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RESEARCH****Focused Review****Stress-induced dendritic remodeling in the medial prefrontal cortex: Effects of circuit, hormones and rest****Rebecca M. Shansky*, John H. Morrison**

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ABSTRACT

The medial prefrontal cortex (mPFC) has been implicated as a site of dysfunction and abnormal morphology in major depressive disorder and post-traumatic stress disorder, two illnesses that can be brought on by exposure to stress. In animal models, stress has long been shown to induce impairments in tasks known to be mediated by the mPFC, and recent work has demonstrated that chronic stress can lead to morphological changes in mPFC pyramidal cells. This review explores the current literature on stress-induced dendritic remodeling in the mPFC, with particular focus on new findings that illuminate modulators of these effects.

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1. Introduction

Stressful experiences can precipitate or exacerbate mental illnesses such as major depressive disorder (MDD; [Lechin et al., 1996](#)) and post-traumatic stress disorder (PTSD; [Turner and Lloyd, 2004](#)), but the mechanisms by which the effects of stress contribute to the development of clinical pathologies are not well understood. Both post-mortem and functional imaging studies of patients with these disorders implicate the medial prefrontal cortex (mPFC) as a site of abnormal structure and function, suggesting a potential vulnerability to stress in this region. Specifically, the brains of suicide victims—who are likely to be depressed ([Hovanesian et al., 2009](#))—are reported to have decreased neuron and glia density compared to healthy controls ([Rajkowska et al., 2001](#)), and mPFC activity is suppressed in patients with MDD ([Liberzon and Phan, 2003](#); [Pizzagalli et al., 2004](#)). Common symptoms of MDD and PTSD—rumination, poor concentration and negative affect, for example—also suggest mPFC dysfunction ([Arnsten, 1998](#)).

Together, these findings identify the mPFC as a key player in the manifestation of stress-related mental illnesses, and an understanding of the effects of stress in this region will be critical to our progress toward better treatments.

2. Stress-induced dendritic remodeling in the mPFC

Though the mechanisms by which stress exposure can lead to clinical pathology are not clear, much work has been done in animals in an attempt to identify possible contributing factors. Animal models of chronic stress commonly involve subjecting an animal to daily restraint or immobilization, a regimen that has been reliably shown to activate the hypothalamic–pituitary–adrenal (HPA) axis, induce corticosterone release and cause morphological changes in several brain regions (reviewed in [McEwen, 1999](#)). In the rat mPFC, repeated restraint stress can cause retraction of the apical dendritic

