Dendritic Spines in Depression: What We Learned from Animal Models

Hui Qiao, 1 Ming-Xing Li, 1 Chang Xu, 1 Hui-Bin Chen, 1 Shu-Cheng An, 1 and Xin-Ming Ma 1,2

1 College of Life Science, Shaanxi Normal University, Xi'an, Shaanxi 710062, China
2 Department of Neuroscience, University of Connecticut Health Center, Farmington, CT 06030, USA

Correspondence should be addressed to Xin-Ming Ma; ma@nso.uchc.edu

Received 7 July 2015; Accepted 26 November 2015
Academic Editor: Maurizio Popoli

Copyright © 2016 Hui Qiao et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Depression, a severe psychiatric disorder, has been studied for decades, but the underlying mechanisms still remain largely unknown. Depression is closely associated with alterations in dendritic spine morphology and spine density. Therefore, understanding dendritic spines is vital for uncovering the mechanisms underlying depression. Several chronic stress models, including chronic restraint stress (CRS), chronic unpredictable mild stress (CUMS), and chronic social defeat stress (CSDS), have been used to recapitulate depression-like behaviors in rodents and study the underlying mechanisms. In comparison with CRS, CUMS overcomes the stress habituation and has been widely used to model depression-like behaviors. CSDS is one of the most frequently used models for depression, but it is limited to the study of male mice. Generally, chronic stress causes dendritic atrophy and spine loss in the neurons of the hippocampus and prefrontal cortex. Meanwhile, neurons of the amygdala and nucleus accumbens exhibit an increase in spine density. These alterations induced by chronic stress are often accompanied by depression-like behaviors. However, the underlying mechanisms are poorly understood. This review summarizes our current understanding of the chronic stress-induced remodeling of dendritic spines in the hippocampus, prefrontal cortex, orbitofrontal cortex, amygdala, and nucleus accumbens and also discusses the putative underlying mechanisms.

1. Introduction

Depression, a severe psychiatric disorder [1, 2], affects up to 20% of the population in the US within their lifetime and is more prevalent in women than men [3–6]. Although depression has been studied for decades, its cellular and molecular mechanisms still remain largely unknown [7]. As many as 30–40% of patients with major depressive disorder have treatment-resistant depression which does not respond to currently available antidepressant therapies [8]. It is therefore important to identify the mechanisms underlying depression in order to develop effective therapeutic strategies.

Chronic stress, especially psychosocial stressors in humans, is one well-known risk factor for the development of depression [6, 9–13]. Enhancement of neuronal plasticity is essential for adaptive intracellular changes during the normal stress response, which promotes dendritic growth, new synapse formation, and facilitates neuronal protein synthesis in the face of an acute challenge. In addition, a successful stress response requires continuity of the response to ensure normal brain function and promote survival [9, 14, 15]. On the one hand, brief or moderate stressors actually enhance neural function in most cases, while severe or chronic stressors are detrimental and can disrupt the ability of the brain to maintain its normal stress response, eventually leading to depression [15–18]. Furthermore, it has been shown that significant but brief stressful events (acute stress) result in the differentiation of stem cells into new nerve cells that improve the mental performance of rats [19]. On the other hand, chronic stress increases the levels of the stress hormone glucocorticoid and suppresses the production of new neurons in the hippocampus. This response results in decreased dendritic spine density and synapse number and impaired memory [17, 20–24]. The relationship between stress and psychiatric diseases has been well established for 20 years in the clinic [25, 26]. Chronic stress paradigms in rodents, the classical animal model of depression, recapitulate many of the core behavioral features
2. The Plasticity of Dendritic Spines

Dendritic spines are tiny membranous protrusions from the dendritic shaft of various types of neurons. They typically receive excitatory input from axons, although sometimes both inhibitory and excitatory connections are present on the same spine. Over 90% of all excitatory synapses that occur in the CNS are localized to dendritic spines [60], which are cellular substrates of brain connectivity and the major sites of information processing in the brain [61, 62]. Billions of neurons contact and communicate with each other via synapses. It is widely accepted that the regulation of dendritic spine number, size, and shape is of importance to the plasticity of synapses, as well as learning and memory [63, 64]. The morphology of spines is highly variable and commonly categorized into three types: thin, mushroom, and stubby (Figure 1) [65, 66]. Large mushroom spines are memory spines that are responsible for the maintenance of neuronal networks and long-term memory [75]. Large mushroom spines with large heads are stable and are likely to contain smooth endoplasmic reticulum, a spine apparatus, polyribosomes, and endosomal compartments in which post-translational modification of proteins, local protein synthesis, local recycling of receptors, and membrane management occur, respectively [64]. Large mushroom spines that contain abundant AMPA receptors are not restricted to pairing with presynaptic axonal terminals containing more synaptic vesicles. They can also associate with presynaptic astroglial terminals, which enhance synapse formation, stabilization, and synapse elimination [64]. Mushroom spines with small heads are motile and unstable and contribute to weak or silent synaptic connections [68].

![Diagram of dendritic spines. Dendritic spines are categorized into mushroom, thin, and stubby spines. Length of spine (L), diameter of spine head (D_h), and diameter of spine neck (D_n). Filopodia are the precursor of dendritic spine.](image)

Dendritic spine pathology is associated with many psychiatric diseases [71, 76–78]. The formation, growth, and elimination of the dendritic spines are precisely controlled, which requires the reorganization of the neural network in response to acute stress or learning processes. These processes are commonly dysregulated or disrupted in chronically stressed animals [46, 79]. Therefore, understanding dendritic spines is fundamental in uncovering the mechanisms underlying depression. It is well established that depression is closely associated with selective structural changes, altered cellular resilience, and neuronal atrophy. Moreover, depression is associated with reduction in astrocytes and reduced/or

of depression and respond to antidepressant treatments [10, 23, 27]. However, the precise nature of relationships among the effects of chronic stress, the dysregulation of spine/synapse plasticity, and the molecular mechanisms of depression remain poorly understood [9]. This minireview summarizes our current understanding, obtained from animal models of chronic stress, of remodeling of dendritic spines in five regions of the brain during depression.
increased volume of some brain regions that affect mood and cognition, which involve structural and molecular remodeling of dendritic spines in the hippocampus, prefrontal cortex, amygdala, and nucleus accumbens [7, 23, 49, 62, 80–83]. Antidepressants have reversed some of these structural changes observed in animal models of depression [13, 83, 84]. These studies have generated the hypothesis that alterations of the dendritic spines and the plasticity at excitatory synapses contribute to symptoms of depression [5, 85–88].

3. Chronic Stress and Animal Models of Depression

Animal models are essential tools for studying and understanding specific symptoms of human psychiatric disorders, though none of the current models fully recapitulate stress-related psychiatric disorders described in humans. Most of the current knowledge about the mechanism underlying depression has come from animal models. Several animal models of depression have been used to understand the mechanisms underlying depression [149]. We only discuss the model of chronic stress in this review. Several chronic stress models have been used to model depression-like behaviors in rodents such as chronic restraint stress (CRS), chronic unpredictable stress (CUS), and chronic social defeat stress (CSDS). Behavioral tests of anhedonia (sucrose preference) or despair (forced swim test and tail suspension test) have been widely used to determine depression-like behaviors induced by these three models [150]. Depression-like behaviors induced by these models can often be reversed by chronic antidepressant treatments [27, 86]. It is, however, worth noting that there are some rats or mice that do not respond to traditional antidepressants, which is similar to treatment-resistant depression in human subjects [151]. Here, we briefly summarize our current understanding about these three animal models.

3.1. Chronic Restraint Stress (CRS). CRS has been used widely to study the morphological, hormonal, and behavioral alteration in several brain regions in rodents, such as the hippocampus, prefrontal cortex, amygdala, and nucleus accumbens because it is inexpensive and relatively easy to implement [152] (Tables 1–4). To study dendritic morphology and spine formation, this method typically involves restraining an animal for 1–6h each day in a restraint device (bag or tube) for a period of 14–21 days or more. A disadvantage of the CRS model is the habituation of rats or mice to repeated exposure to homotypic restraint stressors; the response of plasma corticosterone, the major glucocorticoids in rodents, to the final stressor is diminished in animals that had been stressed for 14 days [153–156]. The pattern of hypothalamic corticotrophin-releasing hormone (CRH) heteronuclear RNA and mRNA responses to CRS is similar to the response of corticosterone, decreasing with increasing frequency of exposure to the repeated restraint stressor [153]. Animals habituate over time and finally show no increase in hypothalamic-pituitary-adrenal (HPA) axis activation and no increase in expression of hypothalamic CRH [30, 153, 156]. The duration of CRS may differentially affect learning/memory and CA3 dendritic atrophy with shorter periods of CRS (7–13 days) serving an adaptive function to enhance learning and memory [157]. On the other hand, longer CRS duration (21 days or more) causes maladaptive changes such as dendrite atrophy, spine loss, and impaired memory [15, 157, 158]. CRS-induced habituation of HPA axis contrasts with the hyperactivity of the HPA axis accompanied by increased CRH levels [43, 159] and the hypersecretion of cortisol [160, 161] in depressed patients, showing that activation of HPA axis is a hallmark of major depression [162, 163]. Depending on duration and intensity of chronic stress, some studies report that exposure of animals to CRS induces depression-like behaviors such as anhedonia (decreased sucrose preference) [164–169], which is a core symptom of human depression [10, 27]. A conflicting report shows CRS could not induce anhedonic-like behavior [170]. The duration and intensity of CRS as well as animal strains may determine whether CRS can be used as a valid animal model of depression to produce anhedonic-like behavior.

3.2. Chronic Unpredictable Mild Stress (CUMS). CUMS is a well-established animal model for depression. The original, three-week chronic unpredictable severe stress (CUS) model with diverse severe and unpredictable stressors (electric shocks, immobilization, cold swimming, isolation housing, and other strong stimuli) was developed by Katz and coworkers [171, 172]. In order to accurately recapitulate the human condition, Willner and colleagues replaced severe stressors in Katz's model with mild stressors. Additionally, Willner and colleagues augmented the CUMS model with a variety of mild and unpredictable stressors (e.g., overnight illumination; presence of novel objects; periods of food and/or water deprivation; cage tilt; change of cage mate) [173]. In Willner's model, exposure of animals to 7–13 mild stressors up to 3 months produced a longer lasting depression-like behavior, anhedonia [173–175]. The CUS model used in Duman's group was modified from Willner's model. In Duman's model, animals were exposed to 10 [108, 176] or 12 [106] unpredictable stressors, 2 times per day, for up to 35 days, which produced depression-like behaviors. The duration of CUS is 21 days for the experiments using CUS alone or 35 days for the experiment using CUS together with antidepressant treatments [106, 108, 176]. It is worth noting that CUS model used by Duman's group is different from the CUMS protocol, not only in the duration and number of stressors/day, but also at the level of stressor intensity (rotation on a shaker 1 hour, cold 4°C 1 hour, lights off for 3 hours, lights on overnight, strobe light overnight, aversive odor overnight, 45° tilted cages overnight, food and water deprivation overnight, crowded housing overnight, and isolation housing overnight) [108, 176]. The modified CUMS model used in our laboratory consists of daily exposure of animals to 8 chronic unpredictable mild stressors, one stressor per day, for 21 days. The same stressor is not applied in two consecutive days [24, 177]. The different abbreviations of chronic unpredictable mild stress (CUS, CMS, or CUMS) were used in several modified versions by different laboratories. We use CUMS as a common denotation in this review. In comparison with the CRS model, CUMS overcomes stress habituation of the
Table 1: The effects of chronic stress on dendritic spines in hippocampus.

| #  | Stress          | Paradigms                                      | Animals          | CA1                  | CA3                                      | References |
|----|-----------------|------------------------------------------------|------------------|----------------------|------------------------------------------|------------|
| 1  | CRS             | 6 h/day for 21 days                            | Male SD rats     | nd                   | Apical, not basal dendritic atrophy      | [28]       |
| 2  | CRS             | 6 h/day for 21 days                            | Male SD rats     | nd                   | ↑ spine density in apical, basal dendrites | [29]       |
| 3  | CRS or multiple stress (CMS): 3 different stressors | CRS, 6 h/day for 21 days CMS: 3 stressors/day for 21 days | Male SD rats     | nd                   | Apical dendritic atrophy; CORT habituates to 21-day CRS but not 21-day CMS | [30]       |
| 4  | CRS             | 6 h/day for 21 days                            | Male SD rats     | nd                   | Apical dendritic atrophy is blocked by cyanoketone or CGP43487 | [31]       |
| 5  | CRS             | 6 h/day for 21 days                            | Male SD rats     | nd                   | ↑ synaptic vesicle density in MFT         | [32]       |
| 6  | CRS             | 6 h/day for 21 days                            | Male SD rats     | nd                   | Apical dendritic atrophy, recovery after 10 days ↓ spine density | [33]       |
| 7  | CRS             | 6 h/day for 21 days                            | Adult male Wistar rats | nd | ↑ excitatory MF-CA3 synapses, recovery after maze learning | [34]       |
| 8  | Acute restraint plus intermittent tail shock | 30 shocks: 1 mA, 1 s, 1/min | Adult male and female SD rats | ↑ spine density in male and ↓ in female apical dendrites, both 100% blocked by CPP | nd | [35] |
| 9  | CRS             | 6 h/day for 21 days                            | Male Wistar rats | nd                   | ↓ PSD number; ↓ spine density in apical dendrites Retraction of dendritic TE with ↓ in their volume | [36]       |
| 10 | CRS             | 6 h/day for 21 days                            | Adult SD adult female rats | ↔ dendritic atrophy ↑ spine density ↑ spine size | Apical dendritic atrophy Spine density, nd | [37, 38] |
| 11 | CRS             | 6 h/day for 21 days                            | Male Wistar rats | ↑ PSD surface and ↑ PSD volume; ↔ excitatory synapses in stratum | nd | [39] |
| 12 | CRS             | 6 h/day for 21 days                            | C57/BL6 male Wt mice | ↓ spine density in apical dendrite ↓ NRI, NR2B, NR2A, and GAP43 | These decreases are tPA and plasminogen dependent | [40] |
| 13 | CRS             | 6 h/day for 21 days                            | C57/BL6 male Wt mice | ↔ dendritic atrophy; ↓ total spine density, ↔ stubby spines ↓ thin and mushroom spine density | Apical, not basal dendritic atrophy ↔ total spine density, ↑ stubby spines, ↓ thin and mushroom spines | [41] |
| 14 | CRS             | 6 h/day for 21 days                            | Adult SD female rats | ↔ dendritic atrophy ↑ spine density ↑ mushroom spine | Apical dendritic atrophy ↓ spine density | [42] |
| 15 | CRS             | 2.5 h/day for 14 days                          | Male rats        | ↓ spine density in apical dendrites | nd | [43] |
| 16 | CRS             | 6 h/day for 21 days                            | Adult SD male rats | ↑ spine density | Apical dendritic atrophy, ↓ spine density, and ↑ spinophilin and Homer1 | [44] |
| 17 | CRS             | 6 h/day for 21 days                            | Female mice      | ↓ spine density in apical dendrites | nd | [45] |
| 18 | CRS             | 2.5 h/day for 14 days                          | Adult male SD rats | ↓ spine density, ↓ cadherin, and ↔ LIMK/cofilin and p-LIMK/p-cofilin | nd | [46] |
| #  | Stress     | Paradigms            | Animals                          | CA1                                                              | CA3                      | References |
|----|------------|----------------------|----------------------------------|------------------------------------------------------------------|--------------------------|------------|
| 19 | CRS        | 6 h/day for 25 days  | Female, male Long-Evans rats     | ↓ spine density in basilar dendrites; ↑ apical dendritic arbors in female, not male ventral CA1 | Deficits in spatial memory in female but not male                  | [47]       |
| 20 | CRS        | 6 h/day for 21 days  | Adult male mice                  | ↓ spine density; ↓ p-Akt, ↓ p-GSK-3β, and ↑ p-Erk1/2             | nd                       | [48]       |
| 21 | CUMS       | 1 stressor/day for 30 days | Male Wister rats                | ↔ apical dendrite                                                | Apical dendritic atrophy; ↓ MF-CA3 synapses                        | [49]       |
| 22 | CUMS       | 2 stressors/day for 10 days | Male Wister rats               | nd                                                              | ↔ CA3 dendrites                                                   | [50]       |
| 23 | CUMS       | 1 stressor/day for 21 days | Male SD rats                   | ↓ CA1 spine density                                             | ↓ Kalirin-7 protein in hippocampus                                | [24]       |
| 24 | CUMS       | 1 stressor/day for 14 days | Male mice                     | nd                                                              | ↑ CA3 spine density                                               | [51]       |
| 25 | CUMS       | 1 stressor/day for 8 weeks | Male SD rats                   | ↓ PSD thickness in CA1, ↓ PSD95 protein                        | ↓ PSD93, ↓ PSD95, ↓ SYN, ↓ spinophilin, and ↓ synapsin 1           | [52]       |
| 26 | CUMS       | 2-3 stressors/day for 21–35 days | Adult SD rats                | Impaired AMPAR-synaptic excitation at TA-CA1 synapses           | mGlu2 deletion in mice results in a more severe susceptibility to stress | [53]       |
| 27 | CUMS       | 2 stressors/day for 28 days | Male C57/b mice               | ↓ mGlu2 receptors in susceptible, not resilient mice            | mGlu2 deletion in mice results in a more severe susceptibility to stress | [54]       |
| 28 | Multimodal stress |             | Adult male C57BL/6 mice        | ↓ synapse numbers in dorsal apical dendrites, ↓ PSD-95-ir puncta | ↓ synapse numbers in dorsal CA3 apical, ↓ PSD-95-ir puncta      | [55]       |
| 29 | Psychosocial stress | 1 h/day for 28 days | Male tree shrews               | nd                                                              | Apical, not basal dendritic atrophy ↔ spine density              | [56]       |
| 30 | Psychosocial stress | 1 h/day for 28 days | Male rats                     | nd                                                              | Apical dendritic atrophy                                          | [57]       |
| 31 | Chronic CORT exposure |             | Male SD rats                  | Impaired AMPAR-synaptic excitation at TA-CA1 synapses           | Induces depression-like behaviors                                  | [58]       |
| 32 | CORT exposure | 35 days             | C57/BL6 male mice             | ↓ CA1 thin and stubby spine density, but not mushroom spines    | ↔ CA3 spine density                                               | [59]       |

