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

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Abstract

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.

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

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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 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 prefrontal cortex (PFC) 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 hr 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 hr 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 hippocampally-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 prelimbic region of medial prefrontal cortex (Cerqueira et al., 2007; Cook and Wellman, 2004; Garrett and Wellman, 2009; Liston et al., 2006; Martin and Wellman, 2011; Radley et al., 2006, 2005, 2004). A similar pattern of stress-induced retraction was seen for apical dendritic branches of neurons within the infralimbic region of medial prefrontal cortex (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 prelimbic cortex (Brown et al., 2005; Wellman, 2001) and 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 medial PFC 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 hr/day for 7 days or 2 hr/day for 10 days) resulted in dendritic proliferation within medial PFC 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 memory, cognitive flexibility, and emotional regulation (Holmes and Wellman, 2009), all of which can be influenced by stress and hormones (Farrell et al., 2013; McEwen and Morrison, 2013). Mice subjected to repeated swim stress (10 min/3 days) had deficits in retrieval of extinction of conditioned fear, a behavior mediated by infralimbic cortex, and accompanied apical dendritic retraction in infralimbic cortex (Izquierdo et al., 2006). Chronic (6hr restraint/day for 3 weeks) stressinduced dendritic retraction within the anterior cingulate cortex predicted the level of impairment on a perceptual attentional set-shifting task (Liston et al., 2006). Finally, prelimbic cortex dendritic spine loss was highly correlated with impaired working memory assessed by the spatial delayed alternation task and T maze after chronic restraint stress (6hr/day for 21 days) (Hains et al., 2009). After OVX, female rats had deficits in performance on a non-spatial object recognition memory task that was associated with a decrease in spine density of mPFC neurons (Wallace et al., 2006). Reproductive experience also influences mPFC structure-function relationships. Mother rats had increased mPFC spine number and improved behavioral flexibility compared to virgin rats (Leuner and Gould, 2010), while gestational stress resulted in reduced mPFC spine density and impaired reversal learning and extradimensional set-shifting (Leuner et al., 2014). Thus, although only correlational, there is evidence to suggest that experience-dependent disruption of prefrontal dendritic integrity is linked to experience-dependent deficits in prefrontal function.

Inconsistencies in Structure-Function Relationships

Straightforward relationships between remodeling of the dendritic tree and behavioral consequences of structural alterations are not always observed. It is possible that changes in dendritic morphology of certain brain structures are not associated with changes in behaviors to which these structures contribute. Dissociations have been observed between hippocampal morphology and fear and spatial learning. For example, preventing chronic stress-induced dendritic atrophy of CA3 does not affect the facilitation of contextual fear conditioning seen in stressed male rats (Conrad et al., 1999). In this case, Conrad and colleagues propose that stress-induced remodeling in the hippocampus leads to dysfunctional hypothalamic-pituitary-adrenal (HPA) axis regulation, and it is the HPA dysfunction that in turn modulates spatial memory deficits. Similarly, chronically stressed OVX females have functional spatial memory despite CA3 dendritic retraction. Chronic stress did not alter CA3 dendrites in OVX rats treated with estradiol, yet these same rats showed a stress-induced facilitation of water maze performance (McLaughlin et al., 2005). The authors propose that other regions of the hippocampus, namely the CA1, change in response to chronic stress to produce alterations in spatial learning and memory.

Further examples of inconsistencies in structure-function relationship patterns are present in the addiction and drug abuse field. In the prefrontal cortex, opiate administration decreases spine density (Robinson and Kolb, 2004), while stimulants increase dendritic arborization and spine density (Robinson and Kolb, 1999). However, despite opposite effects of opiates versus stimulants on dendritic morphology, both classes of drugs induce similar behavioral effects (Russo et al., 2010). To resolve this point, Russo and colleagues suggest that morphological changes may mediate addictive phenotypes in a bidirectional pattern such that a positive or negative change in baseline dendritic structure can alter behavior responses. Alternatively, experience-dependent alterations of dendritic complexity may not be accurate predictors of experience-dependent changes in synaptic strength, and synaptic efficacy, electrophysiological synaptic changes, and circuit-specific changes may better account for functional consequences (Russo et al., 2010)