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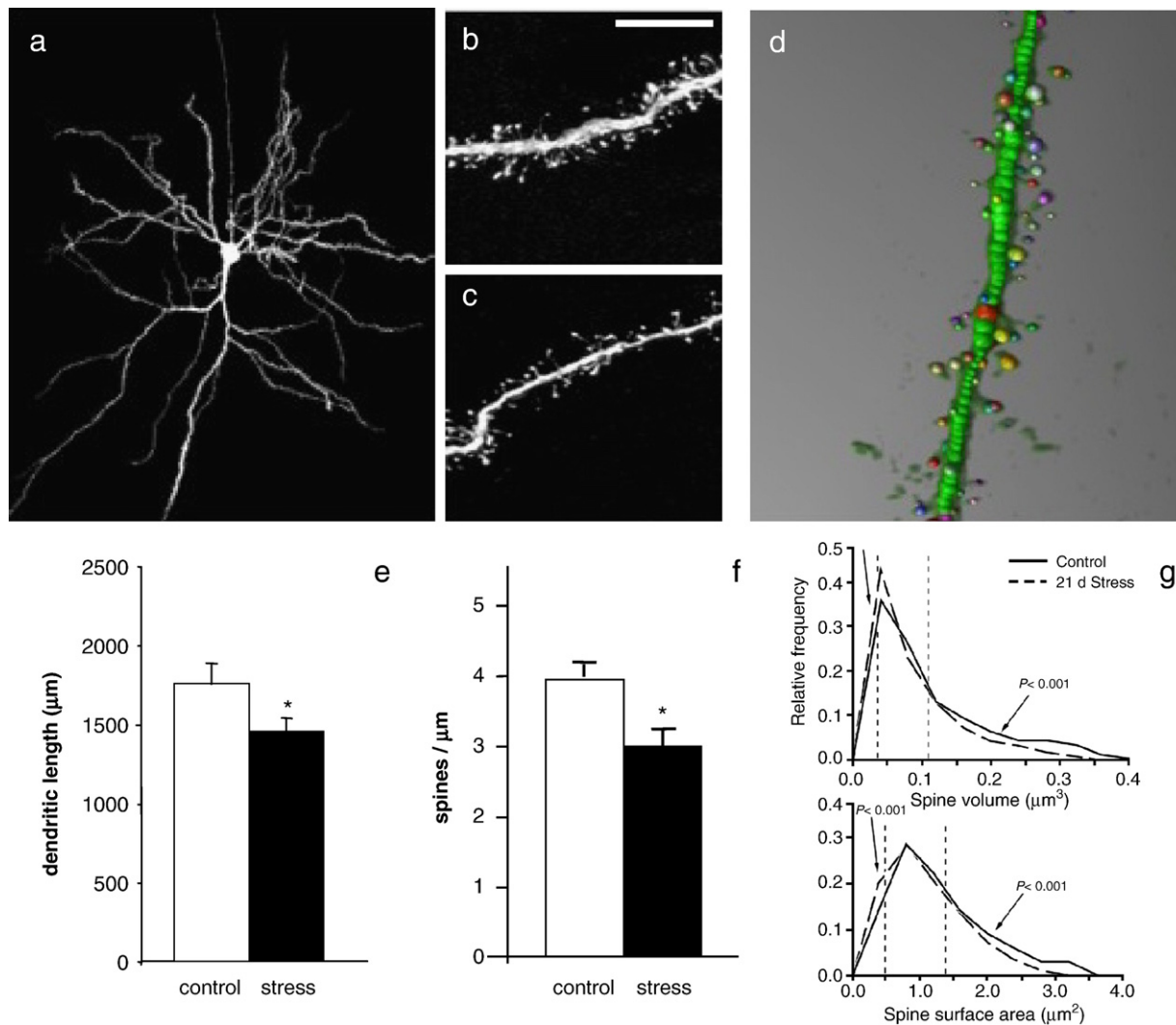


Fig. 1 – Chronic restraint stress causes dendritic remodeling in mPFC dendrites and spines. (a) A layer II/III pyramidal mPFC neuron filled with Lucifer Yellow to allow for dendrite visualization. **(b and c)** Dendrite segments from control and stress groups, demonstrating spine loss. **(d)** NeuronStudio software re-construction of a dendritic segment, demonstrating spine size measurements. **(e and f)** 21 days restraint stress causes significant decrease in total apical dendrite length and in spine density. **(g)** Chronic restraint stress also causes a shift in spine size, with dendrites exhibiting a smaller percentage of large spines. Adapted from Radley et al. (2004, 2006, 2008). * $p < 0.05$.

arbor in layer II/III pyramidal cells, an effect that has been demonstrated in the anterior cingulate (AC), prelimbic (PL; Izquierdo et al., 2006; Radley et al., 2004) and infralimbic (IL; Shansky et al., *in press*) subregions (Fig. 1). These changes in dendritic length have been shown to be accompanied by impairments in cognitive tasks selectively mediated by the mPFC while sparing non-mPFC-specific abilities (Liston et al., 2006), suggesting that stress-induced remodeling in the mPFC may have distinct functional consequences.

