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Review article

# The influence of stress and gonadal hormones on neuronal structure and function

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ABSTRACT

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The brain is highly plastic, allowing us to adapt and respond to environmental and physiological challenges and experiences. In this review, we discuss the relationships among alterations in dendritic arborization, spine morphology, and behavior due to stress exposure, endogenous hormone fluctuation, or exogenous hormonal manipulation. Very few studies investigate structure–function associations directly in the same cohort of animals, and there are notable inconsistencies in evidence of structure–function relationships in the prefrontal cortex and hippocampus. Moreover, little work has been done to probe the causal relationship between dendritic morphology and neuronal excitability, leaving only speculation about the adaptive versus maladaptive nature of experience-dependent dendritic remodeling. We propose that future studies combine electrophysiology with a circuit-level approach to better understand how dendritic structure contributes to neuronal functional properties and behavioral outcomes.



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## Introduction

The brain is highly plastic, allowing us to adapt and respond to environmental and physiological challenges and experiences. Dendritic branches and spines can undergo remarkably specialized modifications in number, complexity, and morphology, which in turn alter the profile of synaptic input for a given neuron. Because the size and shape of dendritic arbors determine many functional properties of neurons (Grudt and Perl, 2002; Koch and Segev, 2000; Lu et al., 2001; Mainen and Sejnowski, 1996; Rall et al., 1992), reorganization of dendritic material may lead to disruption of normal synaptic processing. However, despite robust evidence for experience-based changes in neuronal morphology, synaptic transmission, and behavior, a clear picture of structure–function relationships in the brain has yet to emerge.

A myriad of internal and external environmental manipulations and challenges can alter dendritic morphology and spine density that may in turn alter learning and memory. Briefly, acute or chronic stress exposure, drugs of abuse, sex steroid manipulation, seasonal changes, aging, learning, and environmental enrichment all can induce dendritic remodeling in various brain structures in rats, mice, non-human primates, prairie voles, and tree shrews. However, very few studies have tested structure–function relationships directly, and the outcomes are correlational at best. Further complications arise when attempting to integrate findings across studies, since very few address structural plasticity and behavioral outcomes within the same experiment using

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the same parameters. Variations in environmental manipulations (e.g. type and duration of stressor), animal strain or sex, outcome measures (e.g. different protocols in memory acquisition and testing), and morphological technique (e.g. Golgi method versus iontophoretic intracellular filling) make it impossible to directly compare morphological findings with behavioral outcomes across the literature.

In this review, we focus on evidence of structure–behavior relationships in the rodent hippocampus and medial prefrontal cortex (mPFC) in response to stress challenges and ovarian hormone manipulation, identifying key inconsistencies. Then, we discuss work that probes the relationship between dendritic structure and neuronal excitability, which may help us understand the adaptive versus maladaptive nature of dendritic remodeling. Finally, we propose recommendations for future approaches to better characterize relationships between dendritic structure and behavior.

## Relationships between experience-dependent alterations in hippocampal dendritic morphology, spine density, and behavior

There is a wealth of evidence linking various chronic stress manipulations to dendritic atrophy in the hippocampus (see Table 1). Overall, chronic stressors such as restraint, predator exposure, social defeat, immobilization, or chronic unpredictable stress lead to a retraction of apical dendritic material in the CA3 region of the hippocampus (Baran et al., 2005; Kole et al., 2004; Lambert et al., 1998; Magariños and McEwen, 1995; McKittrick et al., 2000; Sousa et al., 2000; Vyas et al., 2002; Watanabe et al., 1992b). These same stressors are linked to deficits in hippocampal-dependent learning and memory tasks, such as performance in the radial arm maze (Gerges et al., 2004; Luine et al., 1994; Park et al., 2001), Y-maze (Conrad et al., 1996; McLaughlin et al., 2007), Morris water maze (Ma et al., 2007; Sandi et al., 2003; Song et al., 2006), and contextual fear conditioning (Conrad et al., 1999). Effects of acute stress (30 min of restraint or tail shock) on hippocampal spine density are region- and sex-dependent. Similar to chronic stress, 5 h of restraint stress on a rotator decreased CA3 spine density (Chen et al., 2008). Interestingly, exposure to intermittent tail shock resulted in an increase in spine density of CA1 neurons in males but a decrease in spine density in females (Shors et al., 2001). Even short, mild stress can have region-dependent effects: after acute 1 h platform stress, male rats had increased spine density of thin and mushroom spines in CA1, but a decrease of stubby spines in CA3 (Sebastian et al., 2013).

Changes in circulating estrogens across the estrous cycle and manipulation of sex steroids also have profound effects on spine density within the hippocampus (reviewed in Woolley, 1998). In female rats, ovarian hormones fluctuate over a 4 to 5 day cycle, characterized by elevated levels of estrogens and progesterone in proestrus compared to lower levels of ovarian hormones in estrus, metestrus, and diestrus (Butcher et al., 1974). Males and ovariectomized (OVX) females have comparable spine densities in CA1, yet intact cycling females have double the spine density of males (Gould et al., 1990; Shors et al., 2001), and females in the proestrus phase have the highest CA1 spine density (Woolley et al., 1990).