Functions of Dendritic Remodeling

One hypothesis regarding the function of dendritic retraction is its role as a maladaptive response, in that dendritic atrophy, whether due to stress or hormone depletion, is associated with impaired function and may underlie stress-, sex-, or age-related psychopathology (Holmes and Wellman, 2009; Leuner and Shors, 2013). In this case, dendritic hypertrophy would be seen as adaptive, allowing for increased surface area for more synaptic connections and improved cognitive function (Fu et al., 2012). Alternatively, dendritic retraction can be seen as a compensatory mechanism to protect the neuron from prolonged excitation (Meller et al., 2008; Rhodes and Llinás, 2001), and thus shorter dendrites would correlate with better performance on a task mediated by a particular brain region. In this case, dendritic proliferation, as seen in the chronically stressed female medial PFC (Garrett and Wellman, 2009; Shansky et al., 2010), would represent a maladaptive profile, potentially exposing neurons to overstimulation. Given that a number of factors can alter the direction of stress-induced morphological changes (for example: brain structure, type/

duration of stressor, sex/age of animal), it is likely that the sum of overall dendritic remodeling processes and changes in neuronal excitability may be most important for functional consequences.

Structure and excitability

As reviewed above, there are inconsistencies in the findings on the relationship between dendritic morphology and behavior. That leads to the question of how dendritic morphology can affect excitability and firing patterns on a single neuron level. Intuitively, one might think that reduced dendritic length would result in reduced excitability as there is less space for synaptic input. However, evidence from computational models and electrophysiological recordings suggests that the relationship between structure and function on a single neuron level is more complicated than that. Kole and colleagues (2004) performed whole-cell recordings of CA3 pyramidal cells from rats that underwent chronic social defeat stress, and subsequently analyzed dendritic morphology of recorded neurons. In accordance with previous findings, chronic social defeat stress induced retraction of distal CA3 apical dendrites and impaired long term potentiation (LTP) induction. However, reduced apical length and branch number was related to increased excitability as measured by EPSP onset latency (Kole et al., 2004). In line with these findings, a computational modeling study simulating stress induced dendritic atrophy in CA3 pyramidal cells showed that reducing apical dendritic length results in increased somatic EPSP amplitude after dendritic stimulation (Narayanan and Chattarji, 2010). In the same computational model, dendritic atrophy of CA3 neurons led to increases in firing rates and changes in firing patterns: bursting cells switched to regular spiking cells with increased atrophy (Narayanan and Chattarji, 2010). This effect is in line with previous findings from computational modeling experiments showing that CA3 neurons with smaller dendritic trees have lower stimulation thresholds for switching from burst to regular spiking (Krichmar et al., 2002). The relationship between dendritic morphology and burst firing patterns is not exclusive to hippocampal neurons. A computational model study using visual cortex pyramidal neurons has shown that both decreased and increased apical length leads to a switch from burst firing to regular firing in pyramidal neurons (van Elburg and van Ooyen, 2010). Additionally, merely rearranging the dendritic tree could switch burst firing neurons to regular spiking neurons, suggesting that dendritic length is not the only factor affecting firing patterns (van Elburg and van Ooyen, 2010).

In the hippocampus, burst firing is associated with facilitation of LTP (Pike et al., 1999; Thomas et al., 1998). Thus, stress induced dendritic remodeling and the reduction in burst firing cells that goes along with it could account for the impairment in hippocampal LTP after stress exposure (Kim and Diamond, 2002; Kole et al., 2004). The relationship between burst firing and LTP seen in the hippocampus cannot be generalized to all brain regions, however. In the somatosensory cortex, for example, burst firing is associated with facilitation of long-term depression (LTD) (Birtoli and Ulrich, 2004). In the mPFC, burst firing in IL seems to be necessary for fear extinction consolidation and the degree of burst firing after extinction learning correlates with extinction recall (Burgos-Robles et al., 2007). It is tempting to speculate that stress induced dendritic remodeling could lead to reduced

burst firing in mPFC, thus contributing to extinction learning deficits seen after chronic stress.