CRS: chronic restraint stress. CUMS: chronic unpredictable mild stress. TA: temporoammonic. CORT: corticosterone. MFT: mossy fiber terminals. TE: thorny excrescences in the stratum lucidum of CA3. ↔: no change. ↓: decrease. ↑: increase. nd: not done.

HPA axis occurring during stress, in which the response of plasma corticosterone to the final stressor is still sustained in animals which had been stressed for 15 to 35 days [27, 30, 106, 155]. Depression-like behaviors and deficits in synaptic plasticity are gradually developed during CUMS [24, 173]. The CUMS model recapitulates many of the core behavioral characteristics of human depression that are reversible by chronic treatments with traditional antidepressant agents [10, 27] and is more relevant to human disease. Therefore, the CUMS model has been widely used as an animal (specifically rat) model of depression. Our results show that, during CUMS, rats require three weeks to develop depression-like behaviors accompanied by both functional changes in CA3-CA1 synapses and decreased spine density in the dendrites of CA1 and CA3 pyramidal neurons [24, 177]. This is in line with Willner’s CUMS paradigm [173], in which animals were exposed to initial unpredictable stress for three weeks to develop depression-like behaviors prior to the onset of antidepressant treatments. Because of its advantage of the gradual development of depression-like behaviors during CUMS [24, 173], this model is useful in studying depression-like behaviors such as anhedonia [27, 86, 174, 178]. In addition, this CUMS model is useful for inducing depression-like behaviors in female mice because chronic social defeat...
Table 2: The effects of chronic stress on dendritic spines in the prefrontal cortex (PFC).

| #  | Stress | Paradigms            | Animals                     | PFC                                                                 | Proteins                                                                 | References |
|----|--------|-----------------------|-----------------------------|----------------------------------------------------------------------|--------------------------------------------------------------------------|------------|
| 1  | CRS    | 6 h/day for 21 days   | Male SD rats                | ↓ apical dendrite of layers II and III mPFC                          |                                                                          | [76]       |
| 2  | CRS    | 3 h/day for 21 days   | Male SD rats                | Apical dendrite atrophy ↔ basal dendrites in PL mPFC                |                                                                          | [89]       |
| 3  | CRS    | 6 h/day for 21 days, 21 day recovery | Male SD rats | ↓ apical dendrite length, reversible after 21 d in mPFC             |                                                                          | [90]       |
| 4  | CRS    | 6 h/day for 21 days   | Male SD rats                | ↓ 20% apical dendritic length, ↓ spine density in PL mPFC           |                                                                          | [91]       |
| 5  | CRS    | 6 h/day for 21 days   | Male SD rats                | ↓ 20% apical dendritic arbors in mPFC                               |                                                                          | [92]       |
| 6  | CRS    | 6 h/day for 21 days   | Male SD rats                | ↓ mushroom spine density ↑ thin spine number in PL mPFC              |                                                                          | [93]       |
| 7  | CRS    | 1 h/day for 7 days    | Male SD rats                | ↓ spine density in PL mPFC                                          |                                                                          | [94]       |
| 8  | CRS    | 6 h/day for 21 days   | Male SD rats                | ↓ apical spine density in apical dendrites Inhibition of PKC prevents spine loss |                                                                          | [95]       |
| 9  | CRS    | 6 h/day for 21 days/with 21-day recovery | Male SD rats | ↓ apical dendrite arbors, ↓ spine density; partial recovery of dendrites and spine loss in IL mPFC |                                                                          | [96]       |
| 10 | CRS    | 3 h/day for 7 days    | Male and female SD rats     | ↓ apical dendrite arbors in male, ↑ apical dendrite arbors in female, which is estradiol dependent in mPFC |                                                                          | [97]       |
| 11 | CRS    | 6 h/day for 21 days   | Male SD young and aged rats | ↓ apical dendrite arbors in young, but not aged, rats are reversible; ↓ spine density in young, but not aged, rats |                                                                          | [98]       |
| 12 | CRS    | 6 h/day for 21 days   | Male SD rats young, middle-aged, and aged | ↓ spine density (↓ thin and stubby spines, ↔ mushroom spines) in young but not middle-aged and aged rats in PL mPFC |                                                                          | [99]       |
| 13 | CRS    | 6 h/day for 21 days   | Male SD rats                | ↑ mRNA levels of VAMP2, VAMP1, syntaxin IA, synapsin, synaptotagmins I and III, and synapsins I and II ↓ SNAP-25 mRNA level | ↑ protein levels of VAMP2, syntaxin IA, and SNAP-25 | [100] |
| 14 | CRS    | 2 h/day for 7 days    | Adult male WT mice          | ↓ spine density in mPFC; ↓ apical dendrites                         | ↓ BDNF                                                                   | [101]      |
| 15 | CRS    | 1 h/day for 21 days   | Male GIN mice               | ↔ spine density in mPFC                                             | ↑ NCAM, SYN                                                              | [102]      |
| 16 | CRS    | 6 h/day for 21 days   | Male SD rats                | ↓ spine density in PL mPFC                                          | Alpha-2A-adrenoceptor                                                   | [103]      |
| 17 | CRS    | 3 h/day for 21 days   | Male SD rats PL mPFC        | ↓ dendritic retraction is prevented by D1R antagonist SCH23390 that causes dendritic retraction in unstressed rats |                                                                          | [104]      |
| 18 | CRS    | 2 h/day for 7 days    | Male SD rats                | ↓ glutamatergic transmission in PFC pyramidal neurons               |                                                                          | [105]      |
| 19 | CUMS   | 15 days or 35 days    | Male SD rats                | 35% ↓ cell proliferation in neocortex                              |                                                                          | [106]      |
| 20 | CUMS   | 3 stressors/day for 21 days | Male Wistar rats | ↓ volume of layer I/II of PL and IL ↓ neuronal density of layer II of PL and IL Apical dendritic atrophy in PL and IL ↔ spine density tends to decrease in PL and IL |                                                                          | [107]      |
TABLE 2: Continued.

| #  | Stress | Paradigms | Animals         | PFC                                           | Proteins | References |
|----|--------|-----------|----------------|-----------------------------------------------|----------|------------|
| 21 | CUMS   | 2 stressors/day for 21 days | Male SD rats | ↓ spine density in mPFC; ↓ synapsin I, GluR1, and PSD95 |          | [108]      |
| 22 | CUMS   | 1 stressors/day for 21 days | Male SD rats | ↓ synaptic length of the active zone in CGI mPFC | ↓ spinophilin and synapsin I in CGI | [52]      |
| 23 | CIS    | 2 h/day for 10 days | Male SD rats | ↔ apical dendrites in IL-BLA projecting neurons in IL mPFC | ↔ spine density in IL mPFC |          |
| 24 | Depressed patients | daily injection for 21 days | Male SD rats | ↓ spine density proximal to the soma | GATA1↑ | [110]      |
| 25 | CORT, vehicle | daily injection for 21 days | Adult male C57BL/6J mice | ↓ apical dendrites in IL mPFC; ↔ basal dendrites in IL mPFC | ↓ synaptic-function-related genes | [111]      |
| 26 | Forced swim | 10 min/day for 3 days | Male Wistar rats | ↓ spine density in apical and basal dendrites in mPFC | GluR1, GluR2, αCaMKII, and PSD95↑ | [112]      |

CRS: chronic restraint stress. CUMS: chronic unpredictable mild stress. CIS: chronic immobilization stress. PL: prelimbic region of the mPFC. IL: infralimbic region of the mPFC. CG1: area 1 of cingulate region of mPFC. CORT: corticosterone. ↔: no change. ↓: decrease. ↑: increase.

stress protocol cannot successfully induce depression-like behaviors in C57BL/6J female mice [179]. A recent report shows that C57BL/6 mice, one of the most widely used mouse strains, are resistant to the commonly used CUMS protocol due to the variety of genetically modified lines. A recently revised, eight-week CUMS protocol has been developed and used to induce depression-like behaviors in C57BL/6 mice [180]. Interestingly, male and female rodents are differentially affected by CUMS, depending on the behavioral and neurobiological markers that are being measured [181].

3.3. Chronic Social Defeat Stress (CSDS). CSDS is one of the most frequently used rodent models for depression and has been used to induce depression-like behaviors in mice such as social avoidance and anhedonia [86, 144, 182–185]. During each defeat period, an intruder, a male C57BL/6J mouse, is allowed to interact for 10 minutes with an aggressive and large CD1 mouse during which the intruder is rapidly investigated, attacked, and defeated by the resident CD-1 mouse. The experimental C57BL/6J mice are exposed to a different resident aggressor for 10 minutes each day for 10 consecutive days [183, 184, 186–188]. On the one hand, after completing the social defeats, 30% of animals do not show depression-like behaviors known as “resilient,” a positive adaptation in the face of stress, threat, or severe adversity [189, 190]. On the other hand, a majority of animals (70%) develop depression-like behaviors known as “susceptible.” A disadvantage of this model is that it is limited in studying only male mice because female C57BL/6J mice are not easily defeated by CD-1 mice [86]. This model has been widely used to induce depression-like behaviors and study the molecular mechanisms underlying depression [139, 141, 142, 146, 149, 191, 192]. This model is also used to induce depression-like behaviors in rats [192, 193].

4. The Effects of Chronic Stress on Dendritic Spines in Different Brain Regions

4.1. Hippocampus (Table 1). The hippocampus plays an important role in learning and memory and is particularly sensitive to stress and glucocorticoids [194, 195]. Rodent hippocampus contains high levels of glucocorticoid receptors (GRs) and mineralocorticoid-like receptors (MRs). The affinity of MR for corticosterone is 6- to 10-fold higher than that of GR, but it is GR that is activated after stress and is involved in its feedback action on stress-induced neural plasticity [196]. Chronic stress decreases GR expression or its numbers and finally alters the balance of GR/MR in the male hippocampus [197, 198], which is thought to be a protective mechanism against the damaging effects of chronic stress. Chronic exposure of male rats to glucocorticoids induces depression-like behaviors and causes the synaptic deficits in the hippocampus [58]. A recent report shows that GRs, acting via MR, decrease resilience to stress via downregulation of mGlu2 receptors in mice during CUMS [54]. Chronic stress and glucocorticoids impair hippocampal function, which in turn contributes to the HPA axis dysregulation [195, 198]. The blunting of the feedback mechanism is believed to underlie
| #  | Stress       | Paradigms         | Animals                              | Amygdala                                                                 | Function                                                                 | Proteins                        | References |
|----|-------------|-------------------|--------------------------------------|--------------------------------------------------------------------------|---------------------------------------------------------------------------|---------------------------------|------------|
| 1  | CRS         | 6 h/day for 21 days | WT C57/BL/6 mice                     | ↓ spine density in WT medium spine stellate neurons MeA, ↑ spine density in WT BLA | ↓ spinogenesis in BLA OF tPA-/- mice                                     | tPA-/- mice reverse stress-induced reduction of spine density in MeA | [114]      |
| 2  | CRS         | 6 h/day for 28 days | Male young, Wistar rats               | ↔ spine density in MePD                                                  |                                            |                                |            |
| 3  | CRS         | 1 h/day for 10 days | Male ICR mice                        | ↓ eIPSC, ↑ LTD GABAergic synapse in BLA                                  | MAGL inhibition prevents depression-like behavior                           | 2-AG ↑, MAGL ↓                  | [116, 117] |
| 4  | CRS         | 2 h/d for 10 days  | Male Wt mice                         | ↑ BLA dendritic branching, ↑ spine density in BLA apical and basal dendrites, ↑ spine length, ↑ anxiety behavior |                                            | In Fmr1 KO mice ↔ spine length in BLA, ↓ spine density in BLA | [118]      |
| 5  | CRS         | 1 h/day for 21 days | Male GIN mice                        | ↔ spine density, ↓ dendritic arborization in interneurons in LA and BLA |                                            |                                | [119]      |
| 6  | CRS         | 2 h/day for 10 days | Male ICR mice                        | ↑ dendritic length and branch points in BLA, which are blocked by tianeptine | Depression-like behaviors are blocked by tianeptine                       | Tianeptine is an antidepressant | [120]      |
| 7  | CRS         | 1 h/day for 14 days | Male SD rats                         | Impaired LTP in the NAc 30 days after stress termination                | CB1/2R agonist prevents the stress-impaired LTP                           | ↓ GRs in amygdala and NAc      | [121]      |
| 8  | CRS         | 20 min/day 7 out of 9 days | Male SD rats                       | ↑ dendritic length in BLA, ↑ spine density in LA and BA, but proximal increase in LA, nonproximal increases in BA | ↑ frequency of sEPSC in vivo                                              |                                | [122, 123]|
| 9  | CRS         | 6 h/day for 21 days | C57/Bl6 mice                         | ↑ dendritic arborization ↑ spine density in BLA ↑ anxiety-like behaviors | CRS-induced changes in structure and behaviors are abolished in FAAH KO mice |                                | [124]      |
| 10 | Acute restraint stress CRS | Single 1 h Single 6 h 6 h/day for 28 days | Male young adult                    | ↑ Spine density in the posterodorsal MePD ↔ spine density in MePD |                                            |                                | [115]      |
| 11 | CIS         | 2 h/d for 10 days 10 days | Male Wistar rats                     | ↑ dendritic arborization in BLA pyramidal and stellate neurons | Dendritic atrophy in BLA bipolal neurons                                  |                                | [50]       |
| 12 | CIS         | 2 h/d for 10 days  | Male Wistar rats                     | ↔ dendrites in GEA, ↑ dendrites in BNST                                   |                                            |                                | [125]      |
| #  | Stress          | Paradigms       | Animals               | Amygdala                | Function                        | Proteins                                      | References |
|----|-----------------|-----------------|-----------------------|-------------------------|---------------------------------|-----------------------------------------------|------------|
| 13 | CIS             | 2 h/d for 10 days | Male Wistar rats      | ↑ dendritic length in BLA | ↓ spine density in the BLA      | [126]                                         |            |
| 14 | CIS             | 2 h/d for 10 days | Male Wistar rats      | ↑ dendritic arborization BLA, ↑ spine density ↓ synaptic connectivity | ↑ anxiety-like behavior           | [127]                                         |            |
| 15 | CIS             | 2 h/d for 21 days | Male Wistar rats      | ↑ spine density in BLA   | LTP ↑ (thalamic-LA) sIPSC frequency ↓ | [128]                                         |            |
| 16 | CIS             | 2 h/day for 10 days | Male Wistar rats      | ↑ spine density in BLA   | ↑ dendritic arborization BLA, ↑ spine density ↑ synaptic connectivity ↑ anxiety-like behavior | [129]                                         |            |
| 17 | AIS             | 2 h              | Male Wistar rats      | ↔ spine density or dendritic arborization 1 d later, ↑ spine density 10 d later in BLA |                           | [127]                                         |            |
| 18 | CUMS            | 8 weeks          | Adult male SD rats    | ↑ synaptic length of the active zone in BLA ↑ PSD thickness in BLA ↑ synaptic proteins are correlated with depression-like behaviors ↓ PSD93, ↔ PSD95, and ↔ spinophilin ↔ synapsin ↔ synaptophysin |                           | [52]                                          |            |
| 19 | CUMS            | 14 days          | Male Swiss albino mice| ↑ spine density in BLA ↑ dendritic length in BLA | Associated with depression-like behaviors | [51]                                          |            |
| 20 | Chronic CORT    | 20 days          | C57BL/6 mice          | ↑ spine density in BLA, recovery to normal level with a washout period |                           | [130]                                         |            |
| 21 | CORT drinking water | 50 μg/mL for 14 days | Adult male SD rats    | ↑ GluR1 and synaptophysin in the LA | ↑ IEGs Arc/Arg3.1 and Egr-1 in the LA | [131]                                         |            |
| 22 | Single prolonged stress | 2 h restraint, 20 min forced swimming | Adult male SD rats | ↑ dendritic arborization in BLA ↔ in CeA neurons | ↑ NPY ↔ CaMKII and MR/GR expression in the BLA | [132]                                         |            |
| 23 | Single elevated platform acute stress | 30 min, single | Male SD rats | ↑ total spine density ↑ mushroom spine density in BLA; ↓ number and the length of branches in BLA |                           | [133]                                         |            |
| 24 | Chronic social instability stress | 1 h/day for 35 days | Adolescent 28-day-old SD rat | ↑ spine density in BLA | ↑ spine density in BLA | ↑ truncated TrkB, ↑ full-length TrkB and SNAP-25 ↑ full-length and truncated TrkB | [134] |

