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Review article

# Stress-induced alterations in prefrontal dendritic spines: Implications for post-traumatic stress disorder

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ABSTRACT

The medial prefrontal cortex (mPFC) is involved in a variety of important functions including emotional regulation, HPA axis regulation, and working memory. It also demonstrates remarkable plasticity in an experience-dependent manner. There is extensive evidence that stressful experiences can produce profound changes in the morphology of neurons within mPFC with a variety of behavioral consequences. The deleterious behavioral outcomes associated with mPFC dysfunction have been implicated in multiple psychopathologies, including post-traumatic stress disorder (PTSD). Given the prevalence of these disorders, a deeper understanding of the cellular mechanisms underlying stress-induced morphological changes in mPFC is critical, and could lead to improved therapeutic treatments. Here we give a brief review of recent studies examining the mechanisms underlying changes in mPFC pyramidal neuron dendritic spines – the primary sites of excitatory input in cortical pyramidal neurons. We begin with an overview of the effects of chronic stress on mPFC dendritic spine density and morphology followed by proposed mechanisms for these changes. We then discuss the time course of stress effects on mPFC as well as potential intercellular influences. Given that many psychopathologies, including PTSD, have different prevalence rates among men and women, we end with a discussion of the sex differences that have been observed in morphological changes in mPFC. Future directions and implications for PTSD are discussed throughout.



**Contents**



## 1. Stress, post-traumatic stress disorder, and prefrontal cortex

Stress is linked to many psychological disorders, including post-traumatic stress disorder (PTSD), depression, and schizophrenia [e.g.,5,41]. These stress-sensitive psychological disorders are often characterized by prefrontal cortex dysfunction [5,25]. For instance, PTSD is characterized by both exaggerated, persistent fear responses to a traumatic event and impaired extinction of fear memories [e.g.,39]. Imaging studies have consistently demon-

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strated dysfunction of prefrontal cortex in PTSD patients, though the direction of this effect – hypoactivity versus hyperactivity – varies both across prefrontal subregions and within subregions across studies [25]. Interestingly, Milad and colleagues [39] demonstrated that PTSD patients showed impaired memory for extinction in a laboratory-based fear conditioning and extinction paradigm. This impairment was accompanied by, and correlated with, increased activation of dorsal anterior cingulate cortex and decreased activation of ventromedial prefrontal cortex. This pattern of prefrontal dysfunction is consistent with data from rodent models indicating that the prelimbic region of medial prefrontal cortex (PL; functionally homologous to the primate dorsolateral and dorsal anterior cingulate cortices) plays a role in facilitating the expression of conditioned fear, while the infralimbic region of medial prefrontal cortex (IL; functionally homologous to the primate ventromedial prefrontal cortex) plays a role in extinction or suppression of conditioned fear [33].

Prefrontal cortex is a target of stress-related neurochemicals and hormones [e.g.,17], and contributes to many of the behaviors influenced by both stress and glucocorticoids [e.g.,20,32,37]. Thus, stress-induced changes in prefrontal cortex may contribute to the pathophysiology of stress-related disorders such as PTSD, and understanding how stress influences prefrontal structure and function may elucidate mechanisms underlying them.

Dendritic spines, protrusions that are sites of excitatory synapses, are often categorized by morphology (e.g. stubby, thin, and mushroom) and the shape of these spines plays an important role in their function. For instance, stubby spines are thought to be immature and thin spines are thought to be relatively labile and plastic; mushroom spines are thought to be more stable, and are associated with synaptic strengthening, and may encode memory. *In vitro* work indicates that the morphology of spines is largely determined by the number of AMPA receptors located at the post-synaptic density as well as actin filaments both in the spine head and in the neck [for review see 49]. Both glutamatergic transmission and $Ca^{2+}$ influx are crucial for the normal formation and maintenance of spines. Through the influx of calcium and the sequential downstream effects, NMDA receptors (NMDARs) are involved in the initial formation of spines [31] and AMPA receptors (AMPARs) – anchored in the membrane by actin filaments – are involved in the strengthening of existing spines [31,42]. Thus, with the correct amount of stimulation, spines can be transformed from immature stubby spines to thin spines, and ultimately mature mushroom spines by the growth of a neck supported by actin filaments and an enlarged head as a result of AMPA receptor insertion. Given the evidence for experience-dependent plasticity in spines [49] as well as the influence of spine morphology on the electrophysiological properties of neurons [1], stress-induced changes in spine density and morphology in prefrontal cortex could contribute to the pathophysiology of PTSD.