In addition to dendritic length changes, chronic stress has been shown to induce alterations in mPFC spines on the same neuronal populations that exhibit dendritic remodeling. In the AC and PL, spine density is reduced by 16% in chronically stressed animals (Fig. 1), which, when combined with the decrease in dendritic arborization, translates into a 30% loss of spines on each neuron (Radley et al., 2006). Recent data suggest that spine morphology, e.g. size, may be a critical

reflection of a capacity for synaptic plasticity (Kasai et al., 2003); thus in addition to an overall spine number, it is important to determine which spine classes are preferentially affected. More specifically, it has been proposed that small spines are highly motile and transient, capable of expansion and consolidation under certain circumstances or retraction, while large spines are viewed as more stable and likely to mediate long-term well established neural networks (Kasai et al., 2003). A recent analysis of spine volume and surface area in the mPFC neurons affected by stress revealed that the spine loss can be accounted for primarily by a reduction in large ($>1.0 \mu\text{m}^2$ and/or $>0.2 \mu\text{m}^3$) spines (Radley et al., 2008) (Fig. 1). Since it is unlikely that these large stable spines would retract with stress, this shift in the size profile of spines was interpreted as a reflection of a decreased capacity for the maturation and stabilization of small spines into large stable spines (Radley et al., 2008). This selective decrease in large

spines is notably in opposition to age-related spine loss in PFC of non-human primates in which mainly small spines are vulnerable (Hao et al., 2006). Such considerable spine changes likely alter a neuron's connectivity and functionality, and it has been speculated that while large spines are needed for memory consolidation, small spines are required for neural plasticity and active learning (Kasai et al., 2003). Consistent with this, aged non-human primates show impaired cognitive flexibility in a PFC-mediated task (Hao et al., 2007). In demonstrating the robust effects of chronic stress on the dendritic structure of neurons in the mPFC of rats, these studies lay the groundwork for investigations into the nuances and functional implications of spine dynamics as they relate to behavioral alterations.

3. Circuit-specific stress effects

One avenue of recent exploration is the potential for circuit-specific responses to stress. The mPFC maintains extensive connections with the amygdala, a brain region known to mediate the expression of fear and memory for aversive stimuli (Hendler et al., 2003; Wright et al., 2003). Physiological studies have shown that the mPFC can suppress amygdala activity (Sotres-Bayon et al., 2004), and it is through this pathway that the mPFC likely regulates emotional behavior and inhibits inappropriate responses (e.g., an unwarranted stress response). A compromise in the integrity of this pathway may underlie some of the symptoms of stress-related mental illnesses, and thus an understanding of the effects of stress on mPFC-amygdala projection neurons could help illuminate the nature of these disorders.

Recent work has tested the idea that this pathway may have a unique response to stress (Shansky et al., *in press*). Using a retrograde tracer to identify mPFC neurons that project to the basal nucleus of the amygdala (BLA) combined with Lucifer Yellow cell loading (Fig. 2a), the effects of chronic immobilization stress in this neuronal subset were compared with those in mPFC neurons that are selected at random. As has been demonstrated previously, randomly-selected neurons underwent dendritic retraction with stress (Fig. 2d). Since most layer II/III neurons project inter-cortically, we assume that the majority of randomly-selected pyramidal cell neurons are cortico-cortical. However, BLA-projecting neurons remained morphologically unchanged (Fig. 2e), suggesting, somewhat surprisingly, that this pathway may be particularly resilient against the effects of stress. This resilience may reflect a “healthy” disposition; while MDD is not uncommon, people endure stressful experiences without developing a clinical disorder. Thus, the mPFC-BLA pathway may be protected from the effects of stress under normal circumstances, but particularly vulnerable when predisposing factors are present.

4. Estrogen–stress interactions

Women are twice as likely as men to develop both MDD and PTSD (Weissman et al., 1996), a discrepancy that is most robust during childbearing years (Bebbington et al., 2003). This

phenomenon suggests that circulating estrogen may impart a sensitivity to the detrimental effects of stress, but this hypothesis has not been thoroughly tested. To date, experimental evidence indicates that estrogen's influence on the stress response varies by brain region, conferring protection from stress-induced cognitive impairments (Conrad et al., 2004) (Bowman et al., 2002) and dendritic remodeling in some structures (Galea et al., 1997), but sensitivity in others (Shansky et al., 2004).