CRS: chronic restraint stress. CUMS: chronic unpredictable mild stress. CIS: chronic immobilization stress. AIS: acute immobilization stress. BA: the basal nucleus of the amygdala. BLA: the basolateral nucleus of the amygdala. LA: the lateral nucleus of the amygdala. MePD: posterodorsal medial amygdala. eCB: endocannabinoid. 2-AG: eCB-2-arachidonoylglycerol. MAGL: monoacylglycerol lipase, an enzyme for degrading 2-AG. CORT: corticosterone. Tianeptine: an antidepressant. ↔: no change. ↓: decrease. ↑: increase.
| #  | Stress | Paradigms          | Animals                                      | NAc                                    | Function                                                                 |
|----|--------|--------------------|---------------------------------------------|----------------------------------------|--------------------------------------------------------------------------|
| 1  | CRS    | 10 days            | Male D1R and D2R mice                       | ↓ AMPAR/NMDAR ratio in D1R-MSN via MC4R; induces LTD in D1R-MSN | MC4R activation and LTD in NAc are required for stress-induced anhedonia |
| 2  | CRS    | 1 h/day for 14 days | Male SD rats                                | ↓ AMPAR/NMDAR ratio in D1R-MSN via MC4R; induces LTD in D1R-MSN | CB/2 receptor agonist prevents CRS-induced-impairment LTD in NAc and in the spatial task |
| 3  | CUMS   | 3 stressors/day for 21 days | Male Wistar rats                           | ↑ neuron density in DMS; ↓ neuron density in DLS; ↑ dendritic length in DLS; ↔ spine density in DS | ↓ glucocorticoid receptors in the Amg, NAc, PFC, and hippocampus |
| 4  | CSDS   | 10 min/day for 10 days | Male C57/BL6/J and CD1                      | ↑ ΔFosB induced by CSDS is required for resilience | ↑ ΔFosB in resilience mice |
| 5  | CSDS   | 10 min/day for 10 days | Male C57/BL6/J and CD1                      | ↑ frequency of mEPSCs in NAc of susceptible mice | ↓ NR2B surface and PSD95 in NAc; ↔ NR2A, Syn and NRI |
| 6  | CSDS   | 5 min/each total 3 times | C57BL6/J and CD1                            | ↑ IκK activity; ↓ thin spine density in MSNs | IκK enhances social avoidance behavior |
| 7  | CSDS   | 10 min/day for 10 days | C57BL6/J and CD1                            | ↑ IκK activity; ↓ thin spine density in MSNs | ↑ IκB kinase (IκK) in NAc of susceptible mice |
| 8  | CSDS   | 10 min/day for 10 days | C57BL6/J and CD1                            | ↑ Dnmt3a levels in NAc | Dnmt3a regulates depression-like behaviors |
| 9  | CSDS   | 10 min/day for 10 days | C57BL6/J and CD1                            | ↑ Dnmt3a levels in NAc | ↑ DNA methyltransferases (Dnmt3a) |
| 10 | CSDS   | 10 min/day for 10 days | Male C57/BL6/J and CD1                      | Excitatory transmission at ILT-NAc MSN synapses controls susceptibility to CSDS | ↑ AMPAR/NMDAR ratio only at ILT inputs to MSNs of susceptible mouse |
| 11 | CSDS   | 10 min/day for 10 days | Male C57/BL6/J and CD1                      | ↑ uEPSC amplitude in D1R; ↓ uEPSC amplitude in D2R mushroom, not thin spines in NAc MSN's in resilient, but not susceptible mice | CSDS does affect uEPSC amplitude mushroom or thin spines of D1-MSNs or D2-MSNs in susceptible mouse |
| 12 | CSDS   | 10 min/day for 10 days | C57BL6/J and CD1                            | ↑ firing in VTA DA neurons in susceptible mice | ↑ BDNF, Akt, GSK-3β, and ERK1/2 in NAc of susceptible mice |
| 13 | CSDS   | 10 min/day for 3 days | Male C57/bl6 and CD1                        | ↑ sIPSC frequency in NAc in control, not stressed mice | ↑ sensitivity of striatal GABA synapses to the stimulation of cannabinoid CB1R |
| #  | Stress          | Paradigms                | Animals                | NAc                                                                 | Function                                                                 | Proteins or mRNA                                                                 | References |
|----|----------------|--------------------------|------------------------|----------------------------------------------------------------------|---------------------------------------------------------------------------|---------------------------------------------------------------------------------|------------|
| 14 | CSDS           | 10 min/day for 10 days   | Male C57/bl6 and CD1   | ↑ vHIP-NAc synaptic transmission is prosusceptible                   | vHIP afferents to NAc uniquely regulate susceptibility to CSDS            | ↓ LTD of vHIP-NAc synaptic transmission is proresilient                         | [146]      |
| 15 | Emotional (ES) | 10 min/day for 10 days   | Male C57/bl6 adolescent (P35) or adult (P56) and CD1 | ↑ spine density in NAc in adolescents by ES and PS                   | ES and PS ↓ p-ERK2 in adolescents but ↑ p-ERK2 in adult                    | [147]      |
| 16 | Prenatal stress|                          | Male and female rats   | ↑ spine density in NAc                                              |                                                                            |                                                                                | [148]      |

Syn: synaptophysin. CRS: chronic restraint stress. CUMS: chronic unpredictable mild stress. CIS: chronic immobilization stress. CSDS: chronic social defeat stress. MC4R: melanocortin 4 receptor. DMS: dorsal medium striatum. DLM: dorsal lateral striatum. DS: dorsal striatum. ILT: intralaminar thalamus. MSNs: medium spiny neurons. NAc: nucleus accumbens. vHIP: ventral hippocampus. uEPSCs: unitary excitatory postsynaptic currents. ↔: no change. ↓: decrease. ↑: increase.
sustained high levels of glucocorticoids in some depressed patients [199]. People with depression have a significantly smaller hippocampus than healthy individuals [200–205], which may result from a decrease in dendritic arbors and spine density in hippocampal neurons. Hippocampal atrophy in depressed patients is associated with depression severity [206].

**CA1 and CA3 Dendrites.** Many structural and functional studies show that dendritic retraction or atrophy, characterized by both reduction in total dendritic length and a simplification of dendritic arbor, is found in the dendrites of CA3 pyramidal neurons but not the dendrites of CA1 pyramidal neurons in response to CUMS [49] or CRS [37, 38, 41, 42] (Table 1). Therefore, CA3 dendrites are more sensitive to chronic stress than CA1 dendrites. The different sensitivity of CA1 and CA3 to chronic stress may result from the differences between these two regions in afferents/efferents, the levels of GRs, NMDA receptors, 5-HT receptors, and GABA inhibitory tones [207–211]. GR levels are higher in the CA1 region than the CA3 region, where the receptors are activated by stress hormone corticosteroids [209, 212]. In addition, it has been repeatedly shown that apical dendrites of CA3 pyramidal neurons are more susceptible to the effects of sustained CRS than CA3 basal dendrites. Dendritic retraction in apical but not basal dendrites of CA3 pyramidal neurons is found after CUMS [49], chronic psychosocial stress [56, 57], and CRS [28, 30, 31, 33, 37, 38, 41, 42, 44, 49, 56, 213, 214]. CRS-induced depression-like behaviors and CA3 dendritic atrophy are not permanent but recovered to control levels after certain stress-free period following the end of CRS procedure [33, 49, 158, 213, 215]. Importantly, CA3 dendritic retraction induced by CRS requires corticosterone secretion and intact NMDAR function. Treatments of chronically stressed rats with either the steroid synthesis blocker cyanoketone or competitive NMDA receptor antagonist (CGP 43487) blocked CRS-induced dendritic retraction [31]. Similar to CUMS, rats usually require three weeks to develop depression-like behaviors and CA3 apical dendritic atrophy because only 21 days, but not 7 to 13 days of CRS, induces reversible impairments of spatial memory performance and CA3 apical dendritic atrophy [157, 158]. In addition, atrophy of apical dendrites, but not basal dendrites of CA3 pyramidal neurons, is found after chronic exposure to elevated glucocorticoid levels, which mimics chronic stress [216]. Chronic stress-induced hippocampal CA3 dendritic retraction and elevated glucocorticoid release contribute to impaired spatial memory [217].

**CA3 Dendritic Spines.** Chronic stress-induced alterations of spine density in CA3 pyramidal neurons depend on stressor types, animal species, sex, and the duration of stress. CRS causes either a decrease [30, 33, 36, 42, 44], an increase [29, 34], or no change [56] in the spine density in the dendrites of male rat CA3 pyramidal neurons. CRS-induced loss of synapses in male rat CA3 apical dendrites can be recovered following water maze training [34, 36]. One report shows that CRS causes a decrease in dendritic spine density, especially in thin and mushroom spines in mouse CA1 pyramidal neurons, but does not affect total spine density in mouse CA3 pyramidal neurons, due to increased stubby spine density and decreased thin and mushroom spine density [41]. The degree of stress-induced spine loss in CA3 pyramidal neurons correlates significantly with the memory defects and loss of LTP in mice [79]. In comparison with CRS, both 21-day CUMS and 30-day CUMS decrease spine density in male rat CA3 pyramidal neurons [24, 49], whereas 14-day CUMS increases spine density in male mouse CA3 pyramidal neurons [51], which is consistent with our report that two-week CUMS enhances LTP induction in CA3-CA1 synapses in male rat hippocampus [24]. Psychosocial stress (1h/day for 28 days) does not affect spine density in CA3 pyramidal neurons of male tree shrews [56].

**CA1 Dendritic Spines.** CA1 is a hippocampal region crucial for long-term memory [218]. In comparison with CA3 pyramidal neurons, chronic stress-induced changes in spine density in CA1 pyramidal neurons are less characterized. Stress affects spine density in CA1 pyramidal neurons in a sex-dependent manner. Acute stress (30, 1 sec, 1 mA, 60 Hz shocks to the tail) increases spine density in the apical dendrites of male hippocampal CA1 pyramidal neurons but decreases it in the same area of female hippocampus [219]. These increases and decreases in spine density are dependent on NMDA receptor activation [35]. Similar to acute stress, the same CRS regimen causes a decrease in spine density in the apical dendrites of hippocampal CA1 pyramidal neurons in male rat and male mouse [40, 43, 46, 48] but causes an increase in spine density in the same region in female rats [37, 38, 42]. One recent study shows that CRS decreases spine density in basal dendrites, while it increases apical dendritic arbors in the CA1 pyramidal neurons of the ventral hippocampus in female but not in male rats [47]. In contrast to female rats, female mice show a decrease in spine density in CA1 pyramidal after exposure to same 21-day CRS [45]. Additionally, an ultrastructural study of CA1 synapses shows that 21-day CRS causes an increase in the size of the postsynaptic density in male rat CA1 [39]. Similar to CRS, CUMS also causes a decrease in spine density in the dendrites of CA1 pyramidal neurons in male rat [24]. Stress-induced increase in spine density in the apical dendrites of CA1 pyramidal neurons in female rat and same stress-induced decrease in spine density in the same area in male rat are completely prevented by NMDA receptor antagonist CPP [35, 219], but exposure of NMDA receptor antagonist CPP to the stress procedure does not affect corticosterone levels or the corticosterone response to stress, suggesting a key role of NMDA receptor activation in stress-induced increases or decreases in spine density [35]. Similar to sex-dependent alterations of dendritic spines induced by both acute stress and CRS in hippocampal CA1 pyramidal neurons, there is a sex difference in CRS-induced changes in hippocampal-dependent spatial learning and memory. CRS impairs spatial learning and memory in males but not in females [38, 197]. Furthermore, recent studies suggest that CUMS-induced glutamatergic dysfunction in excitatory temporomammillary-CA1 synapses of the hippocampus serves as an underlying cause of depression.
pyramidal cells and a decrease in spine density of the distal part of apical dendritic arbors of layers II/III accompanied by cognitive impairments, which are mediated by the PFC neurons are chronic stress is accompanied by alterations in fear condition- dendrites of pyramidal neurons in the mPFC induced by [235, 236]. Animal studies show that the retraction of apical major depression, may contribute to pathology of depression size of neurons in the postmortem mPFC of subjects with the mPFC of subjects with major depression disorder [110]. The decreased volume of the mPFC in depressed patients is found in male but not in female depressed patients [234]. It is well documented that CRS results in a retraction of the distal part of apical dendritic arbors of layers II/III pyramidal cells [76, 89, 90, 92] and a decrease in spine density on those neurons [91, 93, 96, 237] in the mPFC of male rats, which is similar to that found in hippocampal CA3 region [41, 42, 44]. The pattern of CRS-induced dendritic reorganization is similar to that seen after daily corticosterone injections [238, 239]. CRS also alters spine morphology with an overall decrease in mean dendritic spine volume and surface area, a reduction in large mushroom spine density, and an increase in small thin spine density in the mPFC of male rats. These findings suggest failure of the spines to mature and stabilize following CRS [93]. One conflicting study, however, reports that CRS-induced decrease in spine density in the male rat mPFC is characterized by a decrease in thin and stubby spine density without affecting mushroom spine density [99]. CRS causes a reduction of length and branch number in the apical dendrites of the neurons in the mPFC of young (3 months) and aged (20 months) male rats. Surprisingly, CRS-induced retraction of apical dendrites, however, is reversed with recovery in young (3 months) but not aged (20 months) animals [98]. In young rats, CRS results in dendritic spine loss and alters the patterns of spine morphology. In contrast, CRS does not affect spine density and spine shape in aged animals, showing that dendritic spines become progressively less plastic in the aging brain [99]. Interestingly, chronic immobilization stress does not affect spine density in a subpopulation of IL neurons in the mPFC that project to the basolateral amygdala (BLA) in male rats, suggesting this pathway may be particularly resilient against the effects of stress [109]. Randomly selected neurons in the IL of the mPFC, however, show dendritic retraction after CRS. Since most layer II/III neurons project intracortically, the majority of randomly selected pyramidal neurons may be local cortical neurons with no projections to the BLA [109]. An independent study reports that IL neurons, but not PL neurons, in the mPFC are highly sensitive to a brief exposure to stress and the same form of stress impairs fear extinction in mice [112]. However, these IL neurons are putative local cortical neurons without projections to the BLA. A conflicting report shows that CRS causes dendritic retraction in PL neurons of rat mPFC, while this dendritic retraction is prevented by the D1R antagonist SCH23390, and the same D1R antagonist causes dendritic retraction in the PL neurons of the mPFC in unstressed rats. However, the effects of CRS on dendrites in the IL neurons of mPFC are not studied in this report [104]. These results show that dopaminergic transmission in the PL neurons of the mPFC during stress may contribute directly to the CRS-induced retraction of apical dendrites, while dopamine transmission in the absence of stress is important in maintaining normal dendritic morphology [104]. Recent reports show that acute foot-shock stress not only produces an increase in the number of excitatory synapses and docked vesicles [240] in the mPFC, but also induces rapid and sustained increases in spine density accompanied by atrophy of apical dendrites in the PL neurons of the mPFC [241]. Importantly, these synaptic changes induced by acute stress are prevented by chronic antidepressant desipramine treatments [240, 241]. Optogenetic activation of the mPFC exerts potent antidepressant-like effects, showing that the activity of the mPFC may play a key role in the development of depression-like behaviors.
and antidepressant responses [242]. Similar to hippocampus, alteration of stress-mediated dendritic arbors in the mPFC is sex dependent. CRS causes retraction of apical dendrite arbors in the mPFC in male, while it increases apical dendrite arbors in the female mPFC in which CRS-induced dendritic plasticity is estrogen dependent [97]. Rat mPFC is sexually dimorphic, which is characterized by a bigger and more complex apical dendritic tree in the PL neurons of the mPFC in healthy male rats than in healthy female rats [243, 244].

