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# Chronic Stress- and Sex-Specific Neuromorphological and Functional Changes in Limbic Structures

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**Abstract** Chronic stress produces sex-specific neuromorphological changes in a variety of brain regions, which likely contribute to the gender differences observed in stress-related illnesses and cognitive ability. Here, we review the literature investigating the relationship between chronic stress and sex differences on brain plasticity and function, with an emphasis on morphological changes in dendritic arborization and spines in the hippocampus, prefrontal cortex, and amygdala. These brain structures are highly interconnected and sensitive to stress and gonadal hormones, and influence a variety of cognitive abilities. Although much less work has been published using female subjects than with male subjects, the findings suggest that the relationship between brain morphology and function is very different between the sexes. After reviewing the literature, we present a model showing how chronic stress influences the morphology of these brain regions and changes the dynamic of how these limbic structures interact with each other to produce altered behavioral outcomes in spatial ability, behavioral flexibility/executive function, and emotional arousal.

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**Keyword** Stress · Hippocampus · Prefrontal cortex · Amygdala · Sex difference · Spatial memory · Emotional arousal · Fear conditioning · Behavioral flexibility · Depression · Post-traumatic stress disorder

**Abbreviations**

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|---|---|
| AMY | Amygdala |
| CA | Cornu ammonis |
| GC | Glucocorticoid |
| HPA | Hypothalamic–pituitary–adrenal |
| MDD | Major depressive disorder |
| OVX | Ovariectomized |
| PFC | Prefrontal cortex |
| PTSD | Post-traumatic stress disorder |

## Introduction

An extensive literature shows that chronic stress alters limbic structure and function, with important sex differences. The limbic region is critical for processing information related to emotions and memory [1–3], with the hippocampus' role in spatial learning and memory receiving much attention [4–7]. Structural damage to the hippocampus or its afferents disrupts spatial learning and memory [8–10]. Similarly, chronic stress alters hippocampal structure and impairs spatial learning and memory in males and, yet, produces different outcomes in females (for review [11–13]). The prefrontal cortex (PFC) and amygdala are two other limbic regions that have been extensively investigated for their role in behavioral flexibility/executive processing [14, 15] and emotionally salient events [16–19], respectively. The behavioral changes arising from PFC or amygdala damage

following lesion [20–22], and the behavioral outcomes produced by chronic stress [23–27] emphasize that the structural modifications caused by chronic stress has functional significance. As found with the hippocampus, these structural and functional outcomes in the amygdala and PFC reveal sex differences, which are likely modulated by gonadal hormones [13, 28, 29]. Chronic stress and/or sex-specific alterations in this neurocircuitry influence function, with gonadal hormones modulating these outcomes.

A general overview of the neurocircuitry connecting the hippocampus, PFC, and amygdala is as follows: The core of the hippocampus is comprised of the cornu ammonis (CA) regions, CA1, CA2, and CA3, with the hippocampal formation extending to the dentate gyrus (DG), entorhinal cortex, subiculum, parasubiculum, and the presubiculum [30]. The traditional trisynaptic circuitry refers to entorhinal cortical projections via the perforant path to the DG (synapse 1), which projects via the mossy fibers to the CA3 (synapse 2), which sends axons via the Schaffer collaterals to the CA1 (synapse 3). CA1 neurons send some projections back to the entorhinal cortex. Moreover, axons of the entorhinal cortex can bypass the DG and synapse with the CA3 or CA1 regions to form additional connections within the hippocampus. For the limbic circuitry, the hippocampal formation, PFC, and amygdala have reciprocal connections among each other. Consequently, changes in structure in any one of these regions could impact the functions of the remaining structures.

The purpose of this review is to present and evaluate current research investigating chronic stress and sex differences on limbic region plasticity and function with an emphasis on neuronal dendritic restructuring. Specifically, this paper will focus on sex-specific dendritic morphological alterations within the hippocampus, PFC, and amygdala and how the interactions between sex and neuromorphological alterations contribute to learning and memory. In this review, we propose that hippocampal CA3 dendritic morphology is coupled with spatial performance in males, while hippocampal CA1 dendritic properties are a better predictor of spatial ability in females. We present a model showing how chronic stress influences the morphology of these brain regions and changes the dynamic of how these limbic structures interact with each other to produce altered behavioral outcomes in spatial ability, behavioral flexibility/executive function, and emotional arousal.

## Clinical Relevance: Brain and Behavioral Changes in Stress-Related Disorders

Stress influences emotional states and cognitive abilities in a variety of mental disorders and diseases. Stressful life events are powerful triggers for post-traumatic stress disorder (PTSD) [31, 32] and major depressive disorder (MDD) [33–36]. The focus of this review is on chronic stress, but acute and severe traumatic events are also important in the etiology of PTSD and MDD [37–42]. PTSD and MDD can be influenced by the stress steroid, cortisol, a glucocorticoid (GC) released by the adrenal glands in response to stress, as prolonged and/or significantly elevated GCs are commonly associated with depressed mood and cognitive impairment found in both childhood-diagnosed PTSD [43, 44] and MDD [32, 45–50]. Moreover, chronic stress is implicated in the onset and development of Alzheimer's disease, where elevated GC levels are associated with learning and memory deficits as well as depressed mood [47, 51, 52]. Thus, chronic stress is linked to cognitive dysfunction and emotional distress found in several human conditions, with GCs as a likely mediator or facilitator of these disorders (for review, see [53]).