The relationship between dendritic structure, dendritic spines and synaptic input, and neural firing rates (Spruston, 2008) suggests that stress- or hormone-induced structural alterations may have important effects on neural function and hippocampal-mediated tasks. In males, 1 month of chronic unpredictable stress resulted in CA3 dendritic retraction and associated deficits in water maze spatial learning, a task mediated by the hippocampus (Sousa et al., 2000). Predator stress before training produced a deficit in consolidation of water maze learning and blocked a training-induced increase in spine density of CA1 basal dendrites (Diamond et al., 2006). The same short platform stress that resulted in region-dependent spine changes also impaired object placement, while platform stress prior to a retention test impaired memory retrieval on a radial arm maze (Sebastian et al., 2013). Thus, exposure to pre-training stressors in males impairs hippocampal function, decreases dendritic length and either decreases or increases spine density. On the other hand, after enrichment via housing in a complex environment, male rats demonstrated enhanced water maze learning and increased spine density in CA1 basal dendrites (Moser et al., 1994).

In females, findings are somewhat conflicting. Shors and colleagues have reported associations between spine density in CA1 of the hippocampus and performance during eyeblink conditioning (Leuner and Shors, 2004; Shors, 2002). In OVX mice, there is a rapid increase in spine density in CA1 40 min after estradiol injection (Phan et al., 2012), and enhancements of social recognition, objection recognition, and objection placement are seen after similar OVX and estradiol treatment immediately after learning acquisition (Fernandez et al., 2008; Inagaki et al., 2010; Luine et al., 2003; Walf et al., 2008). Consistent with these findings, OVX mice treated with estradiol show enhanced performance on an object placement task that is accompanied by an increase in the number of mushroom spines within CA1 (Li et al., 2004). Thus, estradiol-mediated increases in spine density in CA1 may lead to facilitated acquisition of spatial memory. However, another group looking at chronic stress and estradiol administration to OVX rats found a significant negative correlation between CA1 spine density and spatial memory on an object placement task (Conrad et al., 2012). Finally, we have recently reported that heat stress-exposed female rats had increased head diameter of mushroom spines within CA3 that was associated with enhanced freezing during extinction and extinction retrieval (Gruene et al., 2014).

In summary, there are inconsistencies in how structural changes in hippocampal neurons relate to behavioral outcomes in both males and females, and whether increases in spine density are associated with memory impairment or enhancement. Discrepancies across studies may be due to differences in behavioral tasks or manipulation parameters, but these possibilities have not been directly investigated.

## Relationships between experience-dependent alterations in prefrontal dendritic morphology, spine density, and behavior

As in the hippocampus, stress and sex hormones can alter dendritic morphology and spine density of the PFC (see Table 1). In male rodents, chronic restraint stress produces retraction of apical dendrites of pyramidal neurons in the prelimbic region of the mPFC (Cerqueira et al., 2007; Cook and Wellman, 2004; Garrett and Wellman, 2009; Liston et al., 2006; Martin and Wellman, 2011; Radley et al., 2004, 2005, 2006). A similar pattern of stress-induced retraction was seen for apical dendritic branches of neurons within the infralimbic region of the mPFC (Izquierdo et al., 2006; Shansky et al., 2009). As in the hippocampus, milder episodes of stress (10 min of restraint for 7 days, 3 weeks of vehicle injection, forced swimming) are sufficient to produce dendritic atrophy within the prelimbic cortex (Brown et al., 2005; Wellman, 2001) and the infralimbic cortex (Izquierdo et al., 2006).

Medial PFC is also sexually dimorphic, with smaller and less complex apical dendritic arbors in prelimbic cortex pyramidal neurons of gonadally-intact females than gonadally-intact males (Garrett and Wellman, 2009; Kolb and Stewart, 1991; Markham et al., 2002). Exogenous manipulation of estradiol alone did not have an effect on mPFC dendritic morphology, as OVX had no effect on dendritic morphology within prelimbic cortex (Garrett and Wellman, 2009) or in basolateral amygdala-projecting infralimbic cortex neurons (Shansky et al., 2010). In contrast, chronic stress (3 h/day for 7 days or 2 h/day for 10 days) resulted in dendritic proliferation within mPFC neurons of female rats, and the stress-induced morphological effect was dependent on estradiol (Garrett and Wellman, 2009; Shansky et al., 2010).

The functional ramifications of stress- or hormone-mediated structural changes are unclear, because investigations of structure–behavior relationships within the PFC are relatively sparse. The PFC is critical for behavioral tasks that require executive function, such as working