4.3. Orbitofrontal Cortex (OFC). The OFC, a part of the PFC in the frontal lobes in the brain, is involved in cognitive functions, decision-making, and emotional processing [245]. The studies from neuroimaging and neuropathology show that the OFC is involved in pathophysiology of major depression [246]. Decreases in cortical thickness, neuronal size, neuronal density, and glia densities in the II–IV cortical layers of the OFC are found in subjects with major depression [236]. The decrease in neuronal sizes in layer 3 of the OFC from depressed subjects is confirmed by another postmortem study [247]. Neuroimaging and functional studies also show that patients with major depression have reduced OFC volume [248] and reduced density of pyramidal neurons in layers V and III of the OFC [249]. In contrast, animal studies show that 3-week CUMS increases both the volume of layers II/III in the lateral orbital subregion and the volume of layer II in the ventral orbital subregion of the OFC, which is accompanied by an increase in the length of apical dendrites in the ventral orbital subregion of the OFC [107]. Interestingly, CRS causes a 43% increase in the dendritic arbors in the OFC neurons, an effect opposite to what is observed in the mPFC neurons where the same CRS causes 20% retraction of apical dendritic arbors in layer II/III pyramidal neurons of the mPFC [92]. The mechanisms through which CRS increases dendritic arbors of the OFC are not known. Further studies are needed to explore the discrepancy between the data from imaging analysis or postmortem studies and the findings from animal models. Our recent study showed that 3-week CUMS caused a decrease in spine density in the OFC pyramidal neurons, which was accompanied by both depression-like behaviors and decreased expression of Kalirin-7 and PSD95 in the OFC (Chang Xu, Shu-Chen An, and Xin-Ming Ma, unpublished). Kalirin-7 plays an essential role in maintaining dendritic spine density, size, and synaptic functions [250, 251]. Expression of Kalirin-7 in the hippocampus is decreased by 3-week CUMS [24]. Similar to CUMS, chronic exposure of male mice to corticosterone for 20 days that recapitulates blood corticosterone levels found after CRS exposure in mice also decreases spine density in the OFC neurons, which fails to recover after one week of washout period [130]. This suggests that chronic stress-induced decrease in spine density is not reversible in the OFC neurons. Additional study is required to address this question.

4.4. Amygdala (Table 3). The amygdala, a structure within the subcortical limbic system, is involved in the processing of emotion and motivation such as fear and anger. The amygdala is also responsible for determining what memories are stored and where they are stored. There are conflicting reports on amygdala volume in major depression [252]. Imaging studies show an increase [253–255] or decrease [256, 257] or no change [258] in amygdala volume or increased activity of amygdala [201, 259, 260] in patients with major depression. A conflicting MRI study reports a trend towards smaller left amygdala volumes in depressed patients compared with healthy controls [203]. A postmortem study shows that depressed subjects have a larger lateral nucleus and a greater number of total BLA neurovascular cells than controls. There are no differences in the number or density of neurons or glia between depressed and control subjects [252]. To our knowledge, it is not clear whether cell size in BLA is altered in depressed patients.

Animal studies show that chronic stress generally results in an increase in spine density and enhanced dendritic arborization in the amygdala (Table 3). This is in contrast to the hippocampus and PFC (Tables 1 and 2). Acute immobilization also causes an increase in spine density without any effects on dendritic arbors in BLA spiny neurons [127], showing that these neurons are very sensitive to stress. Amygdala-dependent fear learning is enhanced by CRS in rats [33]. Chronic stress causes an increase in dendritic arborization and spine density in the BLA spiny neurons of male rats [122, 123, 125–129] and male mice [114, 118, 120, 124]. These neurons are thought to be glutamatergic neurons [261]. In contrast, CRS causes a decrease in spine density in spiny neurons in the medial amygdala, which are GABAergic neurons [114]. CRS-induced increase in dendritic arbors and spine density in the BLA pyramidal neurons and CRS-induced depression-like behavior in wild-type mice are absent in fatty acid amide hydrolase (FAAH) deficient mice [124] suggesting a key role of FAAH in maintaining normal amygdala function in the face of chronic stress. Chronic immobilization stress-induced dendritic hypertrophy in the BLA spiny neurons is not reversible [126]. This is distinct from hippocampal CA3 and mPFC atrophy, which is reversible within the same period of stress-free recovery [33]. A single dose of corticosterone induces dendritic hypertrophy in the BLA accompanied by enhanced anxiety [262]. Chronic exposure of mice to corticosterone for 20 days mimicking chronic stress increases dendritic length and spine density in the BLA [130]. Chronic exposure of rats to corticosterone for 2 weeks causes an increase in the levels of memory-related genes including Arc/Arg3.1 and Egr-1 and enhances the consolidation of fear memory processes in the lateral amygdala [131]. In addition, tianeptine, an antidepressant, exerts the opposite roles in chronic stress-induced synaptic changes in the amygdala and hippocampus [120].

4.5. Nucleus Accumbens (NAc) (Table 4). Animal studies indicate that the neuronal circuitry of the PFC-NAc-ventral tegmental area (VTA) underlies drug reward responses and contributes to relapse to cocaine seeking [263, 264]. Excitatory axonal terminals from glutamatergic neurons of the PFC form the synapse onto NAc medium spiny neurons (MSNs), which also receive dopaminergic (DA) inputs from the VTA. The VTA receives GABAergic inputs from the NAc and glutamatergic inputs from the PFC [265, 266]. In
addition, the NAc also receives glutamatergic inputs from ventral hippocampus and basolateral amygdala [146]. The NAc serves as a hub of the brain’s reward pathways [267] and plays a central role in mood and emotion regulation [268]. Depressive symptoms, such as anhedonia, and depression severity are correlated with reduced NAc volume and reduced NAc responses to rewards in depressed patients [205, 269]. An optogenetic study shows that inhibition of the VTA-NAc projection induces resilience, whereas inhibition of the VTA-mPFC projection enhances susceptibility [270], highlighting a key role of PFC-NAc-VTA circuitry in the development of depression. Therefore, dysregulation of PFC-NAc-VTA reward circuitry may contribute to the pathophysiology of depression [13, 146, 271]. Similar to the effect of cocaine abuse, chronic stress may alter dendritic spines and synaptic plasticity in the PFC-NAc-VTA circuitry. A recent study, however, reports that chronic social defeat stress (CSDS-) mediated increase in glutamatergic transmission at the intralaminar thalamus- (ILT-) NAc but not PFC-NAc circuitry mediates stress-induced postsynaptic plasticity on the MSNs and depression-like behaviors in susceptible mice [142].

The MSNs of dorsal striatum receive not only glutamatergic inputs from the cerebral cortex and the thalamus, but also DA innervation from the midbrain [272]. These MSNs account for >95% of the neurons in the striatum [273, 274]. The dorsal striatum and the NAc are not distinguishable in their populations and expression of DA receptors (DRs, D1R and D2R). Approximately half of the striatal MSNs express the D1R [274, 275]; other half MSNs express the D2R [276, 277]. The degree of D1R/D2R colocalization remains controversial, ranging from 10% to 30% [275, 278, 279]. D1R signaling enhances dendritic excitability and glutamatergic signaling in striatopallidal MSNs, while D2R signaling exerts the opposite effect in striatopallidal MSNs (indirect pathway) [280–282]. CRS causes a decrease in AMPAR/NMDAR ratio in the D1R-MSN of the NAc compared to nonstressed control, while it does not affect AMPAR/NMDAR ratios in D2R-MSNs of the NAc. This CRS-induced decrease in the ratio of AMPAR/NMDAR in the D1R-MSN is accompanied by depression-like behaviors, showing a role of NAc D1R-MSNs, at least in part, in the development of depression [135]. This is further supported by two recent reports [143, 283]. One report shows that enhanced activity in D1R-MSNs causes resilient behaviors, while inhibition of these D1R-MSNs induces depression-like behaviors after CSDS [283]. Another report shows that CSDS specifically results in an increase in synaptic strength represented by the increased amplitude of uEPSCs (unitary excitatory postsynaptic currents) in large mushroom spines on D1R-MSNs but decreases synaptic strength on D2R-MSNs mushroom spines in the NAc of resilient mice. CSDS does not affect the uEPSC amplitude in small thin spines on both D1R- and D2R-NAc MSNs in resilient mice [143]. CSDS, however, does not alter synaptic strength in mushroom and thin spines on D1R- or D2R-MSNs in the NAc in susceptible mice [143]. These data show that the NAc D1R-MSN of susceptible mice may be resistant to adaptation and play a critical role in the development of chronic stress-induced depression-like behaviors. In addition, the inhibitor of kappaB kinase (IkK) in the NAc is also a critical regulator of depression-like behavior, and the IkK-nuclear factor kappaB (NFκB) plays a key role in the regulation of synaptic signaling and neuronal morphology in vitro and in vivo [138]. Overexpression of IkK increases thin spine density in the NAc MSNs. CSDS-induced increase in IkK activity in the NAc enhances social avoidance behavior and promotes the formation of thin spines. Inhibition of IkK signaling results in a reversal of CSDS-induced social avoidance behaviors, suggesting that CSDS-induced depression-like behaviors are associated with IkK-mediated increase in thin spine density in the NAc [138]. Interestingly, CSDS-induced increases in stubby spine density and the frequency of mEPSCs in the NAc in susceptible mice are accompanied by an increase in the levels of IkK in the NAc [139]. These results show that CSDS-induced increases in stubby spine density and IkK expression in the NAc are correlated with depression-like behaviors. CSDS-mediated downregulation of Rac1 through an epigenetic mechanism contributes to depression-like behaviors and enhanced formation of stubby spines in the NAc MSNs of susceptible mice [141]. Furthermore, DeltaFosB, a transcription factor, plays an essential role in the mechanism of resilience in mice, supported by evidence that CSDS-mediated induction of DeltaFosB in the NAc is not only necessary and sufficient for resilience in mice, but also required for the antidepressant fluoxetine to reverse depression-like behaviors induced by CSDS [136]. NR2B in the NAc plays a key role in the modulation of CSDS-induced depression-like behaviors and synaptic plasticity. CSDS-induced reduction in NR2B surface expression in the mouse NAc neurons is restored by fluoxetine treatment. Behaviorally, restoration of NR2B loss prevents the behavioral sensitization of mice to chronic stress [137]. Overexpression of DNA methyltransferase (Dnmt3a) increases dendritic spine density in the NAc MSNs. CSDS-induced depression-like behaviors are accompanied by an increase in the Dnmt3a levels in the NAc, suggesting that CSDS-induced depression-like behaviors are positively correlated with increased spine density in the NAc neurons [140]. These studies highlight an important role of the NAc in chronic stress-induced depression-like behaviors. It is possible that stress may differentially affect dendritic spines in the D1R-MSNs and D2R-MSNs of the NAc. More studies are required for a better understanding of the roles of D1R-MSNs and D2R-MSNs in chronic stress-induced depression-like behaviors and the underlying mechanisms.

Reduced NAc volume in depressed patients [205, 269] is not in line with the findings from animal models in which stress generally results in an increase in spine density in the NAc MSNs. CSDS causes an increase in spine density and the frequency of mEPSCs in the mouse NAc MSNs [86]. In addition, the shell of the NAc is thought to be a part of the extended amygdala [284]. Chronic stress increases spine density in the neurons of the BLA and the shell of NAc even though these two neuron types are naturally different. The downstream mechanisms of chronic stress-induced spine formation in these two distinct neuron types are not clear.

Taken together, these data show that altered spine density and synaptic plasticity in the NAc MSNs are correlated with depression-like behaviors induced by chronic stress, which...
may be a target for developing the novel treatment strategies for depression.