Chronic stress most likely influences cognitive dysfunction and emotional distress observed in clinical disorders through a variety of mechanisms, but overt neuromorphological changes may represent persistent effects from chronic stress. For example, the hippocampus is highly sensitive to stress hormones [54, 55], and changes in hippocampal volume may contribute to altered cognition and mood in individuals suffering from stress-related disorders (for reviews, see [47, 56–59]). Specifically, decreased hippocampal volume and impaired cognitive function are observed in individuals suffering from PTSD [59–62] or MDD [63–69]. However, not all studies find a relationship between hippocampal volume and/or cognitive function in PTSD or MDD [70–73]. Some interpretations for discrepancies in the literature include history of depression, amount and severity of stress and/or depressive episode, comorbidity with other disorders, and research methodology [66, 74, 75]. Regardless, the consensus that the hippocampus is a key player in PTSD and MDD remains due to the structure's high susceptibility to stress effects and the subsequent morphological changes that influence behavior.

In addition to the hippocampus, the PFC and amygdala are also critical in the stress response and are two of the most studied brain regions involved in mood and cognition. Both brain regions contain corticosteroid receptors [76–78] and help regulate GC activity [79] and show morphological changes in clinical disorders. For example, recent studies show reduced frontal cortex volume in MDD patients [68, 75, 80–82]. Moreover, chronic GC treatment is associated with decreased amygdala volume in patients with rheumatic diseases [83] and MDD [71, 73, 84]. As with studies in the hippocampus, the literature is not unanimous for volumetric changes in the PFC [85] or amygdala [64]. In fact, several studies report amygdala enlargement in MDD patients [66, 67, 86], and some

suggest that increased amygdala activation during stressful events contributes to depression relapse [87]. Taking the literature in its entirety, an alternative interpretation could be that structural alterations in either direction (reduction or enlargement) may impact function. In particular, it has been suggested that the hyper- or hypoactivity of the amygdala, when combined with the hypoactivity of the PFC and perhaps the hippocampus, influences cognition in affective disorders and/or PTSD [50, 88–90], while acknowledging that not all participants show changes in brain structure (for review, see [91]). Therefore, disrupted function can arise when one or several brain structures have been altered. Consequently, changes in neuronal circuitry likely contribute to the subtle differences observed in individuals with similar clinical diagnoses.

The role of gender is gaining recognition as an important variable underlying the etiology or acting as a mitigating factor that can influence stress-related disorders (for review, see [92]). Compared to men, women are at a greater risk to develop PTSD [93, 94] and to be diagnosed with MDD [47, 95–97]. In addition, women are diagnosed with Alzheimer's disease 1.5 times more than men, after being matched for age [98], and recent reports continue to document higher incidence of the disease in women [99]. Gonadal hormones likely contribute to the gender discrepancies observed in stress-related disorders. In women, GC levels are tightly coupled to the reproductive cycle, as increased GC release and stress sensitivity is commonly observed in women during the follicular phase of the menstrual cycle, when estrogen levels are high [100–102]. Moreover, mood is coupled to the phase of the menstrual cycle, puberty, and menopause, which are critical phases involving ovarian hormone changes [103–107]. Consequently, females have a greater incidence of stress-related disorders, with GC activity or upstream stimulators of GC potentially interacting with gonadal hormones to contribute to the gender discrepancies in developing stress-related illnesses.

## Animal Research: The Use of Animal Models to Better Understand Chronic Stress Effects

The use of animal models has become invaluable in understanding brain and behavioral changes related to neuropsychiatric illness and clinical conditions. Of particular interest to the current review, studies that rely upon chronic stress models using immobilization and/or restraint stress have become powerful tools for understanding the etiology of PTSD and MDD (for review, see [108]), aging, and neurodegenerative diseases, such as Alzheimer's disease (for review, see [51]), as well as other health-related conditions (for review, see [109]). In addition, animal models allow us to further investigate the effects of gonadal hormones and stress on the brain, a complex relationship that likely contributes to the gender differences observed in the onset and severity of stress-related disorders.

In our laboratory, chronic restraint stress using rats as subjects produces many symptoms that are similar to those observed in MDD, such as attenuated body weight gain [110, 111], altered cognition [110], changed hypothalamic–pituitary–adrenal (HPA) axis activity and sensitivity [112], reduced motivation to obtain palatable food [113], and comorbidity with anxiety [114]. Moreover, chronic stress and MDD exhibit parallels in brain plasticity and show that studying chronic stress in animal models provides insight into the possible mechanisms underlying MDD. As mentioned earlier, several studies report that MDD patients typically show decreased volumes of the hippocampus [63–68] and PFC [68, 75, 80–82] and increased volume of the amygdala [66, 67, 86]. Similarly, chronic stress alters structural plasticity at many levels in the rodent, including decreased neurogenesis in the dentate gyrus [115, 116], reduced dendritic complexity of the hippocampus [23, 117–119] and PFC [120–122], and increased dendritic arborization in the amygdala [117, 123, 124]. Moreover, studies finding decreased hippocampal volume in MDD patients report restored volumes following antidepressant treatment [65, 125]. In rodents, hippocampal dendritic retraction can also be restored or prevented through the administration of antidepressants [110, 126, 127]. These findings demonstrate that changes observed in brain morphology and plasticity are highly similar between MDD patients and chronically stressed rodents. Therefore, animal models have face and predictive validity in that they share stress-related symptoms with several clinical conditions and they benefit from antidepressant treatment [128].