Very little is known about estrogen–stress interactions in the mPFC, but recent work suggests that this specificity is reflected at the level of the circuit as well (unpublished observations). When ovariectomized (OVX) female rats with and without estrogen treatment (OVX+E and OVX+veh, respectively) were tested in the retrograde tracer/chronic stress experiment described above, IL neurons responded in a pattern wholly opposite from that of male rats. While no dendritic remodeling was observed in OVX+veh animals regardless of neuron set (randomly-selected or BLA-projecting), OVX+E exhibited a stress-induced increase in dendritic arborization exclusively in the BLA-projecting neurons (Figs. 2b–e). That no remodeling was observed in randomly-selected neurons in either treatment group (unlike males, whose randomly-selected neurons underwent significant retraction) suggests that the mPFC in females may be, in general, protected from the morphological effects of stress. However, the stress-induced increase in arborization in BLA-projecting neurons of OVX+E animals indicates that estrogen may confer a sensitivity to the effects of stress in a circuit that is particularly relevant to stress-related disorders.

These studies also revealed several novel findings regarding the effects of estrogen and stress on spine density in the mPFC. While stress had no effect on spine density in males, it caused an increase in spine density in OVX+veh in all neurons, and an increase in spine density in OVX+E in BLA-projecting neurons only, again indicating a circuit-specific interaction of estrogen and stress (Fig. 2f).

Because BLA-projecting neurons in stressed OVX+E animals not only have longer dendrites but also more spines per micron, each neuron then has substantially more total spines than control neurons. Together, these findings suggest that the subset of IL neurons that project to the BLA is particularly responsive to the effects of stress when estrogen is present. Though the functional implications of these phenomena remain to be explored, that estrogen can impart such a specific set of stress effects in females emphasizes the need to approach future studies with such potential hormonal interactions in mind. Given the gender discrepancy in the prevalence of stress-related disorders, these findings may help identify new therapeutic targets for women.

5. Reversal of dendritic remodeling

Studies of the biology underlying stress's effects in the brain are presumably done with the expectation that ultimately a way of preventing or reversing these effects will be found. Though lithium treatment has been shown to prevent stress-induced dendritic remodeling in hippocampal neurons (Wood et al., 2004), the ability of pharmacological agents to prevent or