5. The Mechanisms of Chronic Stress-Induced Alterations in Dendritic Spines

The molecular mechanisms underlying spine loss and dendritic retraction induced by chronic stress in the hippocampus and PFC as well as enhanced spine formation found in the amygdala and NAc in chronically stressed animals are not well understood. Expression of several synapse-related genes is decreased in the postmortem PFC of subjects with major depressive disorder [110]. One of these genes is GATA1 (GATA-binding factor 1), a transcriptional repressor that plays a key role in the formation of dendritic spines and dendrite arbor maintenance [110]. Furthermore, a nuclear pore complex protein, nucleoporin p62 (NUP62), and tyrosine phosphorylation of NUP62 play a critical role in CRS-induced dendritic retraction of hippocampal CA3 pyramidal neurons [285]. Many synaptic proteins including Kalirin-7, spinophilin, Homer1, cofilin, Rac-1, cadherin, p-Akt, p-GSK-3β, p-ERK1/2, PKC, NCAM, PSA-NCAM, SNAP-25, SNAP-29, VAMP1/2, syntaxin IA, synaptophysin, synapsin 1, Vglut2, GluR1, GluR2, NRI, NR2A, NR2B, PSD95, αCaMKII, melanocortin 4 receptors, CRH receptor 1, and PI90RhoGAP play an important role in the regulation of the spine formation and/or synaptic plasticity; expression of these synaptic proteins in the brain is altered by chronic stress, and these proteins may play a key role in chronic stress-induced both depression-like behaviors and spine alterations (Table 1–4) [24, 40, 44, 46, 53, 100, 102, 113, 130, 141, 142, 144, 286–292]. In addition, chronic stress-induced alterations of several signal transduction pathways including cAMP-PKA-CREB, cAMP-ERK1/2-CREB, cAMP-PKA, Ras-ERK, PI3K-Akt, TNFα- NFκb, GSK-3β, mTOR, and CREB may be also associated with chronic stress-induced spine loss or increase in certain brain areas [7, 22, 293]. A recent report shows that the Homer1/mGluR5 complex is involved in the development of CSDS-induced depression-like behaviors [294], suggesting a role of this complex in chronic stress-mediated spine plasticity. Presynaptic mGlu2 receptors play a key role in CUMS-induced depression-like behaviors in male susceptible mice [54]. The rapid antidepressant properties of ketamine, an NMDA receptor antagonist, result from increased synaptic signaling proteins and increased number and function of new spine synapses via activating the mammalian target of rapamycin (mTOR) pathway in the rat mPFC and hippocampus [295–298]. S6K1, a key mediator of activity-dependent synaptic protein synthesis, is the downstream of mTORC1 and plays a critical role in CUMS-induced depression-like behaviors [299]. Postmortem studies show that the levels of NR2A, NR2B, mGluR5, PSD-95, and mTOR as well as the levels of S6K, eIF4B, and p-eIF4B, the core downstream signaling targets of mTOR, are decreased in the PFC of depressed patients [300]. These studies suggest that mTOR signaling is a promising target for the development of novel antidepressant drugs [297, 301, 302].

Taken together, understanding chronic stress- and/or depression-induced alterations in dendritic spines, synapse plasticity, synaptic proteins, and their upstream/downstream signaling pathways may pave the path for developing efficiency therapeutic strategies for depression. The search for the mechanisms through which chronic stress alters dendritic spines or synapse numbers in different brain regions should be a major future direction.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Acknowledgments

This work was supported by National Science Foundation of China (81371512) and Connecticut Innovation Fund (145CBUC11). Thanks are due to Boyu Ma and Dr. Mason Yeh for their reading of the paper.

References

[1] V. Patel, M. Abas, J. Broadhead, C. Todd, and A. Reeler, “Depression in developing countries: lessons from Zimbabwe,” The British Medical Journal, vol. 322, no. 7284, pp. 482–484, 2001.
[2] K. S. Kendler, M. Gatz, C. O. Gardner, and N. L. Pedersen, “A Swedish national twin study of lifetime major depression,” The American Journal of Psychiatry, vol. 163, no. 1, pp. 109–114, 2006.
[3] M. R. Levinstein and B. A. Samuels, “Mechanisms underlying the antidepressant response and treatment resistance,” Frontiers in Behavioral Neuroscience, vol. 8, article 208, 2014.
[4] R. C. Kessler, T. C. Wai, O. Demler, and E. E. Walters, “Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication,” Archives of General Psychiatry, vol. 62, no. 6, pp. 617–627, 2005.
[5] S. M. Thompson, A. J. Kallarackal, M. D. Kvarta, A. M. Van Dyke, T. A. LeGates, and X. Cai, “An excitatory synapse hypothesis of depression,” Trends in Neurosciences, vol. 38, no. 5, pp. 279–294, 2015.
[6] D. A. Bangasser and R. J. Valentino, “Sex differences in stress-related psychiatric disorders: neurobiological perspectives,” Frontiers in Neuroendocrinology, vol. 35, no. 3, pp. 303–319, 2014.
[7] W. N. Marsden, “Synaptic plasticity in depression: molecular, cellular and functional correlates,” Progress in Neuro-Psychopharmacology & Biological Psychiatry, vol. 43, pp. 168–184, 2013.
[8] X. Zhou, K. D. Michael, Y. Liu et al., “Systematic review of management for treatment-resistant depression in adolescents,” BMC Psychiatry, vol. 14, article 340, 2014.
[9] P. W. Gold, “The organization of the stress system and its dysregulation in depressive illness,” Molecular Psychiatry, vol. 20, no. 1, pp. 32–47, 2015.
[10] M. N. Hill, K. G. C. Helleman, P. Verma, B. B. Gorzalka, and J. Weinberg, “Neurobiology of chronic mild stress: parallels to major depression,” Neuroscience and Biobehavioral Reviews, vol. 36, no. 9, pp. 2085–2117, 2012.
[11] R. C. Kessler, “The effects of stressful life events on depression,” Annual Review of Psychology, vol. 48, pp. 191–214, 1997.
Neural Plasticity

[12] C. Kiyohara and K. Yoshimasu, “Molecular epidemiology of major depressive disorder,” *Environmental Health and Preventive Medicine*, vol. 14, no. 2, pp. 71–87, 2009.

[13] C. Pittenger and R. S. Duman, “Stress, depression, and neuroplasticity: a convergence of mechanisms,” *Neuropsychopharmacology*, vol. 33, no. 1, pp. 88–109, 2008.

[14] J. Herbert, I. M. Goodyer, A. B. Grossman et al., “Do corticosteroids damage the brain?” *Journal of Neuroendocrinology*, vol. 18, no. 6, pp. 393–411, 2006.

[15] J. Radley, D. Morilak, V. Vlau, and S. Campeau, “Chronic stress and brain plasticity: mechanisms underlying adaptive and maladaptive changes and implications for stress-related CNS disorders,” *Neuroscience & Biobehavioral Reviews*, 2015.

[16] E. R. de Kloet, M. S. Oitzl, and M. Joëls, “Stress and cognition: are corticosteroids good or bad guys?” *Trends in Neurosciences*, vol. 22, no. 10, pp. 422–426, 1999.

[17] B. S. McEwen, “Glucocorticoids, depression, and mood disorders: structural remodeling in the brain,” *Metabolism: Clinical and Experimental*, vol. 54, no. 5, pp. 20–23, 2005.

[18] S. J. Lupien and B. S. McEwen, “The acute effects of corticosteroids on cognition: integration of animal and human model studies,” *Brain Research Reviews*, vol. 24, no. 1, pp. 1–27, 1997.

[19] E. D. Kirby, S. E. Muroy, W. G. Sun et al., “Acute stress enhances adult rat hippocampal neurogenesis and activation of newborn neurons via secreted astrocytic FGF2,” *eLife*, vol. 2013, no. 2, Article ID e00362, 2013.

[20] C. O. Bondi, G. Rodriguez, G. G. Gould, A. Frazer, and D. A. Morilak, “Chronic unpredictable stress induces a cognitive deficit and anxiety-like behavior in rats that is prevented by chronic antidepressant drug treatment,” *Neuropsychopharmacology*, vol. 33, no. 2, pp. 320–331, 2008.

[21] Y. Xu, J. Pan, J. Sun et al., “Inhibition of phosphodiesterase 2 reverses impaired cognition and neuronal remodeling caused by chronic stress,” *Neurobiology of Aging*, vol. 36, no. 2, pp. 955–970, 2015.

[22] Z. Z. Wang, W. X. Yang, Y. Zhang et al., “Phosphodiesterase-4D knock-down in the prefrontal cortex alleviates chronic unpredictable stress-induced depressive-like behaviors and memory deficits in mice,” *Scientific Reports*, vol. 5, Article ID 11332, 2015.

[23] C. H. Duman and R. S. Duman, “Spine synapse remodeling in the pathophysiology and treatment of depression,” *Neuroscience Letters*, vol. 601, pp. 20–29, 2015.

[24] H. Qiao, S. C. An, W. Ren, and X. M. Ma, “Progressive alterations of hippocampal CA3-CA1 synapses in an animal model of depression,” *Behavioural Brain Research*, vol. 275, pp. 191–200, 2014.

[25] C. Heim, M. J. Owens, P. M. Plotsky, and C. B. Nemeroff, “The role of early adverse life events in the etiology of depression and posttraumatic stress disorder,” *Annals of the New York Academy of Sciences*, vol. 821, pp. 194–207, 1997.

[26] R. M. Sapolsky, “Why stress is bad for your brain,” *Science*, vol. 273, no. 5276, pp. 794–795, 1996.

[27] P. Willner, “Chronic mild stress (CMS) revisited: consistency and behavioural-neurobiological concordance in the effects of CMS,” *Neuropsychobiology*, vol. 52, no. 2, pp. 90–110, 2005.

[28] Y. Watanabe, E. Gould, and B. S. McEwen, “Stress induces atrophy of apical dendrites of hippocampal CA3 pyramidal neurons,” *Brain Research*, vol. 588, no. 2, pp. 341–345, 1992.

[29] Sunanda, M. S. Rao, and T. R. Raju, “Effect of chronic restraint stress on dendritic spines and excrescences of hippocampal CA3 pyramidal neurons—a quantitative study,” *Brain Research*, vol. 694, no. 1–2, pp. 312–317, 1995.

[30] A. M. Magariños and B. S. McEwen, “Stress-induced atrophy of apical dendrites of hippocampal CA3c neurons: comparison of stressors,” *Neuroscience*, vol. 69, no. 1, pp. 83–88, 1995.

[31] A. M. Magariños and B. S. McEwen, “Stress-induced atrophy of apical dendrites of hippocampal CA3c neurons: involvement of glucocorticoid secretion and excitatory amino acid receptors,” *Neuroscience*, vol. 69, no. 1, pp. 89–98, 1995.

[32] A. M. Magaríños, J. M. Verdugo, and B. S. McEwen, “Chronic stress alters synaptic terminal structure in hippocampus,” *Proceedings of the National Academy of Sciences of the United States of America*, vol. 94, no. 25, pp. 14002–14008, 1997.

[33] C. D. Conrad, J. E. LeDoux, A. M. Magarinós, and B. S. McEwen, “Repeated restraint stress facilitates fear conditioning independently of causing hippocampal CA3 dendritic atrophy,” *Behavioral Neuroscience*, vol. 113, no. 5, pp. 902–913, 1999.

[34] C. Sandi, H. A. Davies, M. I. Cordero, J. J. Rodriguez, V. I. Popov, and M. G. Stewart, “Rapid reversal of stress induced loss of synapses in CA3 of rat hippocampus following water maze training,” *European Journal of Neuroscience*, vol. 17, no. 11, pp. 2447–2456, 2003.

[35] T. J. Shors, J. Falduto, and B. Leuner, “The opposite effects of stress on dendritic spines in male vs. female rats are NMDA receptor-dependent,” *European Journal of Neuroscience*, vol. 19, no. 1, pp. 145–150, 2004.

[36] M. G. Stewart, H. A. Davies, C. Sandi et al., “Stress suppresses and learning induces plasticity in CA3 of rat hippocampus: a three-dimensional ultrastructural study of thorny excrescences and their postsynaptic densities,” *Neuroscience*, vol. 131, no. 1, pp. 43–54, 2005.

[37] K. J. McLaughlin, S. E. Baran, R. L. Wright, and C. D. Conrad, “Chronic stress enhances spatial memory in ovariectomized female rats despite CA3 dendritic retraction: possible involvement of CA1 neurons,” *Neuroscience*, vol. 135, no. 4, pp. 1045–1054, 2005.

[38] K. J. McLaughlin, J. O. Wilson, J. Harman et al., “Chronic 17beta-estradiol or cholesterol prevents stress-induced hippocampal CA3 dendritic retraction in ovariectomized female rats: possible correspondence between CA1 spine properties and spatial acquisition,” *Hippocampus*, vol. 20, no. 6, pp. 768–786, 2010.

[39] H. S. Donohue, P. L. A. Gabbott, H. A. Davies et al., “Chronic restraint stress induces changes in synapse morphology in stratum lacunosum-moleculare CA1 rat hippocampus: a stereological and three-dimensional ultrastructural study,” *Neuroscience*, vol. 140, no. 2, pp. 597–606, 2006.

[40] R. Pawlak, B. S. S. Rao, J. P. Melchor, S. Chattarji, B. McEwen, and S. Strickland, “Tissue plasminogen activator and plasminogen mediate stress-induced decline of neuronal and cognitive functions in the mouse hippocampus,” *Proceedings of the National Academy of Sciences of the United States of America*, vol. 102, no. 50, pp. 18201–18206, 2005.

[41] A. M. Magaríños, C. L. Li, J. G. Toth et al., “Effect of brain-derived neurotrophic factor haploinsufficiency on stress-induced remodeling of hippocampal neurons,” *Hippocampus*, vol. 21, no. 3, pp. 253–264, 2011.

[42] C. D. Conrad, K. J. McLaughlin, T. N. Huynh, M. El-Ashmawy, and M. Sparks, “Chronic stress and a cyclic regimen of estradiol administration separately facilitate spatial memory: relationship with hippocampal CA1 spine density and dendritic complexity,” *Behavioral Neuroscience*, vol. 126, no. 1, pp. 142–156, 2012.

[43] A. Fernández-Guasti, J. L. Fiedler, L. Herrera, and R. J. Handa, “Sex, stress, and mood disorders: at the intersection of adrenal
and gonadal hormones,” *Hormone and Metabolic Research*, vol. 44, no. 8, pp. 607–618, 2012.

[44] D. Orłowski, B. Elfving, H. K. Müller, G. Wegener, and C. R. Bjarkam, “Wistar rats subjected to chronic restraint stress display increased hippocampal spine density paralleled by increased expression levels of synaptic scaffolding proteins,” *Stress*, vol. 15, no. 5, pp. 514–523, 2012.

[45] M. S. Kassem, J. Lagopoulos, T. Stait-Gardner et al., “Stress-induced grey matter loss determined by MRI is primarily due to loss of dendrites and their synapses,” *Molecular Neurobiology*, vol. 47, no. 2, pp. 645–661, 2013.

[46] P. Castañeda, M. Muñoz, G. García-Rojo et al., “Association of N-cadherin levels and downstream effectors of Rho GTPases with dendritic spine loss induced by chronic stress in rat hippocampal neurons,” *Journal of Neuroscience Research*, vol. 93, no. 10, p. Spcl, 2015.

[47] A. M. Rico, A. L. Mendoza, D. A. Durán, H. de la Luz Torres, G. A. Mendoza, and A. B. Silva Gómez, “The effects of chronic restraint on the morphology of ventral CA1 neurons in female Long Evans rats,” *Stress*, vol. 18, no. 1, pp. 67–75, 2015.

[48] P. Huang, C. Li, T. Fu et al., “Flupirtine attenuates chronic restraint-stress-induced cognitive deficits and hippocampal apoptosis in male mice,” *Behavioural Brain Research*, vol. 288, pp. 1–10, 2015.

[49] N. Sousa, N. V. Lukoyanov, M. D. Madeira, O. F. X. Almeida, and M. M. Paula-Barbosa, “Reorganization of the morphology of hippocampal neurites and synapses after stress-induced damage correlates with behavioral improvement,” *Neuroscience*, vol. 97, no. 2, pp. 253–266, 2000.

[50] A. Vyas, R. Mitra, B. S. Shankaranarayana Rao, and S. Chattarji, “Chronic stress induces contrasting patterns of dendritic remodeling in hippocampal and amygdaloid neurons,” *Journal of Neuroscience*, vol. 22, no. 15, pp. 6810–6818, 2002.

[51] H. R. Sharma and M. K. Thakur, “Correlation of ERα/ERβ expression with dendritic and behavioural changes in CUMS mice,” *Physiology & Behavior*, vol. 145, pp. 71–83, 2015.

[52] X. L. Li, Y. G. Yuan, H. Xu et al., “Changed synaptic plasticity in neural circuits of depressive-like and escitalopram-treated rats,” *International Journal of Neuropsychopharmacology*, vol. 18, no. 10, 2015.

[53] A. J. Kallarackal, M. D. Kvarta, E. Cammarata et al., “Chronic stress induces a selective decrease in AMPA receptor-mediated synaptic excitation at hippocampal temporoammonic-CA1 synapses,” *The Journal of Neuroscience*, vol. 33, no. 40, pp. 15669–15674, 2013.