Animal models also provide the opportunity to explore morphological changes in the brain with behavioral outcomes in the same subjects, which can be challenging in clinical populations. Dendritic structure is coupled with spines/synaptic input and neuronal firing rates [129–132]. Increased dendritic complexity allows for additional spines and synaptic contacts, as well as enhanced cognitive function [133, 134], whereas reduced or abnormal dendritic and/or synaptic plasticity is proposed to underlie many clinical conditions, including mood and stress-related disorders [135–138]. The correspondence among dendritic structure, spines, and synaptic activity indicates that plasticity at any one of these morphological structures can impact the remaining morphological regions, as well as the corresponding functional outcomes (for review, see [139]).

Another important factor when evaluating sex differences in response to chronic stress is the ability to monitor or

manipulate the role of gonadal hormones, as a closely tied and complex relationship exists between the HPA axis and the hypothalamic–pituitary–gonadal axis (for review, see [140, 141]). Due to the increased risk for women to develop stress-related disorders, significant research has emerged investigating the role of estrogens on the female brain and behavior. For females (both human and rodent), changes in estrogens during the reproductive cycle are tightly coupled with changes in GC levels. Increased levels of estrogens and GCs during the follicular phase of the menstrual cycle (when estrogens peak in women) and proestrous phase of the estrous cycle (when estrogens peak rodents) alter stress sensitivity in women [101, 102, 142] and rodents [143–146]. Indeed, some research suggests that female rodents may be more susceptible to certain stressors compared to their male counterparts [147], further supporting the use of animal models to better understand sex differences in response to stress disorders.

## Sex-Specific Effects of Chronic Stress on Hippocampal Morphology and Spatial Memory

Seminal studies established that chronic stress and/or chronic GC administration alters male rodent hippocampal morphology and function [for reviews, see 11, 148–150], and these outcomes extend across species [for review, see 134]. While chronic stress influences several areas of the hippocampus [151, 152], hippocampal CA3 neurons in particular are highly sensitive to chronic stress effects and are one of the first areas within the hippocampus to show dendritic remodeling [119, 153–155] although other hippocampal regions will show dendritic alterations as chronic stress continues [152] or intensifies [151, 156]. Therefore, our laboratory and others have primarily focused on chronic stress-induced changes in hippocampal CA3 neuronal properties as evidence for the onset of chronic stress influence on hippocampal structure and spatial memory in a rodent model.

Similar to previous reports, we observe a relationship between CA3 dendritic structure and function in males. Chronic restraint stress for 6 h/day/21 days [23, 113, 118] or chronic GC administration (corticosterone in drinking water) [157] induces robust CA3 apical dendritic retraction in the male hippocampus (Fig. 1a). Moreover, chronic stress-induced CA3 apical dendritic retraction in males often coincides with hippocampal-dependent spatial memory deficits. Male rats exposed to chronic stress perform poorly on such tasks as the appetitively motivated radial arm maze [158, 159], water escape radial arm maze [160–162], Y-maze [110, 111, 114, 118], T-maze [163], holeboard task [164], and the Morris water maze [155, 165–169]. When CA3 dendritic retraction is blocked pharmacologically [126, 170], spatial memory remains intact in chronically stressed male rats [110, 148, 159]. We have recent evidence that CA3 dendritic retraction indirectly mediates spatial memory because spatial memory can be restored in chronically stressed male rats when a corticosterone synthesis inhibitor is administered once on the day of training in a spatial task [112]. Our results demonstrate that this one-time pharmacological intervention decreases circulating GC levels, suggesting that HPA axis responsivity at the time of cognitive assessment is an important contributor to function [112]. Consequently, the presence of CA3 dendritic retraction does not necessarily predict impaired spatial memory and instead reveals a vulnerability to impaired spatial function. We previously presented a hypothesis for this outcome (see [134]), in that stress-induced CA3 dendritic retraction compromises the ability of the hippocampus to regulate the HPA axis in males, which in turn influences spatial ability (for information about the role of the hippocampus regulating hormones, see [171]). In its entirety, these data emphasize a relationship between hippocampal morphology and function in males and support the hypothesis that chronic stress-induced CA3 dendritic retraction contributes to, but is not the primary mediator of, impaired spatial ability in male rats.