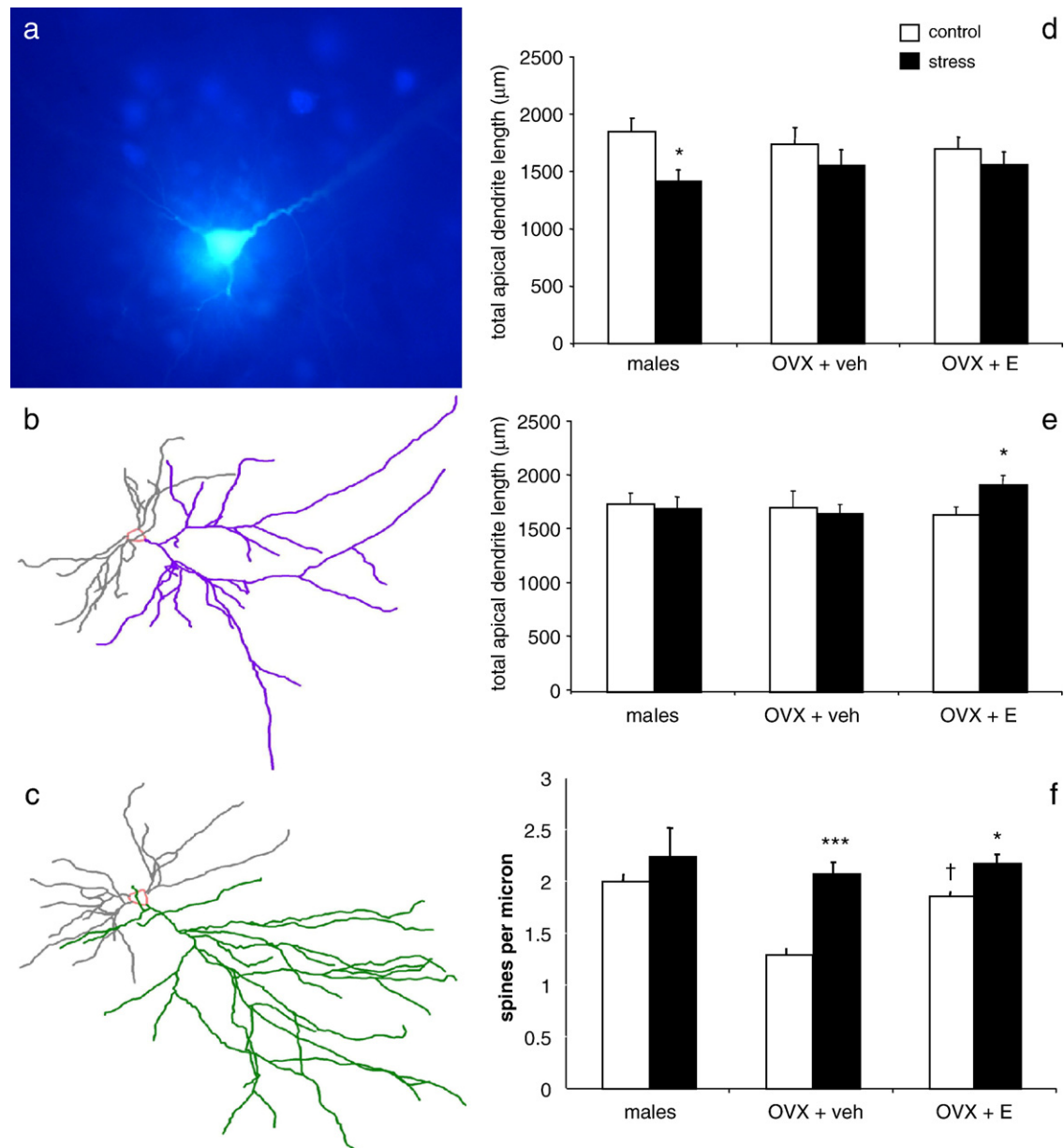


Fig. 2 – The effects of chronic stress in the mPFC are circuit- and estrogen-dependent. (a) A Lucifer Yellow-filled mPFC pyramidal cell surrounded by FastBlue-labeled cells, demonstrating the technique for selectively loading BLA-projecting neurons. Representative Neurolucida tracings of BLA-projecting neurons from OVX+E control (b) and stress (c) groups. In randomly-selected neurons (d), males, but not females, displayed stress-induced dendritic retraction. However, in BLA-projecting neurons (e), males and OVX+veh showed no stress-induced changes, while OVX+E exhibited stress-induced dendritic expansion. Stress-induced increases in spine density (f) were seen in BLA-projecting neurons of both OVX+veh and OVX+E but not males, and estrogen alone increased spine density in control animals. * $p < 0.05$ compared to same-group control; *** $p < 0.0001$ compared to same-group control; † $p < 0.05$ compared to OVX+veh control. Adapted from the observations of Shansky et al. (in press and unpublished).

reverse this remodeling in the mPFC has not yet been tested. However, an extended period of rest following chronic stress exposure has been shown to induce potentially compensatory dendrite growth in mPFC neurons (Radley et al., 2005). As described above, male rats that are stressed for 21 days will show retraction in apical dendrites. But if these rats are allowed to remain undisturbed in their cages for another 21 days after the cessation of stress, these neurons will re-

extend their branches, suggesting that rest alone may be sufficient to reverse the effects of stress in this region. Interestingly, this recovery period has been reported not to reverse stress-induced dendritic remodeling in the amygdala (Vyas et al., 2004). Whether this recovery is sufficient to restore the functional consequences of chronic stress is currently under investigation; preliminary work has found that while stress can reduce the dopamine D1 receptor population and

suppress dopamine's ability to enhance LTP in the mPFC, a rest period can restore both of these parameters to control levels (unpublished observations).