[54] C. Nasca, B. Bigio, D. Zelli, F. Nicoletti, and B. S. McEwen, “Mind the gap: glucocorticoids modulate hippocampal glutamate tone underlying individual differences in stress susceptibility,” *Molecular Psychiatry*, vol. 20, pp. 755–765, 2015.

[55] P. M. Maras, J. Molet, Y. Chen et al., “Preferential loss of dorsal-hippocampus synapses underlies memory impairments provoked by short, multimodal stress,” *Molecular Psychiatry*, vol. 19, no. 7, pp. 811–822, 2014.

[56] A. M. Magarinos, B. S. McEwen, G. Flügge, and E. Fuchs, “Chronic psychosocial stress causes apical dendritic atrophy of hippocampal CA3 pyramidal neurons in subordinate tree shrews,” *Journal of Neuroscience*, vol. 16, no. 10, pp. 3534–3540, 1996.

[57] C. R. McKittrick, A. M. Magarinos, D. C. Blanchard, R. J. Blanchard, B. S. McEwen, and R. R. Sakai, “Chronic social stress reduces dendritic arbors in CA3 of hippocampus and decreases binding to serotonin transporter sites,” *Synapse*, vol. 36, no. 2, pp. 85–94, 2000.

[58] M. D. Kvarta, K. E. Bradbrook, H. M. Dantressay, A. M. Bailey, and S. M. Thompson, “Corticosterone mediates the synaptic and behavioral effects of chronic stress at rat hippocampal temporoammonic synapses,” *Journal of Neurophysiology*, vol. 114, no. 3, pp. 1713–1724, 2015.

[59] G. Wang, Y. Cheng, M. Gong et al., “Systematic correlation between spine plasticity and the anxiety/depression-like phenotype induced by corticosterone in mice,” *NeuroReport*, vol. 24, no. 12, pp. 682–687, 2013.

[60] K. M. Harris and S. B. Kater, “Dendritic spines: cellular specializations imparting both stability and flexibility to synaptic function,” *Annual Review of Neuroscience*, vol. 17, pp. 341–371, 1994.

[61] D. A. Fortin, T. Srivastava, and T. R. Soderling, “Structural modulation of dendritic spines during synaptic plasticity,” *The Neuroscientist*, vol. 18, no. 4, pp. 326–341, 2012.

[62] M. Banasr, J. M. Dwyer, and R. S. Duman, “Cell atrophy and loss in depression: reversal by antidepressant treatment,” *Current Opinion in Cell Biology*, vol. 23, no. 6, pp. 730–737, 2011.

[63] K.-O. Lai and N. Y. Ip, “Structural plasticity of dendritic spines: the underlying mechanisms and its dysregulation in brain disorders,” *Biochimica et Biophysica Acta—Molecular Basis of Disease*, vol. 1832, no. 12, pp. 2257–2263, 2013.

[64] C. H. Bailey, E. R. Kandel, and K. M. Harris, “Structural components of synaptic plasticity and memory consolidation,” *Cold Spring Harbor Perspectives in Biology*, vol. 7, no. 7, Article ID a021758, 2015.

[65] K. M. Harris, F. E. Jensen, and B. Tsoa, “Three-dimensional structure of dendritic spines and synapses in rat hippocampus (CA1) at postnatal day 15 and adult ages: implications for the maturation of synaptic physiology and long-term potentiation,” *The Journal of Neuroscience*, vol. 12, no. 7, pp. 2685–2705, 1992.

[66] A. Tashiro and R. Yuste, “Structure and molecular organization of dendritic spines,” *Histochemistry and Histopathology*, vol. 18, no. 2, pp. 617–634, 2003.

[67] J. Bourne and K. M. Harris, “Do thin spines learn to be mushroom spines that remember?” *Current Opinion in Neurobiology*, vol. 17, no. 3, pp. 381–386, 2007.

[68] H. Kasai, M. Matsuura, J. Noguchi, N. Yasumatsu, and H. Nakahara, “Structure-stability-function relationships of dendritic spines,” *Trends in Neurosciences*, vol. 26, no. 7, pp. 360–368, 2003.

[69] E. A. Nimchinsky, B. L. Sabatini, and K. Svoboda, “Structure and function of dendritic spines,” *Annual Review of Physiology*, vol. 64, pp. 313–353, 2002.

[70] X.-M. Ma, J. Huang, Y. Wang, B. A. Lipper, and R. E. Mains, “Kalirin, a multifunctional Rho guanine nucleotide exchange factor, is necessary for maintenance of hippocampal pyramidal neuron dendrites and dendritic spines,” *Journal of Neuroscience*, vol. 23, no. 33, pp. 10593–10603, 2003.

[71] C. Sala and M. Segal, “Dendritic spines: the locus of structural and functional plasticity,” *Physiological Reviews*, vol. 94, no. 1, pp. 141–188, 2014.

[72] L. J. Petrak, K. M. Harris, and S. A. Kirov, “Synaptogenesis on mature hippocampal dendrites occurs via filopodia and immature spines during blocked synaptic transmission,” *Journal of Comparative Neurology*, vol. 484, no. 2, pp. 183–190, 2005.

[73] M. Segal, “Dendritic spines for neuroprotection: a hypothesis,” *Trends in Neurosciences*, vol. 18, no. 11, pp. 468–471, 1995.
[74] J. Noguchi, M. Matsuzaki, G. C. R. Ellis-Davies, and H. Kasai, “Spine-neck geometry determines NMDA receptor-dependent Ca2+ signaling in dendrites,” Neuron, vol. 46, no. 4, pp. 609–622, 2005.

[75] J. N. Bourne and K. M. Harris, “Balancing structure and function at hippocampal dendritic spines,” Annual Review of Neuroscience, vol. 31, pp. 47–67, 2008.

[76] J. J. Radley, H. M. Sisti, J. Hao et al., “Chronic behavioral stress induces apical dendritic reorganization in pyramidal neurons of the medial prefrontal cortex,” Neuroscience, vol. 125, no. 1, pp. 1–6, 2004.

[77] K. Fénelon, B. Xu, C. S. Lai et al., “The pattern of cortical dysfunction in a mouse model of a schizophrenia-related microdeletion,” The Journal of Neuroscience, vol. 33, no. 37, pp. 14825–14839, 2013.

[78] P. Penezes, M. E. Cahill, K. A. Jones, I.-E. VanLeeuwen, and K. M. Woolfrey, “Dendritic spine pathology in neuropsychiatric disorders,” Nature Neuroscience, vol. 14, no. 3, pp. 285–293, 2011.

[79] Y. Chen, E. A. Kramár, L. Y. Chen et al., “Impairment of synaptic plasticity by the stress mediator CRH involves selective destruction of thin dendritic spines via RhoA signaling,” Molecular Psychiatry, vol. 18, no. 4, pp. 485–496, 2013.

[80] O. von Bohlen und Halbach, “Structure and function of dendritic spines within the hippocampus,” Annals of Anatomy, vol. 191, no. 6, pp. 518–531, 2009.

[81] R. S. Duman and G. K. Aghajanian, “Synaptic dysfunction in depression: potential therapeutic targets,” Science, vol. 338, no. 6103, pp. 68–72, 2012.

[82] G. Rajkowska and C. A. Stockmeier, “Astrocyte pathology in the hippocampus is affected by chronic psychosocial stress and concomitant fluoxetine treatment,” Neuropsychopharmacology, vol. 33, no. 37, pp. 535–549, 2011.

[83] B. Czéh, M. Simon, B. Schmelting, C. Hiemke, and E. Fuchs, “Astrogial plasticity in the hippocampus is affected by chronic psychosocial stress and concomitant fluoxetine treatment,” Neuropsychopharmacology, vol. 31, no. 8, pp. 1616–1626, 2006.

[84] C. Rocher, M. Spedding, C. Munoz, and T. M. Jay, “Acute stress-induced changes in hippocampal/prefrontal circuits in rats: effects of antidepressants,” Cerebral Cortex, vol. 14, no. 2, pp. 224–229, 2004.

[85] E. Castreñ, “Neuronal network plasticity and recovery from depression,” JAMA Psychiatry, vol. 70, no. 9, pp. 983–989, 2013.

[86] D. J. Christoffel, S. A. Golden, and S. J. Russo, “Structural and synaptic plasticity in stress-related disorders,” Reviews in the Neurosciences, vol. 22, no. 5, pp. 535–549, 2011.

[87] R. S. Duman, “Pathophysiology of depression and innovative treatments: remodeling glutamatergic synaptic connections,” Dialogues in Clinical Neuroscience, vol. 16, no. 1, pp. 11–27, 2014.

[88] M. Popoli, Z. Yan, B. S. McEwen, and G. Sanacora, “The stressed synapse: the impact of stress and glucocorticoids on glutamate transmission,” Nature Reviews Neuroscience, vol. 13, no. 1, pp. 22–37, 2012.

[89] S. C. Cook and C. L. Wellman, “Chronic stress alters dendritic morphology in rat medial prefrontal cortex,” Journal of Neurobiology, vol. 60, no. 2, pp. 236–248, 2004.

[90] J. J. Radley, A. B. Rocher, W. G. M. Janssen, P. R. Hof, B. S. McEwen, and J. H. Morrison, “Reversibility of apical dendritic retraction in the rat medial prefrontal cortex following repeated stress,” Experimental Neurology, vol. 196, no. 1, pp. 199–203, 2005.

[91] J. J. Radley, A. B. Rocher, M. Miller et al., “Repeated stress induces dendritic spine loss in the rat medial prefrontal cortex,” Cerebral Cortex, vol. 16, no. 3, pp. 313–320, 2006.

[92] C. Liston, M. M. Miller, D. S. Goldwater et al., “Stress-induced alterations in prefrontal cortical dendritic morphology predict selective impairments in perceptual attentional set-shifting,” Journal of Neuroscience, vol. 26, no. 30, pp. 7870–7874, 2006.

[93] J. J. Radley, A. B. Rocher, A. Rodriguez et al., “Repeated stress alters dendritic spine morphology in the rat medial prefrontal cortex,” Journal of Comparative Neurology, vol. 507, no. 1, pp. 114–1150, 2008.

[94] C. Perez-Cruz, M. Simon, B. Czéh, G. Flügge, and E. Fuchs, “Hemispheric differences in basilar dendrites and spines of pyramidal neurons in the rat prelimbic cortex: activity- and stress-induced changes,” European Journal of Neuroscience, vol. 29, no. 4, pp. 738–747, 2009.

[95] A. B. Hains, M. A. T. Vu, P. K. Maciejewski, C. H. Van Dyck, M. Gottron, and A. F. T. Arnsten, “Inhibition of protein kinase C signaling protects prefrontal cortex dendritic spines and cognition from the effects of chronic stress,” Proceedings of the National Academy of Sciences of the United States of America, vol. 106, no. 42, pp. 17957–17962, 2009.

[96] D. S. Goldwater, C. Pavlides, R. G. Hunter et al., “Structural and functional alterations to rat medial prefrontal cortex following chronic restraint stress and recovery,” Neuroscience, vol. 164, no. 2, pp. 798–808, 2009.

[97] J. E. Garrett and C. L. Wellman, “Chronic stress effects on dendritic morphology in medial prefrontal cortex: sex differences and estrogen dependence,” Neuroscience, vol. 162, no. 1, pp. 195–207, 2009.

[98] E. B. Bloss, W. G. Janssen, B. S. McEwen, and J. H. Morrison, “Interactive effects of stress and aging on structural plasticity in the prefrontal cortex,” The Journal of Neuroscience, vol. 30, no. 19, pp. 6726–6731, 2010.

[99] E. B. Bloss, W. G. Janssen, D. T. Ohm et al., “Evidence for reduced experience-dependent dendritic spine plasticity in the aging prefrontal cortex,” The Journal of Neuroscience, vol. 31, no. 21, pp. 7831–7839, 2011.

[100] H. K. Müller, G. Wegener, M. Popoli, and B. Elfwing, “Differential expression of synaptic proteins after chronic restraint stress in rat prefrontal cortex and hippocampus,” Brain Research, vol. 1385, pp. 26–37, 2011.

[101] H. Yu, D.-D. Wang, Y. Wang, T. Liu, F. S. Lee, and Z.-Y. Chen, “Variant brain-derived neurotrophic factor Val66met polymorphism alters vulnerability to stress and response to antidepressants,” Journal of Neuroscience, vol. 32, no. 12, pp. 4092–4101, 2012.

[102] J. Gilabert-Juan, E. Castillo-Gomez, R. Guirado, M. D. Molto, and J. Nacher, “Chronic stress alters inhibitory networks in the medial prefrontal cortex of adult mice,” Brain Structure and Function, vol. 218, no. 6, pp. 1591–1605, 2013.

[103] A. B. Hains, Y. Yabe, and A. F. Arnsten, “Chronic stimulation of alpha-2A-adrenoceptors with guanfacine protects rodent prefrontal cortex dendritic spines and cognition from the effects of chronic stress,” Neurobiology of Stress, vol. 2, pp. 1–9, 2015.

[104] G. L. Lin, C. B. Borders, L. J. Lundewall, and C. L. Wellman, “Di receptors regulate dendritic morphology in normal and stressed prefrontal cortex,” Psychoneuroendocrinology, vol. 31, pp. 101–111, 2015.

[105] E. Y. Yuen, J. Wei, W. Liu, P. Zhong, X. Li, and Z. Yan, “Repeated stress causes cognitive impairment by suppressing glutamate...
receptor expression and function in prefrontal cortex,” *Neuron*, vol. 73, no. 5, pp. 962–977, 2012.

[106] M. Banasr, G. W. Valentine, X.-Y. Li, S. L. Gourley, J. R. Taylor, and R. S. Duman, “Chronic unpredictable stress decreases cell proliferation in the cerebral cortex of the adult rat,” *Biological Psychiatry*, vol. 62, no. 5, pp. 496–504, 2007.

[107] E. Dias-Ferreira, J. C. Sousa, I. Melo et al., “Chronic stress causes frontostriatal reorganization and affects decision-making,” *Science*, vol. 325, no. 5940, pp. 621–625, 2009.

[108] N. Li, R.-J. Liu, J. M. Dwyer et al., “Glutamate N-methyl-D-aspartate receptor antagonists rapidly reverse behavioral and synaptic deficits caused by chronic stress exposure,” *Biological Psychiatry*, vol. 69, no. 8, pp. 754–761, 2011.

[109] R. M. Shansky, C. Hamo, P. R. Hof, B. S. McEwen, and J. H. Morrison, “Stress-induced dendritic reorganization in the prefrontal cortex is circuit specific,” *Cerebral Cortex*, vol. 19, no. 10, pp. 2479–2484, 2009.

[110] H. J. Kang, B. Voleti, T. Hajszan et al., “Decreased expression of synapse-related genes and loss of synapses in major depressive disorder,” *Nature Medicine*, vol. 18, no. 9, pp. 1413–1417, 2012.

[111] L. M. Seib and C. L. Wellman, “Daily injections alter spine density in rat medial prefrontal cortex,” *Neuroscience Letters*, vol. 337, no. 1, pp. 29–32, 2003.

[112] A. Izquierdo, C. L. Wellman, and A. Holmes, “Brief uncontrollable stress causes dendritic retraction in infralimbic cortex and resistance to fear extinction in mice,” *The Journal of Neuroscience*, vol. 26, no. 21, pp. 5733–5738, 2006.

[113] A. Chocyk, B. Bobula, D. Dudy et al., “Early-life stress affects the structural and functional plasticity of the medial prefrontal cortex in adolescent rats,” *European Journal of Neuroscience*, vol. 38, no. 1, pp. 2089–2107, 2013.

[114] S. Bennis, B. S. Shankaranarayana Rao, R. Pawlak, S. Strickland, B. S. McEwen, and S. Chattarji, “Stress-induced spine loss in the medial amygdala is mediated by tissue-plasminogen activator,” *Neuroscience*, vol. 144, no. 1, pp. 8–16, 2007.