In females, the relationship between CA3 structure and function has just recently begun to be explored, and thus far, research has failed to find a direct relationship between hippocampal CA3 morphology and spatial ability. To begin, the reliable finding in males that chronic stress induces CA3 dendritic retraction does not appear to apply to females. Chronic stress administered to gonadally intact, cycling females produces either mild basal CA3 dendritic retraction [172] or fails to alter CA3 dendritic complexity [173]. When female rats are ovariectomized (OVX), chronic stress produces drastic CA3 dendritic retraction [173, 174]. However, spatial learning and memory remains functional or even facilitated in chronically stressed female rats, whether or not the female rats are gonadally intact [175–178] or OVX [173, 174, 179], even when CA3 dendritic retraction is confirmed [173, 174]. Taken together, these findings suggest that females may be resilient to the potential deleterious effects of chronic stress on behavior, even under OVX conditions that allow for CA3 dendritic atrophy.

The disconnection between hippocampal CA3 dendritic arborization and spatial memory in females may be attributed to ovarian hormones, which likely influence hippocampal morphology and function via separate mechanisms than does stress. Estrogens have numerous actions within the hippocampus and are key modulators of brain activity and cognitive function [for review, see 180, 181, 266], revealing neuroprotective actions that extend beyond the hippocampus. Within the hippocampus, the CA3 region expresses receptors for estrogen [182–185]. Indeed, when a neurotoxin is directed at the hippocampal CA3 region following a history

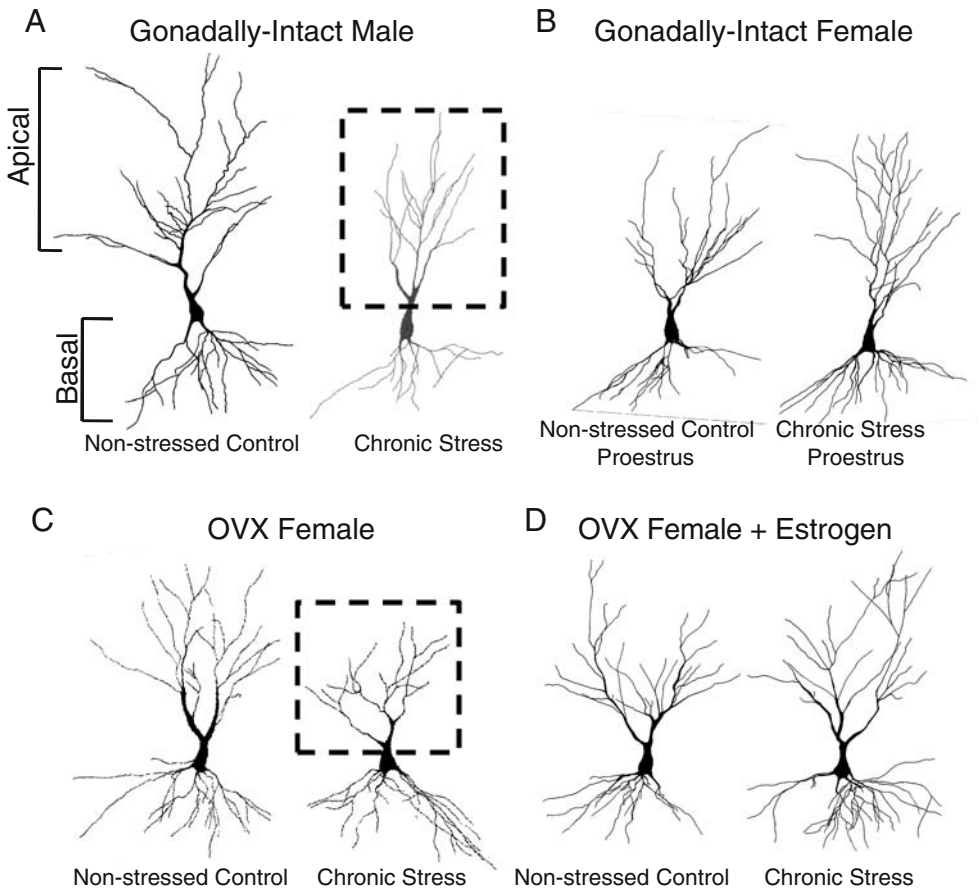


**Fig. 1** Hippocampal CA3 neuronal dendritic arborization in males and females. Camera Lucida tracings (×360) represent apical and basal CA3 hippocampal dendritic morphology. **a** In gonadally intact, young male rats, chronic stress produces dendritic retraction of the apical region (boxed), but not the basal region, of CA3 neurons. **b** In gonadally intact, young female rats, chronic stress fails to produce dendritic retraction in either the apical or basal regions of CA3 neurons. Note that the females showed regular estrous cycles and were euthanized at proestrus (high estrogen levels) or estrus (low estrogen levels). CA3 dendritic complexity was similar when assessed at proestrus or estrus and so CA3 neurons from proestrus are represented only in this illustration. **c** In ovariectomized (*OVX*) female rats, chronic stress causes apical dendritic retraction (boxed) in short shaft neurons and in both the apical and basal regions of long shaft neurons (not shown). **d** In OVX rats implanted with silastic capsules filled with estrogen (17β-estradiol) or even cholesterol (not shown), chronic stress-induced CA3 dendritic retraction was blocked. For both **a** and **c**, the *black dotted box* highlights regions with significant dendritic retraction, typically characterized by decreased dendritic branch points and/or reduced dendritic length. Apical dendritic retraction is commonly observed in chronically stressed gonadally intact males and chronically stressed OVX females. Note: Chronic stress refers to 6 h/day/21 days restraint stress. These figures have been adapted from the following sources: [118, 173, 174]