The computational modelling studies described above are advantageous because they can investigate causal relationships between dendritic morphology and physiological properties of neurons. However, these studies only look at morphology of the dendritic tree and do not account for the possible influence of dendritic spines. It is unclear if changes in spine density or morphology can influence neuronal firing patterns. But in the hippocampus, higher spine density is associated with increased neuronal excitability (Mucha et al., 2011). Thus, increased excitability in neurons with reduced dendritic length could be either countered by reduced spine density or enhanced by increased spine density. In addition to potential differences in spine density, spine head volume and distinct spine head morphology have emerged as potential mechanisms of plasticity (Humeau et al., 2005; Matsuzaki et al., 2001). However, many morphology studies look at either morphology of the dendritic tree or morphology of dendritic spines, rather than looking at both measures, which makes it more difficult to infer functional implications of morphological changes. Differences in spine density in an examined brain region may be present without differences in overall dendritic branch number and length. For example, long-term estradiol administration did not alter total dendritic length and branching of pyramidal neurons in prelimbic cortex of female rhesus monkeys. However, estradiol administration increased both apical and basilar dendritic spine density and enhanced the number of thin spines (Hao et al., 2006), an effect that would have been obscured by looking at dendritic morphology alone. On the other hand, differences in overall dendritic branch number and length can be observed in absence of changes in spine density. Chronic stress (28 days psychosocial stress) produced apical dendritic atrophy but did not alter spine density in tree shrews (Magarinos et al., 1996). Measuring dendritic length and branching together with dendritic spine morphology in future studies will increase our understanding of the relationship between dendritic spines and dendritic length and its implications on a single neuron level and for behavioral outcomes. Additionally, investigating dendritic morphology together with electrophysiological properties in the same neurons will be necessary to understand how morphology relates to changes in excitability and firing patterns.

Circuit-level structural changes

In the previous sections, most of the studies reviewed have investigated relationships between morphological changes within a single structure and a behavior mediated by the same structure. Though morphological alterations are found in specific regions linked to a behavior (for example, greater spine density in CA1 is associated with better performance during eyeblink conditioning (Leuner and Shors, 2004; Shors et al., 2001), most behavioral outcomes are more likely attributable to experience-dependent dendritic remodeling in multiple structures within a circuit of interest (Leuner and Shors, 2013). For example, in male rats, chronic restraint stress can remodel dendritic arbors across multiple structures: within the CA1 and CA3 structures of the hippocampus, the prelimbic region of the medial PFC, the basolateral amygdala (BLA), and BLA-projecting neurons in the infralimbic cortex. It is important to consider how structural alteration of regional networks can affect behavioral outcomes. Thus, looking at multiple structures within a circuit is necessary, as

the balance of relative strength of synaptic activity within circuits may be a better predictor of behavioral outcomes than dendritic or spine changes within a single structure.