[115] S. Marcuzzo, A. Dall’Oglio, M. F. M. Ribeiro, M. Achaval, and A. A. Rasia-Filho, “Dendritic spines in the posterodorsal medial amygdala after restraint stress and ageing in rats,” *Neuroscience Letters*, vol. 424, no. 1, pp. 16–21, 2007.

[116] J. J. Sumislawski, T. S. Ramikie, and S. Chattarji, “Reversible gating of endocannabinoid plasticity in the amygdala by chronic stress: a potential role for monoacylglycerol lipase inhibition in the prevention of stress-induced behavioral adaptation,” *Neuropepsychopharmacology*, vol. 36, no. 13, pp. 2750–2761, 2011.

[117] S. Patel, P. J. Kingsley, K. MacKie, L. J. Marnett, and D. G. Winder, “Repeated homotypic stress elevates 2-arachidonoylglycerol levels and enhances short-term endocannabinoid signaling at inhibitory synapses in basolateral amygdala,” *Neuropsychopharmacology*, vol. 34, no. 13, pp. 2699–2709, 2009.

[118] M. Qin, Z. Xia, T. Huang, and C. B. Smith, “Effects of chronic immobilization stress on anxiety-like behavior and basolateral amygdala morphology in Fmr1 knockout mice,” *Neuroscience*, vol. 194, pp. 282–290, 2011.

[119] J. Gilabert-Juan, E. Castillo-Gomez, M. Pérez-Rando, M. D. Moltó, and J. Nacher, “Chronic stress induces changes in the structure of interneurons and in the expression of molecules related to neuronal structural plasticity and inhibitory neurotransmission in the amygdala of adult mice,” *Experimental Neurology*, vol. 232, no. 1, pp. 33–40, 2011.

[120] A. G. Pillai, S. Anilkumar, and S. Chattarji, “The same antidepressant elicits contrasting patterns of synaptic changes in the amygdala vs hippocampus,” *Neuropsychopharmacology*, vol. 37, no. 12, pp. 2702–2711, 2012.

[121] H. Abush and I. Akirav, “Cannabinoids ameliorate impairments induced by chronic stress to synaptic plasticity and short-term memory,” *Neuropsychopharmacology*, vol. 38, no. 8, pp. 1521–1534, 2013.

[122] M. A. Padival, S. R. Blume, and J. A. Rosenkranz, “Repeated restraint stress exerts different impact on structure of neurons in the lateral and basal nuclei of the amygdala,” *Neuroscience*, vol. 246, pp. 230–242, 2013.

[123] M. Padival, D. Quinette, and J. A. Rosenkranz, “Effects of repeated stress on excitatory drive of basal amygdala neurons in vivo,” *Neuropsychopharmacology*, vol. 38, no. 9, pp. 1748–1762, 2013.

[124] M. N. Hill, S. A. Kumar, S. B. Filipski et al., “Disruption of fatty acid amide hydrolase activity prevents the effects of chronic stress on anxiety and amygdalar microstructure,” *Molecular Psychiatry*, vol. 18, no. 10, pp. 1125–1135, 2013.

[125] A. Vyas, S. Bernal, and S. Chattarji, “Effects of chronic stress on dendritic arborization in the central and extended amygdala,” *Brain Research*, vol. 96S, no. 1-2, pp. 290–294, 2003.

[126] A. Vyas, A. G. Pillai, and S. Chattarji, “Recovery after chronic stress fails to reverse amygdaloid neuronal hypertrophy and enhanced anxiety-like behavior,” *Neuroscience*, vol. 128, no. 4, pp. 667–673, 2004.

[127] R. Mitra, S. Jadhav, B. S. McEwen, A. Vyas, and S. Chattarji, “Stress duration modulates the spatiotemporal patterns of spine formation in the basolateral amygdala,” *Proceedings of the National Academy of Sciences of the United States of America*, vol. 102, no. 26, pp. 9371–9376, 2005.

[128] A. Vyas, S. Jadhav, and S. Chattarji, “Prolonged behavioral stress enhances synaptic connectivity in the basolateral amygdala,” *Neuroscience*, vol. 143, no. 2, pp. 387–393, 2006.

[129] A. Suvrathan, S. Bennis, S. Ghosh, A. Tomar, S. Anilkumar, and S. Chattarji, “Stress enhances fear by forming new synapses with greater capacity for long-term potentiation in the amygdala,” *Philosophical Transactions of the Royal Society B: Biological Sciences*, vol. 369, no. 1633, Article ID 20130515, 2014.

[130] M. N. Hill, S. A. Kumar, and S. J. Koleske, “Corticosterone-induced neural remodeling predicts behavioral vulnerability and resilience,” *Journal of Neuroscience*, vol. 33, no. 7, pp. 3107–3112, 2013.

[131] M. S. Monsey, L. M. Boyle, M. L. Zhang et al., “Chronic corticosterone exposure persistently elevates the expression of memory-related genes in the lateral amygdala and enhances the consolidation of a Pavlovian fear memory,” *PLoS ONE*, vol. 9, no. 3, Article ID e91530, 2014.

[132] H. Cui, H. Sakamoto, S. Higashi, and M. Kawata, “Effects of single-prolonged stress on neurons and their afferent inputs in the amygdala,” *Neuroscience*, vol. 152, no. 3, pp. 703–712, 2008.

[133] M. Maroun, P. J. Ioannides, K. L. Bergman, A. Kavushansky, A. Holmes, and C. L. Wellman, “Fear extinction deficits following acute stress associate with increased spine density and dendritic retraction in basolateral amygdala neurons,” *European Journal of Neuroscience*, vol. 38, no. 4, pp. 2611–2620, 2013.

[134] S.-F. Tsai, T.-Y. Huang, C.-Y. Chang et al., “Social instability stress differentially affects amygdalar neuron adaptations and memory performance in adolescent and adult rats,” *Frontiers in Behavioral Neuroscience*, vol. 8, article 27, 2014.

[135] B. K. Lim, K. W. Huang, B. A. Grueter, P. E. Rothwell, and R. C. Malenka, “Anhedonia requires MC4R-mediated synaptic plasticity,” *Neurology*, vol. 76, no. 20, pp. 1779–1786, 2011.
adaptations in nucleus accumbens,” *Nature*, vol. 487, pp. 183–189, 2012.

[136] V. Vialou, A. J. Robison, Q. C. Laplan et al., “ΔFosB in brain reward circuits mediates resilience to stress and antidepressant responses,” *Nature Neuroscience*, vol. 13, no. 6, pp. 745–752, 2010.

[137] B. Jiang, W. Wang, F. Wang et al., “The stability of NR2B in the nucleus accumbens controls behavioral and synaptic adaptations to chronic stress,” *Biological Psychiatry*, vol. 74, no. 2, pp. 143–155, 2013.

[138] D. J. Christoffel, S. A. Golden, M. Heshmati et al., “Effects of inhibitor of xB kinase activity in the nucleus accumbens on emotional behavior,” *Neuropsychopharmacology*, vol. 37, no. 12, pp. 2615–2623, 2012.

[139] D. J. Christoffel, S. A. Golden, D. Dumitriu et al., “xB kinase regulates social defeat stress-induced synaptic and behavioral plasticity,” *The Journal of Neuroscience*, vol. 31, no. 1, pp. 314–321, 2011.

[140] Q. LaPlant, V. Vialou, H. E. Covington III et al., “Dnmt3a regulates emotional behavior and spine plasticity in the nucleus accumbens,” *Nature Neuroscience*, vol. 13, no. 9, pp. 1137–1143, 2010.

[141] S. A. Golden, D. J. Christoffel, M. Heshmati et al., “Epigenetic regulation of RAC1 induces synaptic remodeling in stress disorders and depression,” *Nature Medicine*, vol. 19, no. 3, pp. 337–344, 2013.

[142] D. J. Christoffel, S. A. Golden, J. J. Walsh et al., “Excitatory transmission at thalamo-striatal synapses mediates susceptibility to social stress,” *Nature Neuroscience*, vol. 18, no. 7, pp. 962–964, 2015.

[143] L. A. Khilnik, M. Beaumont, M. Doyle et al., “Stress and cocaine trigger divergent and cell type-specific regulation of synaptic transmission at single spines in nucleus accumbens,” *Biological Psychiatry*, 2015.

[144] V. Krishnan, M.-H. Han, D. L. Graham et al., “Molecular adaptations underlying susceptibility and resistance to social defeat in brain reward regions,” *Cell*, vol. 131, no. 2, pp. 391–404, 2007.

[145] S. Rossi, V. De Chiara, A. Musella et al., “Chronic psychoemotional stress impair cannabinoi receptor-mediated control of GABA transmission in the striatum,” *The Journal of Neuroscience*, vol. 28, no. 29, pp. 7284–7292, 2008.

[146] R. C. Bagot, E. M. Parise, C. J. Pena et al., “Ventral hippocampal afferents to the nucleus accumbens regulate susceptibility to depression,” *Nature Communications*, vol. 6, article 7062, 2015.

[147] B. L. Warren, O. K. Sial, L. F. Alcantara et al., “Altered gene expression and spine density in nucleus accumbens of adolescent and adult male mice exposed to emotional and physical stress,” *Developmental Neuroscience*, vol. 36, no. 3–4, pp. 250–260, 2014.

[148] A. Muhammad and B. Kolb, “Mild prenatal stress-modulated behavior and neuronal spine density without affecting amphetamine sensitization,” *Developmental Neuroscience*, vol. 33, no. 2, pp. 85–98, 2011.

[149] V. Krishnan and E. J. Nestler, “Animal models of depression: molecular perspectives,” *Current Topics in Behavioral Neurosciences*, vol. 7, no. 1, pp. 121–147, 2011.

[150] E. J. Nestler and S. E. Hyman, “Animal models of neuropsychiatric disorders,” *Nature Neuroscience*, vol. 13, no. 10, pp. 1161–1169, 2010.

[151] B. I. Calderone, V. Zachariou, and S. L. King, “Rodent models of treatment-resistant depression,” *European Journal of Pharmacology*, vol. 753, pp. 51–65, 2015.

[152] T. BuyBITSky and D. I. Mostofsky, “Restraint stress in biobehavioral research: recent developments,” *Neuroscience and Behavioral Reviews*, vol. 33, no. 7, pp. 1089–1098, 2009.

[153] X.-M. Ma and S. L. Lightman, “The arginine vasopressin and corticotrophin-releasing hormone gene transcription responses to varied frequencies of repeated stress in rats,” *Journal of Physiology*, vol. 510, no. 2, pp. 605–614, 1998.

[154] O. Marti and A. Armario, “Anterior pituitary response to stress: time-related changes and adaptation,” *International Journal of Developmental Neuroscience*, vol. 16, no. 3–4, pp. 241–260, 1998.

[155] J. P. Herman, “Neural control of chronic stress adaptation,” *Frontiers in Behavioral Neuroscience*, vol. 7, article 61, 2013.

[156] N. Grissom and S. Bhatnagar, “Habituation to repeated stress: get used to it,” *Neurobiology of Learning and Memory*, vol. 92, no. 2, pp. 215–224, 2009.

[157] V. Luine, C. Martinez, M. Villegas, A. M. Magarinos, and B. S. McEwen, “Restraint stress reversibly enhances spatial memory performance,” *Physiology and Behavior*, vol. 59, no. 1, pp. 27–32, 1996.

[158] V. Luine, M. Villegas, C. Martinez, and B. S. McEwen, “Repeated stress causes reversible impairments of spatial memory performance,” *Brain Research*, vol. 639, no. 1, pp. 167–170, 1994.

[159] F. C. Raadsheer, W. J. G. Hoogendijk, F. C. Stam, F. J. H. Tilders, and D. F. Swaab, “Increased numbers of corticotropic-releasing hormone expressing neurons in the hypothalamic paraventricular nucleus of depressed patients,” *Neuroendocrinology*, vol. 60, no. 4, pp. 436–444, 1999.

[160] K. J. Parker, A. F. Schatzberg, and D. M. Lyons, “Neuroendocrine aspects of hypercortisolism in major depression,” *Hormones and Behavior*, vol. 43, no. 1, pp. 60–66, 2003.

[161] F. Holsboer, “The corticosteroid receptor hypothesis of depression,” *Neuropsychopharmacology*, vol. 23, no. 5, pp. 477–501, 2000.

[162] F. P. Varghese and E. S. Brown, “The hypothalamic-pituitary-adrenal axis in major depressive disorder: a brief primer for primary care physicians,” *Primary Care Companion to the Journal of Clinical Psychiatry*, vol. 3, no. 4, pp. 151–155, 2001.

[163] M. Belvederi Murri, C. Pariente, V. Mondelli et al., “HPA axis and aging in depression: systematic review and meta-analysis,” *Psychoneuroendocrinology*, vol. 41, pp. 46–62, 2014.

[164] S. Aboul-Fotouh, “Chronic treatment with coenzyme Q10 reverses restraint stress-induced anhedonia and enhances brain mitochondrial respiratory chain and creatine kinase activities in rats,” *Behavioural Pharmacology*, vol. 24, no. 7, pp. 552–560, 2013.

[165] S. Chiba, T. Numakawa, M. Ninomiya, M. C. Richards, C. Wakabayashi, and H. Kunugi, “Chronic restraint stress causes anxiety- and depression-like behaviors, downregulates glucocorticoid receptor expression, and attenuates glutation release induced by brain-derived neurotrophic factor in the prefrontal cortex,” *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, vol. 39, no. 1, pp. 112–119, 2012.

[166] A. Zafir, A. Ara, and N. Banu, “In vivo antioxidant status: a putative target of antidepressant action,” *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, vol. 33, no. 2, pp. 220–228, 2009.

[167] J. A. Bravo, G. Díaz-Veliz, S. Mora et al., “Desipramine prevents stress-induced changes in depressive-like behavior and hippocampal markers of neuroprotection,” *Behavioural Pharmacology*, vol. 20, no. 3, pp. 273–285, 2009.
Neural Plasticity

[203] S. C. Caetano, J. P. Hatch, P. Brambilla et al., “Anatomical MRI study of hippocampus and amygdala in patients with current and remitted major depression,” *Psychiatry Research — Neuroimaging*, vol. 132, no. 2, pp. 141–147, 2004.

[204] K. Sawyer, E. Corsentino, N. Sachs-Ericsson, and D. C. Steffens, “Depression, hippocampal volume changes, and cognitive decline in a clinical sample of older depressed outpatients and non-depressed controls,” *Aging and Mental Health*, vol. 16, no. 6, pp. 753–762, 2012.

[205] V. Lorenzetti, N. B. Allen, A. Fornito, and M. Yücel, “Structural brain abnormalities in major depressive disorder: a selective review of recent MRI studies,” *Journal of Affective Disorders*, vol. 117, no. 1-2, pp. 1–17, 2009.

[206] W. D. Taylor, D. R. McQuoid, M. E. Payne, A. S. Zannas, J. R. MacFall, and D. C. Steffens, “Hippocampus atrophy and the longitudinal course of late-life depression,” *The American Journal of Geriatric Psychiatry*, vol. 22, no. 12, pp. 1504–15012, 2014.

[207] S. J. Coultrap, K. M. Nixon, R. M. Alvestad, C. F. Valenzuela, and M. D. Browning, “Differential expression of NMDA receptor subunits and splice variants among the CA1, CA3 and dentate gyrus of the adult rat,” *Molecular Brain Research*, vol. 135, no. 1-2, pp. 104–111, 2005.

[208] L. C. Berumen, A. Rodriguez, R. Miledi, and G. Garcia-Alcocer, “Serotonin receptors in hippocampus,” *The Scientific World Journal*, vol. 2012, Article ID 823493, 15 pages, 2012.

[209] J. P. Herman, P. D. Patel, H. Aki, and S. J. Watson, “Localization and regulation of glucocorticoid and mineralocorticoid receptor messenger RNAs in the hippocampal formation of the rat,” *Molecular Endocrinology*, vol. 3, no. 11, pp. 1886–1894, 1989.