of chronic stress, neuroprotection against cell loss is more robust in females than in males [186], with estrogens hypothesized to contribute to this neuroprotective outcome. Additional support comes from the finding that estrogens prevent chronic stress-induced hippocampal neuronal loss [187]. More recently, we support our hypothesis proposed earlier that estrogen may mitigate chronic stress-induced CA3 dendritic remodeling [174], by demonstrating that estrogen or cholesterol replacement protects against stress-induced CA3 dendritic remodeling (Fig. 1) [173]. We also assessed spatial learning and memory within the same females and failed to find evidence that chronic stress-induced CA3 dendritic retraction influenced spatial memory. Given these findings, we evaluated the effects of chronic stress on gonadally intact, cycling females and euthanized the chronically stressed females when ovarian hormones were high (proestrus) or low (estrus) to determine whether rapid remodeling, such as that found in some species (for review, see [134]), could explain some of the contradictory outcomes from the current findings and previous work [172]. Even when the stage of the estrous cycle was monitored, we were unable to find chronic stress effects on CA3 dendritic retraction in females (Fig. 1b) [173]. A parsimonious interpretation is that estrogens can be neuroprotective against chronic stress-induced CA3 dendritic retraction, whether it is partial [172] or complete prevention [173]. Consistent with these findings is that estrogen protects against acute stress-induced inhibition of a form of plasticity called long term potentiation in the CA1 region [267]. Therefore, the combination of behavioral

findings suggests that while estrogens protect females against stress-induced CA3 dendritic remodeling, the changes in CA3 dendritic morphology are unlikely to be responsible for spatial ability because chronically stressed females perform similar, if not better, than their control counterparts [173, 174, 188].

Alterations in CA1 dendritic properties may be one potential mechanism driving spatial ability in females. Neurobiological studies investigating hippocampal-dependent behaviors are commonly based on the trisynaptic pathway. However, recent research has begun to emphasize the role of the direct projection from the entorhinal cortex onto the CA1 region [189–194]. In general, while hippocampal activation is crucial for spatial tasks, each subregion contributes differently [189, 193, 195–198]. Some propose that the CA3 region may be responsible for receiving multimodal cortical inputs for acquisition and spatial processing [199–201], whereas the CA1 region may unite spatial and temporal contexts [195, 201]. Indeed, CA1 neurons are theorized to mediate single trial and novelty processing [194], components tested in our spatial tasks, whereas CA3 neurons are thought to integrate multimodal sensory processing [191]. Moreover, damage to CA1 neurons are thought to be more disruptive in spatial navigation than CA3 neurons [197]. Taken together, these findings support the idea that CA3 and CA1 neuronal structure influences spatial ability, but with CA1 neurons being particularly involved in spatial recognition memory, such as the type used in our laboratory.

Gonadal hormones and stress may modulate learning and memory through activation of the CA1 region. Both androgens [202–204] and estrogens [205–207] increase CA1 apical dendritic spine density, alter spine shape and functional plasticity [267]. CA1 spine density naturally fluctuates across the female estrous cycle with CA1 spine density greatest at proestrus [173, 208], an effect that can be produced in OVX females injected with estradiol [207, 209, 210] or implanted with silastic capsules filled with estradiol [173, 211] or even cholesterol [173]. Many studies speculate that increased CA1 spine density following appropriately timed estrogen treatment underlies the improved spatial ability in female rats [207, 212–214]. Stress also influences CA1 dendritic/spine morphology, with chronic stress increasing CA1 branching [152] and post-synaptic density [215]. Moreover, sex differences in CA1 spine density emerge following an acute stressor, with males expressing increased apical and/or basal spine density compared to females (for review, see [216]), and this effect can be reproduced through the masculinization of females [217]. In addition, CA1 basal spine shape can be influenced by acute stress [218] and chronic stress [173, 174] by facilitating the maturation of spines. Our laboratory has found that, for females, chronic stress increases the ratio of CA1 basal spine shape (heads or mature spines as a ratio of headless or immature spines), which is associated with enhanced spatial learning and memory [173, 174] and similar results have been reported for males [218]. Although there are a few studies that evaluate CA1 morphology and behavior in the same subjects, the available findings suggest that CA1 spines contribute to spatial memory [174, 216]. The relationship between gonadal hormones and stress on CA1 spine properties is important because it may provide additional mechanisms to explain the sex differences observed in hippocampal-dependent behaviors.

## Sex-Specific Chronic Stress Effects on PFC and Amygdala Morphology and Function

While the bulk of the chronic stress literature has focused on the hippocampus, recent work has begun to elucidate the effects of chronic stress on the PFC and related behaviors (for review, see [219, 220]). The PFC interacts extensively with the stress response. Exposure to stressors results in increased PFC activity [221] and influences neurotransmitter release/activity in the PFC including acetylcholine [222], dopamine [222, 223], glutamate [224], and norepinephrine [225]. The PFC also influences the stress response by regulating GC release [226]. In addition, the PFC contains a high density of corticosteroid receptors [76–78]. Given that chronic stress-induced dendritic retraction in the hippocampus is dependent on stimulation of corticosteroid receptors, as well as changes in neurotransmitter release, any of these stress-related changes in the PFC may contribute to the morphological changes seen in the PFC.