## 2. Effects of chronic stress on dendritic spines in prefrontal cortex

The vast majority of studies examining the effects of stress on dendritic and spine morphology have focused on chronic stressors. Chronic [9,52], mild [6], and acute stressors [21] cause retraction of apical dendrites of pyramidal neurons in the anterior cingulate, prelimbic, and infralimbic regions of rat medial prefrontal cortex (mPFC). Chronic restraint stress in rats impairs prefrontally mediated behaviors such as retrieval of extinction of conditioned fear [4,11,40], working memory [16,38], and attentional set-shifting [28]. Further, prior stress dampens mPFC single-unit firing during extinction [56] and impairs induction of long-term potentiation (LTP) in mPFC [35,48,50]. This dendritic retraction and impairment of mPFC function is coupled with a decrease in spine density in anterior cingulate and prelimbic cortices [16,29,45,46]. Importantly, this decrease in spine density correlates with impairment of working memory, and prevention of the stress-induced spine loss prevents the working memory deficit [16]. Conversely, chronic restraint stress (6 h/day for 3 weeks) does not appear to significantly alter spine density in infralimbic cortex [52], suggesting that subregions of mPFC may be differentially sensitive to stress (see Fig. 1).

Interestingly, a shift in spine morphology from large mushroom spines to smaller thin spines, and thus an overall reduction in spine volume and surface area, has also been seen following chronic restraint stress [46]. This shift has been localized to a subpopulation of pyramidal cells projecting from PL to anterior bed nucleus of the stria terminalis (aBNST) following 14 days of chronic restraint stress [43]. As these neurons play an important role in regulating the hypothalamic-pituitary-adrenal (HPA) axis [44], the loss of mushroom spines may diminish the ability of aBNST-projecting neurons to efficiently inhibit the HPA axis in response to stress.

## 3. Neurochemical and intracellular mechanisms of chronic stress-induced spine loss

Whereas glucocorticoid receptors [29,55], NMDARs [36], and dopaminergic D1 receptors [26] have all been implicated in the dendritic remodeling in mPFC that results from chronic restraint stress, surprisingly little work has focused on the mechanisms of stress-induced changes in mPFC spine density and morphology. However, daily corticosterone administration mimics the chronic stress-induced spine loss [14,29], and administration of the glucocorticoid receptor (GR) antagonist RU486 during daily restraint prevents spine loss [29]. Thus, stress-induced increases in glucocorticoids likely contribute to alterations in mPFC spine density.

In addition, a small literature implicates NMDARs and AMPA receptors (AMPARs) in chronic stress-induced loss of spines. For instance, a single dose of either the NMDAR blocker ketamine or the specific NMDAR 2B blocker Ro25–6981 following 21 days of chronic unpredictable mild stress (including cold, disruption of light-dark cycle, crowding, shaking, and exposure to an aversive odor) rescues spines, particularly in layer V of PL [24]. This effect involved activation of the mTOR (mammalian target of rapamaycin) signaling pathway, as the beneficial effect of NMDAR blockade was prevented by administration of rapamycin. Additionally, NMDAR- and AMPAR-excitatory post-synaptic currents (EPSCs) are reduced following 5 or 7 days, but not 1 or 3 days, of repeated behavioral stressors [24,60]. Further examination of the mechanisms underlying decreased activity at these glutamatergic receptors demonstrated that the reduction in EPSC amplitude is dependent on ubiquitin/proteasome degradation of GluR1 and NR1 subunits [60].

Brain derived neurotrophic factor (BDNF) appears to play a key role in synaptic remodeling in hippocampus [2] and amygdala [15] following stress. Evidence for its role in mPFC is mixed, with some reports of stress-induced downregulation of BDNF mRNA (reviewed in [7]), and other studies failing to find stress-induced changes [8,27]. However, Yu and colleagues [57] recently demonstrated that 7 days of chronic restraint stress reduced spine density in mPFC of Val66Met knock-in mice, in which levels of BDNF are reduced, compared to stressed wild type (WT) mice. Interestingly, although the behavioral and neuroendocrine profile of these knock-in mice was comparable to that of WT prior to stress exposure, spine density was not different in unstressed WT versus knock-in mice. Nonetheless, stress-induced increases in plasma corticosterone and adrenocorticotropic hormone (ACTH) were greater in knock-in mice relative to WT. Thus, low basal levels of BDNF are