[210] G. Cellot and E. Cherubini, “Functional role of ambient GABA in refining neuronal circuits early in postnatal development,” *Frontiers in Neural Circuits*, vol. 7, article 136, 2013.

[211] N. M. van Strien, N. L. M. Cappaert, and M. P. Witter, “The anatomy of memory: an interactive overview of the parahippocampal-hippocampal network,” *Nature Reviews Neuroscience*, vol. 10, no. 4, pp. 272–282, 2009.

[212] J. A. M. Van Eekelen, W. Jiang, E. R. De Kloet, and M. C. Bohn, “Distribution of the mineralocorticoid and the glucocorticoid receptor mRNAs in the hippocampal formation of the rat,” *Journal of Neuroscience Research*, vol. 21, no. 1, pp. 88–94, 1988.

[213] A. N. Hoffman, A. Krigbaum, J. B. Ortiz et al., “Recovery after chronic stress within spatial reference and working memory domains: correspondence with hippocampal morphology,” *European Journal of Neuroscience*, vol. 34, no. 6, pp. 1023–1030, 2011.

[214] L. A. M. Galea, B. S. McEwen, P. Tanapat, T. Deak, R. L. Spencer, and F. S. Dhabhar, “Sex differences in dendritic atrophy of CA3 pyramidal neurons in response to chronic restraint stress,” *Neuroscience*, vol. 81, no. 3, pp. 689–697, 1997.

[215] J. B. Ortiz, C. M. Mathewson, A. N. Hoffman, P. D. Hanavan, E. F. Terwilliger, and C. D. Conrad, “Hippocampal brain-derived neurotrophic factor mediates recovery from chronic stress-induced spatial reference memory deficits,” *European Journal of Neuroscience*, 2014.

[216] C. S. Woolley, E. Gould, and B. S. McEwen, “Exposure to excess glucocorticoids alters dendritic morphology of adult hippocampal pyramidal neurons,” *Brain Research*, vol. 531, no. 1-2, pp. 225–231, 1990.

[217] C. D. Conrad, “What is the functional significance of chronic stress-induced CA3 dendritic retraction within the hippocampus?” *Behavioral and Cognitive Neuroscience Reviews*, vol. 5, no. 1, pp. 41–60, 2006.

[218] S. C. McQuown, R. M. Barrett, D. P. Mathews et al., “HDAC3 is a critical negative regulator of long-term memory formation,” *Journal of Neuroscience*, vol. 31, no. 2, pp. 764–774, 2011.

[219] T. J. Shors, C. Chua, and J. Falduto, “Sex differences and opposite effects of stress on dendritic spine density in the male versus female hippocampus,” *The Journal of Neuroscience*, vol. 21, no. 16, pp. 6292–6297, 2001.

[220] X. Cai, A. J. Kallarackal, M. D. Kvarta et al., “Local potentiation of excitatory synapses by serotonin and its alteration in rodent models of depression,” *Nature Neuroscience*, vol. 16, no. 4, pp. 464–472, 2013.

[221] K. M. Moench and C. L. Wellman, “Stress-induced alterations in prefrontal dendritic spines: implications for post-traumatic stress disorder,” *Neuroscience Letters*, vol. 601, pp. 41–45, 2015.

[222] G. Bush, P. J. Whalen, B. R. Rosen, M. A. Jenike, S. C. McNernery, and S. L. Rauch, “The counting Stroop: an interference task specialized for functional neuroimaging—validation study with functional MRI,” *Human Brain Mapping*, vol. 6, no. 4, pp. 270–282, 1998.

[223] A. W. MacDonald III, J. D. Cohen, V. A. Stenger, and C. S. Carter, “Dissociating the role of the dorsolateral prefrontal and anterior cingulate cortex in cognitive control,” *Science*, vol. 288, no. 5472, pp. 1835–1838, 2000.

[224] H. J. Groenewegen and H. B. M. Uylings, “The prefrontal cortex and the integration of sensory, limbic and autonomic information,” *Progress in Brain Research*, vol. 126, pp. 3–28, 2000.

[225] D. Diorio, V. Viau, and M. J. Meaney, “The role of the medial prefrontal cortex (cingulate gyrus) in the regulation of hypothalamic-pituitary-adrenal responses to stress,” *The Journal of Neuroscience*, vol. 13, no. 9, pp. 3839–3847, 1993.

[226] R. S. Ahima and R. E. Harlan, “Differential corticosteroid regulation of type II glucocorticoid receptor-like immunoreactivity in the rat central nervous system: topography and implications,” *Endocrinology*, vol. 129, no. 1, pp. 226–236, 1991.

[227] J. M. McIlveen, B. Myers, J. N. Flak et al., “Role of prefrontal cortex glucocorticoid receptors in stress and emotion,” *Biological Psychiatry*, vol. 74, no. 9, pp. 672–679, 2013.

[228] R. J. Hussain and L. Jacobson, “Increased antidepressant sensitivity after prefrontal cortex glucocorticoid receptor gene deletion in mice,” *Physiology and Behavior*, vol. 138, pp. 113–117, 2015.

[229] W. C. Drevets, J. L. Price, J. R. Simpson Jr. et al., “Subgenual prefrontal cortex abnormalities in mood disorders,” *Nature*, vol. 386, no. 6627, pp. 824–827, 1997.

[230] P. C. M. P. Koolschijn, N. E. M. van Haren, G. J. L. M. Lensvelt-Mulders, H. E. Hulshoff Pol, and R. S. Kahn, “Brain volume abnormalities in major depressive disorder: a meta-analysis of magnetic resonance imaging studies,” *Human Brain Mapping*, vol. 30, no. 11, pp. 3719–3735, 2009.

[231] M. J. Kempton, Z. Salvador, M. R. Munafò et al., “Structural neuroimaging studies in major depressive disorder. Meta-analysis and comparison with bipolar disorder,” *Archives of General Psychiatry*, vol. 68, no. 7, pp. 675–690, 2011.

[232] E. Bora, B. J. Harrison, C. G. Davey, M. Yücel, and C. Pantelis, “Meta-analysis of volumetric abnormalities in cortico-striatal-pallidal-thalamic circuits in major depressive disorder,” *Psychological Medicine*, vol. 42, no. 4, pp. 671–681, 2012.
[233] M. T. Treadway, M. L. Waskom, D. G. Dillon et al., “Illness progression, recent stress, and morphometry of hippocampal subfields and medial prefrontal cortex in major depression,” *Biological Psychiatry*, vol. 77, pp. 285–294, 2015.

[234] J. M. Carlson, E. Depetrio, J. Maxwell, E. Harmon-Jones, and G. Hajcak, “Gender moderates the association between dorsal medial prefrontal cortex volume and depressive symptoms in a subclinical sample,” *Psychiatry Research: Neuroimaging*, vol. 233, no. 2, pp. 285–288, 2015.

[235] D. Cotter, D. Mackay, G. Chana, C. Beasley, S. Landau, and J. P. Everall, “Reduced neuronal size and glial cell density in area 9 of the dorsolateral prefrontal cortex in subjects with major depressive disorder,” *Cerebral Cortex*, vol. 12, no. 4, pp. 386–394, 2002.

[236] G. Rajkowska, J. J. Miguel-Hidalgo, J. Wei et al., “Morphometric evidence for neuronal and glial prefrontal pathology in major depression,” *Biological Psychiatry*, vol. 45, no. 9, pp. 1085–1098, 1999.

[237] J. J. Radley, A. B. Rocher, M. Miller et al., “Repeated stress induces dendritic spine loss in the rat medial prefrontal cortex,” *Cerebral Cortex*, vol. 16, no. 3, pp. 313–320, 2005.

[238] C. L. Wellman, “Dendritic reorganization in pyramidal neurons in medial prefrontal cortex after chronic corticosterone administration,” *Journal of Neurobiology*, vol. 49, no. 3, pp. 245–253, 2001.

[239] S. M. Brown, S. Henning, and C. L. Wellman, “Mild, short-term stress alters dendritic morphology in rat medial prefrontal cortex,” *Cerebral Cortex*, vol. 15, no. 11, pp. 1714–1722, 2005.

[240] N. Nava, G. Treccani, N. Liebenberg et al., “Chronic desipramine prevents acute stress-induced reorganization of medial prefrontal cortex architecture by blocking glutamate vesicle accumulation and excitatory synapse increase,” *International Journal of Neuropsychopharmacology*, vol. 18, no. 3, 2015.

[241] N. Nava, G. Treccani, A. Alabsi et al., “Temporal dynamics of acute stress-induced dendritic remodeling in medial prefrontal cortex and the protective effect of desipramine,” *Cerebral Cortex*, 2015.

[242] H. E. Covington III, M. K. Lobo, I. Maze et al., “Antidepressant effect of optogenetic stimulation of the medial prefrontal cortex,” *The Journal of Neuroscience*, vol. 30, no. 48, pp. 16082–16090, 2010.

[243] M. R. Farrell, D. R. Sengelaub, and C. L. Wellman, “Sex differences and chronic stress effects on the neural circuitry underlying fear conditioning and extinction,” *Physiology and Behavior*, vol. 122, pp. 208–215, 2013.

[244] B. Kolb and J. Stewart, “Sex-related differences in dendritic branching of cells in the prefrontal cortex of rats,” *Journal of Neuroendocrinology*, vol. 3, no. 1, pp. 95–99, 1991.

[245] A. Bechara, H. Damasio, and A. R. Damasio, “Emotion, decision making and the orbitofrontal cortex,” *Cerebral Cortex*, vol. 10, no. 3, pp. 295–307, 2000.

[246] W. C. Drevets, “Orbitofrontal cortex function and structure in depression,” *Annals of the New York Academy of Sciences*, vol. 1121, pp. 499–527, 2007.

[247] D. Cotter, L. Hudson, and S. Landau, “Evidence for orbitofrontal pathology in bipolar disorder and major depression, but not in schizophrenia,” *Bipolar Disorders*, vol. 7, no. 4, pp. 358–369, 2005.

[248] J. Scheuerereck, E. M. Meisenzahl, N. Koutsouleris et al., “Orbitofrontal volume reductions during emotion recognition in patients with major depression,” *Journal of Psychiatry & Neuroscience*, vol. 35, pp. 311–320, 2010.

[249] G. Rajkowska, J. J. Miguel-Hidalgo, P. Dubey, C. A. Stockmeier, and K. R. R. Krishnan, “Prominent reduction in pyramidal neurons density in the orbitofrontal cortex of elderly depressed patients,” *Biological Psychiatry*, vol. 58, no. 4, pp. 297–306, 2005.

[250] P. Mandela and X. M. Ma, “Kalirin, a key player in synapse formation, is implicated in human diseases,” *Neural Plasticity*, vol. 2012, Article ID 728161, 9 pages, 2012.

[251] X.-M. Ma, D. D. Kiraly, E. D. Gaier et al., “Kalirin-7 is required for synaptic structure and function,” *The Journal of Neuroscience*, vol. 28, no. 47, pp. 12368–12382, 2008.

[252] M. J. Rubinow, G. Mahajan, W. May et al., “Basolateral amygdala volume and cell numbers in major depressive disorder: a postmortem stereological study,” *Brain Structure and Function*, pp. 1–4, 2014.

[253] C. Lange and E. Ire, “Enlarged amygdala volume and reduced hippocampal volume in young women with major depression,” *Psychological Medicine*, vol. 34, no. 6, pp. 1059–1064, 2004.

[254] T. Frodl, E. Meisenzahl, T. Zetzschke et al., “Enlargement of the amygdala in patients with a first episode of major depression,” *Biological Psychiatry*, vol. 51, no. 9, pp. 708–714, 2002.

[255] K. Vassilopoulos, M. Papathanasiou, I. Michopoulos et al., “A magnetic resonance imaging study of hippocampal, amygdala and subgenual prefrontal cortex volumes in major depression subtypes: melancholic versus psychotic depression,” *Journal of Affective Disorders*, vol. 146, no. 2, pp. 197–204, 2013.

[256] G. Kronenberg, L. Tebartz van Elst, F. Regen, M. Deuschle, I. Heuser, and M. Colla, “Reduced amygdala volume in newly admitted psychiatric in-patients with unipolar major depression,” *Journal of Psychiatric Research*, vol. 43, no. 13, pp. 1112–1117, 2009.

[257] Y. Tang, F. Wang, G. Xie et al., “Reduced ventral anterior cingulate and amygdala volumes in medication-naïve females with major depressive disorder: a voxel-based morphometric magnetic resonance imaging study,” *Psychiatry Research: Neuroimaging*, vol. 156, no. 1, pp. 83–86, 2007.

[258] S. H. Joshi, R. T. Espinoza, T. Pirmia et al., “Structural plasticity of the hippocampus and amygdala induced by electroconvulsive therapy in major depression,” *Biological Psychiatry*, 2015.

[259] P. W. Gold, R. Machado-Vieira, and M. G. Pavlatou, “Clinical and biochemical manifestations of depression: relation to the neurobiology of stress,” *Neural Plasticity*, vol. 2015, Article ID 581976, II pages, 2015.

[260] W. C. Drevets, T. O. Videen, J. L. Price, S. H. Preshkorn, S. T. Carmichael, and M. E. Raichle, “A functional anatomical study of unipolar depression,” *Journal of Neuroscience*, vol. 12, no. 9, pp. 3628–3641, 1992.

[261] P. Sah, E. S. L. Faber, M. L. De Armentia, and J. Power, “The amygdaloid complex: anatomy and physiology,” *Physiological Reviews*, vol. 83, no. 3, pp. 803–834, 2003.

[262] R. Mitra and R. M. Sapolsky, “Acute corticosterone treatment is sufficient to induce anxiety and amygdaloid dendritic hypertrophy,” *Proceedings of the National Academy of Sciences of the United States of America*, vol. 105, no. 14, pp. 5573–5578, 2008.

[263] P. W. Kalivas and K. R. Krishnan, “Profound reduction in pyramidal neurons density in the orbitofrontal cortex of elderly depressed patients,” *Biological Psychiatry*, vol. 58, no. 4, pp. 297–306, 2005.

[264] P. Mandela and X. M. Ma, “Kalirin, a key player in synapse formation, is implicated in human diseases,” *Neural Plasticity*, vol. 2012, Article ID 728161, 9 pages, 2012.

[265] S. E. Hyman, R. C. Malenka, and E. J. Nestler, “Neural mechanisms of addiction: the role of reward-related learning and memory,” *Annual Review of Neuroscience*, vol. 29, pp. 565–598, 2006.
AMPA receptors-mediated upregulation of mTOR and BDNF in rat hippocampus and prefrontal cortex, "European Psychiatry," vol. 29, no. 7, pp. 419–423, 2014.

[298] J.-J. Yu, Y. Zhang, Y. Wang et al., "Inhibition of calcineurin in the prefrontal cortex induced depressive-like behavior through mTOR signaling pathway," Psychopharmacology, vol. 225, no. 2, pp. 361–372, 2013.

[299] J. M. Dwyer, J. G. Maldonado-Avilés, A. E. Lepack, R. J. DiLeone, and R. S. Duman, "Ribosomal protein S6 kinase 1 signaling in prefrontal cortex controls depressive behavior," Proceedings of the National Academy of Sciences of the United States of America, vol. 112, no. 19, pp. 6188–6193, 2015.

[300] C. S. Jernigan, D. B. Goswami, M. C. Austin et al., "The mTOR signaling pathway in the prefrontal cortex is compromised in major depressive disorder," Progress in Neuro-Psychopharmacology and Biological Psychiatry, vol. 35, no. 7, pp. 1774–1779, 2011.

[301] S. W. Park, J. G. Lee, M. K. Seo et al., "Differential effects of antidepressant drugs on mTOR signalling in rat hippocampal neurons," International Journal of Neuropsychopharmacology, vol. 17, pp. 1831–1846, 2014.

[302] X. Liu, L. Luo, R. Mu et al., "Fluoxetine regulates mTOR signalling in a region-dependent manner in depression-like mice," Scientific Reports, vol. 5, Article ID 16024, 2015.