Chronic stress impacts PFC morphology in a number of ways that has implications for behavior. In males, chronic stress reduces PFC dendritic arbors [120, 122, 227–229], decreases PFC dendritic spine density [122], and blocks the development of extinction-related potentials in the hippocampus–PFC pathway [26]. Interestingly, daily injections of either GC or vehicle alter PFC dendritic spine density [230], which suggest that the PFC is perhaps hypersensitive to external factors, including the mild stress associated with injections [231] and could even show neuronal loss [232]. Consequently, these studies suggest that chronic stress-induced alterations in the PFC of males may be expressed in PFC-mediated behaviors as well.

Several studies have investigated the effects of chronic stress on PFC function and report compromised behaviors that correspond with chronic stress-mediated changes in the PFC. Impairments in PFC-dependent behaviors, such as fear extinction recall [25–27], fear extinction acquisition [229], working memory [223, 232, 233], and attention [227], are reported in male rodents following chronic stress

exposure. For recall of fear extinction, animals are trained to associate a neutral stimulus (i.e., tone) with an aversive event (i.e., mild footshock). The resulting behavior, freezing, exhibited during the tone is used to indicate that the rodent associates the tone with the aversive event. While male rodents with ventral–medial PFC lesions or chronic stress exposure are able to perform this aspect of fear conditioning [20, 25, 27], anomalies are observed during extinction when the tone is presented alone without footshock. During extinction to tone, rodents must learn and adapt (i.e., demonstrate flexibility) to the changed meaning of the tone, which is that the tone no longer signifies an impending footshock. While impairments of extinction have been reported in chronically stressed male mice [229], normal extinction can be detected in male rats following chronic stress or after PFC lesions under carefully considered training parameters [20, 25, 27]. Under conditions that extinction is similar for control and chronically stressed male rats, however, chronically stressed rats will not remember the extinction experience after a delay [20, 25, 27]. This deficit in impaired recall of fear extinction by chronically stressed male rodents is an indicator of impaired flexibility and consistent with performance of male rats with PFC lesions.

The maintenance of the previously learned association (tone with footshock) may appear to be a form of perseveration, and some have suggested that chronic stress increases perseverative behaviors in male mice [234, 235]. The PFC is suggested to contribute to behavioral flexibility and allows individuals to modify their behaviors as environmental information is updated. This inability of chronically stressed subjects to be "flexible" in response to changing environmental information was recently demonstrated in male mice exposed to chronic psychological stress (predator) and in male and female humans who self-reported a high stress history [236]. Both chronically stressed subject groups showed a bias for using inflexible, cued-based strategies over flexible, spatial strategies. In fact, 94% of the chronically stressed human population favored a cued strategy compared to near chance levels (52%) of the nonstressed group [236]. In the clinical study, both males and females show similar outcomes, but future studies should incorporate extensive examinations, such as the type of stress and duration because males and females respond to stressor type differently (i.e., physical vs. psychological). With regard to males, chronic stress alters PFC function, which is consistent with the changes observed in PFC morphology.

How sex differences influence chronic stress-mediated alterations in the morphology and function of the PFC is starting to be addressed in the basic science literature, and recent findings show that the process occurring in males does not necessarily apply to females. While both sexes exhibit chronic stress-induced alterations in dendritic complexity of PFC pyramidal neurons [120, 122, 227, 228], chronic stress decreases dendritic arbors in males and increases them in females [228]. In addition, the increase in dendritic complexity seen in females is dependent on the presence of estrogens [229], but OVX does not produce the male pattern of dendritic arborization [229]. Importantly, these sex-specific morphological changes in the PFC appear to influence behavior. A recent study from our laboratory, comparing fear conditioning, extinction, and extinction recall in male and female rats, show sex-specific impairments following chronic stress [27]. Chronic stress produced the expected impairment in PFC-dependent fear extinction recall in males, while unexpectedly impairing the recall of the fear *conditioning* experience (acquisition) in females, an event that may involve the amygdala. This difference indicates that chronic stress produces sex-specific effects on the mechanisms driving recall of fear conditioning and extinction. Since chronically stressed females exhibited impaired ability to recall the fear conditioning experience itself, we were unable to determine the impact of chronic stress on the PFC-mediated extinction recall. However, data from our laboratory assessing chronically stressed females' exploration on the Y-maze suggest that chronically stressed females show perseverative tendencies (Fig. 2). These data suggest that females may be influenced by the morphological changes in the PFC. The different patterns of dendritic retraction observed between males and females may partially underlie the sex differences displayed in fear conditioning and Y-maze exploration.

