca^{2+}$  channels (VDCC), leading to release of BDNF and stimulation of TrkB receptors and activation of Akt, which then increases mTORC1 signaling, leading to the increased synthesis of proteins that are required for synapse maturation and formation (i.e., GluA1 and PSD95). Under conditions in which BDNF release is blocked or neutralized, or in which mTORC1 signaling is blocked by rapamycin, the synaptic and behavioral actions of ketamine are blocked. Scopolamine also causes a glutamate burst via blockade of acetylcholine muscarinic  $M_1$  (ACh- $M_1$ ) receptors on GABA interneurons. Antagonists of mGluR2/3 also produce rapid antidepressant actions via blockade of presynaptic autoreceptors that inhibit the release of glutamate. Relapse to a depressive state is associated with a decrease of synapses on mPFC neurons, which could occur via stress and imbalance of endocrine hormones (cortisol), estrogen, inflammatory cytokines, and metabolic and cardiovascular illnesses (from [23•])