In addition, limitations of the Golgi method have prevented a complete neuroanatomical profile of neurons undergoing structural changes. For example, some morphological changes may be specific to a certain population of neurons dependent upon their efferent target. We have explored sex differences in circuit-specific responses to chronic stress within the medial prefrontal cortex-basolateral amygdala pathway. The interconnectivity between prefrontal cortex and amygdala is important for prefrontal inhibition of amygdala activity (Quirk and Gehlert, 2003; Sotres-Bayon et al., 2004), and connections between these two regions are critical modulators of a model of the regulation of emotional behavior, fear conditioning and extinction. Though chronic stress-induced dendritic retraction of medial prefrontal cortex has been demonstrated in male rats (McEwen, 2010), these neurons were selected at random and therefore little is known about their projection targets. However, when infralimbic cortex neurons that project to the BLA are identified via a retrograde tracer, neurons within this specific pathway do not show stress-induced alterations (Shansky et al., 2009). On the other hand, female rats showed stress-induced dendritic proliferation in prelimbic cortex neurons, and this effect was estradiol-dependent (Garrett and Wellman, 2009). In contrast to the circuit-specific effect seen in males, BLA-projecting infralimbic neurons of female rats showed dendritic proliferation in response to chronic stress while unlabeled, randomly selected neurons were not altered by chronic stress (Shansky et al., 2010). Additionally, Radley and colleagues (2013) examined chronic stress effects on dendritic morphology in anterior bed nuclei of the stria terminalis (aBST) projecting PL neurons. While there was no difference in stress induced dendritic retraction and reduction of overall spine density between aBST-projecting and randomly labelled neurons, aBST-projecting neurons were especially vulnerable to reductions in mushroom spine density. Thus, it is important to identify specific neural circuits that may be especially important mediators of behavior, and intra-circuit dendritic changes may be more revealing of structure-function relationships than extra-circuit dendritic changes.

Conclusions and Future Directions

In order to directly assess a causal relationship between neuronal structure and function, it will be necessary to directly measure synaptic strength. Though changes in spine morphology have been conventionally used as a marker for synaptic strength, there are still many unanswered questions. What is the identity of inputs synapsing on plastic spines? What does the localization of changes in dendritic morphology or spine density (proximal versus distal to the soma) confer about the functional properties of the neuron? Are compensatory mechanisms in play that may obscure experience-dependent morphological effects? Converging electrophysiological data with measures of dendritic morphology are a first step in better demonstrating the link between dendritic arborization and behavior. However, the electrophysiology studies reviewed in this paper were done in slice preparations, in which many synaptic connections are severed. Future studies could alternatively use approaches combining in vivo recordings with juxtacellular labelling of neurons for morphology analysis as was done by Inokawa and colleagues (2010). Additionally, future research should analyze morphology of specific subtypes of neurons

that have a closer link to behavioral outcome measures. This can be achieved by combining retrograde tracer labelling (Gruene et al., 2014; Radley et al., 2013; Shansky et al., 2010, 2009) with iontophoretic microinjection, or by targeting neurons that express a marker of neuronal activity indicating their involvement during a certain behavioral paradigm. Finally, a more direct way to uncover a causal link between dendritic structure and function is to pharmacologically manipulate dendritic length or spine density and then determine a behavioral outcome. For example, tianeptine treatment prior to restraint prevented both stress-induced dendritic retraction in CA3 of the hippocampus and stress-induced impairment of radial maze learning (Conrad et al., 1996; McEwen et al., 1997; Watanabe et al., 1992a). However, because tianeptine delivery was not localized to a specific brain region, a causal relationship between CA3 structure and function cannot be confirmed. A more recent study utilized viral-mediate gene transfer to selectively manipulate Rac1, a small GTPase involved in cytoskeleton remodeling, to alter spine density within the nucleus accumbens and behavioral responses to cocaine exposure (Dietz et al., 2012). With the increased availability of optogenetics and DREADDs technology, similar approaches should be used to investigate structure-function relationships in the hippocampus and mPFC. It is clear that further study is required to explore the complex causal relationships among dendritic arborization, spine morphology, and behavior.

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Highlights

1. Stress and gonadal hormones alter neuronal structure in the prefrontal cortex and hippocampus
2. Direct evaluation of the functional significance of structural plasticity is difficult.
3. Integrating electrophysiological measures with behavior and neuroanatomy may lead to better insights.