Steroid hormones may also account for sex differences in PFC-dependent behavior. As mentioned previously, endogenous GC release is higher in females than in males during both baseline and stress conditions. When GCs are chronically elevated in males via injection, dendritic retraction in the PFC is similar to chronically stressed males [237, 238]. Interestingly, dendritic retraction is also present in rats injected with vehicle [237]. This suggests that the pattern of dendritic retraction in the PFC is dependent upon the amount of GC present. In males, this pattern is associated with minor decreases in behavioral flexibility [238]. Whether a similar behavioral effect is seen in GC-treated females is unknown. Moreover, ovarian hormones also appear to modulate the chronic stress-induced dendritic remodeling in the PFC of females. The enhancement in PFC dendritic complexity following chronic stress occurs in OVX females treated with estrogens, but not in untreated OVX females [228]. Consistent with these morphological findings in the PFC of females is that estrogens impair some PFC-dependent behaviors, such as delayed spatial alternation and differential reinforcement of low rates of responding [239].

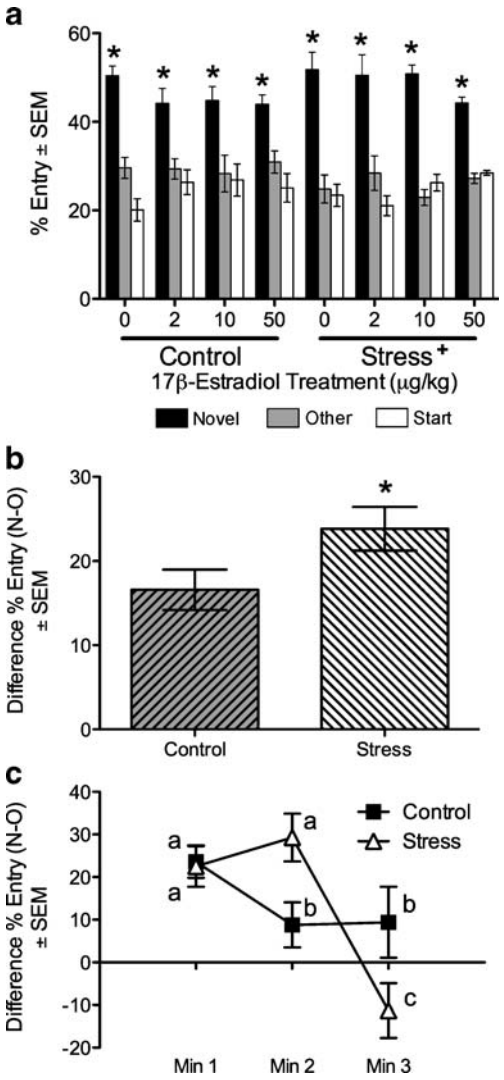


**Fig. 2** Performance of OVX females on the Y-maze. Both non-stressed controls and chronically stressed females demonstrated spatial memory, but the chronically stressed female rats showed perseverative tendencies. In this spatial paradigm, rats were placed in a symmetrical Y-maze with one of the three arms blocked. Rats will explore the remaining two arms due to their innate tendency to explore novelty. Following the exploration trial, the rats are removed, the mazes are cleaned and switched to remove the possibility of using intra-maze, nonhippocampal-based strategies, and the rats are placed back in the maze after a 4-h delay. Typically, rats will enter the arm in the location that was previously inaccessible and hence is termed the "novel" arm, with remaining arms called the start and other. Data representing the performance on this test trial reveal that all rats entered the novel arm more than the remaining arms (**a**) and that difference scores computed by the total entries into the other (O) arm subtracted from the total entries into the novel (N) arm show positive difference scores, which reflect preference for the novel arm (**b**). However, both measures show that chronic stress facilitates this novel arm preference. A timeline across minutes shows that chronically stressed rats maintain interest in the novel arm longer than nonstressed controls by entering the novel arm over min 1 and 2, while controls decrease entries into the novel arm after min 1 (**c**). Rats were injected with 17β-estradiol 2 h prior to the first trial of the Y-maze, as was done previously, and did not alter performance. The mechanism for 17β-estradiol action here was not likely from changes in CA1 spines as the timeline is too brief; however, these data emphasize a role for chronic stress influencing a PFC-mediated function. Data represent means ± S.E.M. Note: $*p<0.05$ for panels a and b. In panel c, means with different letters indicate values that are statistically different ($p<0.05$, i.e., compare "a" vs. "b"), whereas means with similar letters represent values that are statistically similar (i.e., compare "a" vs. "a")

These data suggest that levels of GC, as well as gonadal hormones, play a major role in the pattern of dendritic retraction following chronic stress and likely influence behavior as well.

The amygdala is another region that is highly involved in the morphological and functional effects of stress. The amygdala is critical for the processing of emotionally salient events [18, 240, 241] and mediates the effects of stress and GCs on a variety of cognitive functions [242, 243]. The basolateral amygdala (BLA), a subregion of the amygdala, modulates the function of other limbic brain regions in the presence of GCs. Specifically, inactivation of the BLA inhibits hippocampal memory consolidation and retrieval following administration of GCs [24, 244–246], and the BLA mediates GC-induced working memory impairments [247]. These studies demonstrate the interactive nature of the amygdala with stress-related changes in the function of other limbic regions.