6. Functional and clinical implications

The studies described above reveal a remarkable degree of plasticity in the pyramidal neurons in the mPFC, capable of both expansion and retraction in response to stress, as well as re-expansion after a post-stress recovery period. The functional implications of these morphological changes remain unclear, however, especially with regard to whether retraction and expansion reflect detrimental or beneficial responses to stress. Common wisdom may dictate that dendritic loss be interpreted as maladaptive, while dendritic growth adaptive. Indeed, evidence in both hippocampal and mPFC neurons demonstrates that stress-induced dendritic retraction and spine loss are accompanied by cognitive impairments in tasks mediated by each respective structure (Conrad, 2006; Liston et al., 2006). Moreover, the function of brain structures that show stress-induced dendritic expansion or that are spared from the morphological effects of stress altogether appears not to be compromised after stress (Conrad et al., 1999).

However, the circuit specificity with which the mPFC responds to stress may suggest that the relationship between morphology changes and neuronal function is not so simple. Behaviorally, the projection pathway from the IL to the BLA is known to mediate the recall of extinction following fear conditioning (Lebron et al., 2004; Morgan et al., 1993; Milad and Quirk, 2002), a task consistent with the mPFC's regulation of amygdala activity and suppression of inappropriate responses. Extinction recall has been reported to be impaired after chronic stress (Miracle et al., 2006), but since BLA-projecting IL neurons appear to be resilient against the morphological effects of stress, this impairment is likely due to other stress-related changes. Additionally, the stress-induced expansion in BLA-projecting IL neurons of estrogen-treated females may indicate a potential for over-stimulation, and thus possible dysfunction. These hypotheses will likely need to be tested using careful physiology techniques in order for more confident causal claims to be made.

The cumulative findings here demonstrate that the morphological effects of stress in the mPFC are complex, varying with circuit, sex, hormonal status, and opportunity for recovery. These factors, then, must be taken into consideration in future studies, if progress in the treatment of stress-related disorders is to be made.

7. Future directions

The degree to which the morphology of pyramidal neurons in mPFC can be altered by stress has been recognized for a fairly short period of time, and the heterogeneity of neuronal responses described above is only beginning to be revealed. Thus it is not surprising that the data summarized above raise numerous questions worthy of pursuit. For example, while we refer to the dendritic extension with rest as recovery, we know nothing about the degree to which the synaptic inputs and

receptor profile of these spines are equivalent to controls (i.e., never stressed) or altered in a manner that changes the character of axospinous synapses on the affected dendrites. In addition, we do not know if the behavior altered by stress recovers as the neurons recover. In a related manner, we know little about the molecular mechanisms of dendritic retraction with stress and even less about the mechanisms for extension with rest. With increased knowledge of the mechanisms of retraction and expansion, we could presumably design interventions that could modulate both the response to stress and the potential for recovery. In addition, while it appears that the neuronal effects of stress are related to gender and the presence of estrogen, how do these neuronal effects impact behavior and are the behavioral effects gender-specific and estrogen-dependent? Finally, does the occurrence of stress and recovery alter the neurons' future response to stress, capacity for recovery, or vulnerability to aging? All of these questions are addressable with current methodology and as the answers emerge, it will be critically important to develop therapeutic strategies that target and harness neuronal plasticity for protection against and recovery from affective disorders in humans.

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