Table 1

Sex	Manipulation	Region	Dendrites	Spines	Behavior	Reference
Male	*Stress:*					
	21 days/6 h restraint	CA3	↓			(Watanabe et al., 1992)
	21 days predator stress + high fat diet	CA3	↓			(Baran et al., 2005)
	6 days activity stress + food restriction	CA3	↓			(Lambert et al., 1998)
	1 month CUS	CA3 CA1	↓ ↓		Stress-induced impairment in Morris water maze	(Sousa et al., 2000)
	Chronic immobilization 2 hr/day for 10 days	CA3	↓		Stress-induced decrease in open arm activity in elevated plus maze	(Vyas et al., 2002)
	21 days CUS	CA3	↓			(Magariños and McEwen, 1995)
	Repeated social defeat every other day for 21 days	CA3	↓			(Kole et al., 2004)
	14 days social defeat	CA3	↓			(McKittrick et al., 2000)
	21 days/6 hr restraint	CA3	↓		Stress facilitated fear conditioning	(Conrad et al., 1999)
	4–5 hr restraint on a rotator	CA3	↓			(Chen et al., 2008)
	Intermittent tailshock	CA1		↑		(Shors et al., 2001)
	1 hr elevated platform	CA1 CA3		↑ thin and mushroom spines ↓ stubby spines	Stress-induced impairment of object placement and radial arm maze	(Sebastian et al., 2013)
	30 min predator stress pre-training	CA1		↓ stubby spines basal dendrites	Stress-induced impairment of spatial learning on water maze	(Diamond et al., 2006)
	21 days/3 hr restraint	PL	↓			(Cook and Wellman, 2004)
	7 days/3 hr restraint	PL	↓			(Garrett and Wellman, 2009; Martin and Wellman, 2011)
	21 days/6 hr restraint	PL	↓	↓		(Radley et al., 2006, 2005, 2004)
	21 days/6 hr restraint	ACg OFC	↓ ↑		Stress-induced impairment of perceptual attentional set shifting	(Liston et al., 2006)
	10 min of forced swim	IL	↓		Stress-induced impairment in extinction	(Izquierdo et al., 2006)
	10 days/2 hr restraint	IL	↓			(Shansky et al., 2009)
	7 days/10 min restraint	PL	↓			(Brown et al., 2005)

Sex	Manipulation	Region	Dendrites	Spines	Behavior	Reference
	21 days vehicle injection	PL	↓			(Wellman, 2001)
	21 days/6 hr restraint	PL		↓	Stress-induced impaired delayed alternation/T maze	(Hains et al., 2009)
Female	*Stress:*					
	Intermittent tailshock	CA1		↓		(Shors et al., 2001)
	4 days environmental heat exposure	CA3		↑mushroom spine head diameter	Heat-induced increase in freezing during extinction	(Gruene et al., 2014)
	7 days/3 hr restraint	PL	↑			(Garrett and Wellman, 2009)
	10 days/2 hr restraint	BLA-projectin g IL	↑			(Shansky et al., 2010)
	Gestational day (GD) 7–13: 20 min of forced swim 2× daily; GD 14–20: 30 min restraint 2x daily	PL ACg		↓	Stress-induced impairment of reversal learning/set shifting	(Leuner et al., 2014)
Female	*Hormonal manipulation:*					
	Estrous cycle (proestrous effect)	CA1		↑		(Woolley et al., 1990)
	OVX	CA1		↓		(Gould et al., 1990)
	OVX + estradiol injection	CA1		↑ ↑ mushroom spines	Estradiol improved social and object recognition Estradiol enhanced performance on object placement task	(Phan et al., 2012) (Li et al., 2004)
	OVX + chronic restraint (6hr/day for 21 days) OR OVX + 2 acute estradiol injections	CA1		↓	Stress-induced improved object placement index	(Conrad et al., 2012)
	OVX	mPFC		↓	OVX-induced recognition memory impairment	(Wallace et al., 2006)
	Reproductive experience	mPFC	No change	↑	Enhanced performance in attentional set shifting in mothers versus virgins	(Leuner and Gould, 2010)

Abbreviations: CA1: cornu ammonis 1 of hippocampus; CA3: cornu ammonis 3 of hippocampus; CUS: chronic unpredictable stress; PL: prelimbic cortex; ACg: anterior cingulate; OFC: orbitofrontal cortex; BLA: basolateral amygdala; IL: infralimbic cortex; OVX: ovariectomy; mPFC: medial prefrontal cortex