Alterations in amygdala morphology and function may be involved in sex differences following chronic stress. The amygdala is necessary for acquisition of fear conditioning [22, 248], which is enhanced by chronic stress in males [23, 249] or GC [24]. Similarly, chronic stress enhances dendritic arborization in the amygdala of males [117, 123, 250], a mechanism that may contribute to enhanced acquisition of fear conditioning. Moreover, stress-induced enhanced acquisition of fear conditioning extends to the human literature. Stress-induced levels of GC correlate with enhanced acquisition [251] and consolidation [252] of fear conditioning in men, while neither acquisition nor consolidation of fear conditioning correlates with GC levels in women [251, 252]. In females, chronic stress effects on amygdala morphology are unknown, but chronic stress impairs recall of the fear conditioning experience [27], which seems to contradict the outcome in males as males remember the fear conditioning experience [27]. This sex difference is also observed with acute stress, whereby acute stress impairs classical conditioning in females and facilitates conditioning in males [253–256]. Subsequent studies show that the BLA reverses these sex differences; BLA inactivation produces functional classical conditioning in acutely stressed females and impairs classical conditioning in acutely stressed males [257]. Combined, these data support the speculation that the impairments in the recall of fear conditioning expressed in chronically stressed females likely reflect chronic stress-

induced changes in the amygdala. Whether reduced dendritic arborization or another mechanism contributes to the functional outcomes observed in the chronically stressed females has yet to be empirically tested.

## Summary and Model

How chronic stress influences limbic morphology and function is complicated, as sex differences are clearly

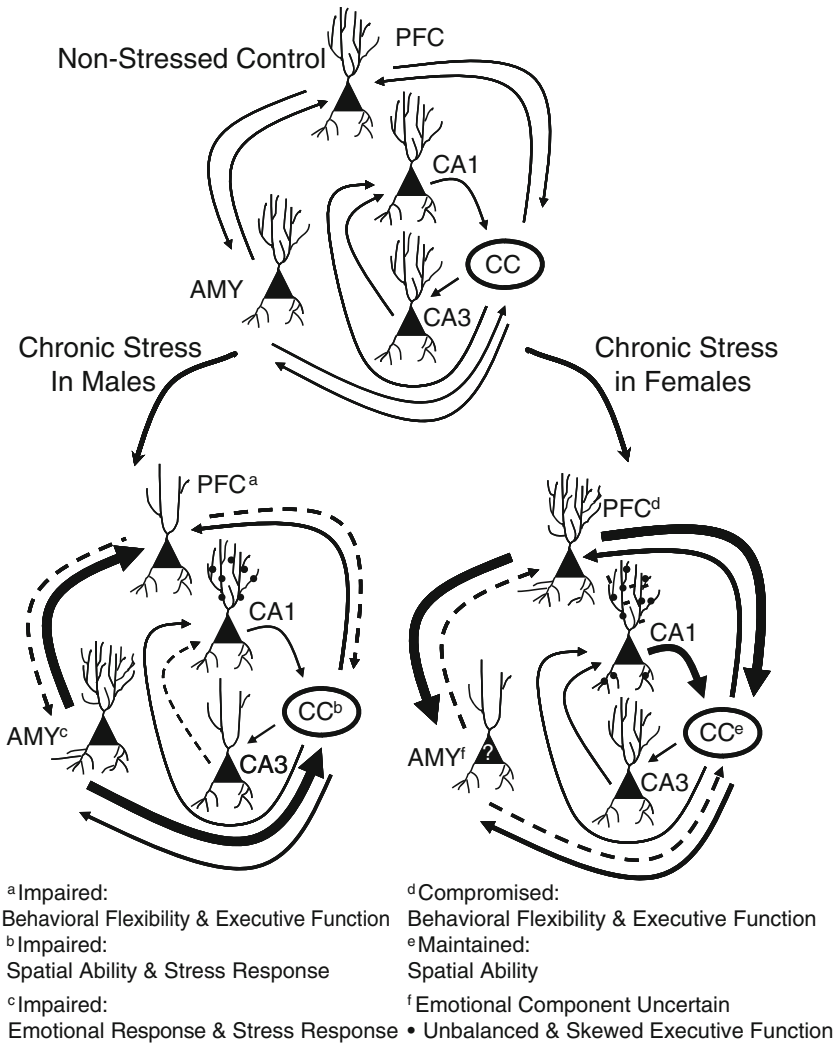


**Fig. 3** Schematic of the general neurocircuitry connecting the hippocampus, PFC, and amygdala. Limbic structures described in this review include the hippocampal subregions (CA1, CA3), prefrontal cortex (*PFC*), and the amygdala (*AMY*). For simplicity, cortical connections (*CC*) into and out of the hippocampus are illustrated with a single cortical structure, referring to many cortical regions such as the entorhinal cortex, parahippocampal regions, etc. *Top figure*, In an unstressed, gonadally intact system, reciprocal connections among the PFC, AMY, and C are represented with *equally weighted arrows* (i.e., similar thickness) to show a balanced influence among the structures. Within the hippocampus, information tends to flow from the CC to the CA3 and fewer connections from the CC to the CA1, then from the CA3 region to the CA1, and from the CA1 region back to the CC. The *arrowheads* indicate the direction of information flow. Predominate connections are listed for simplicity. *Bottom left*, Schematic of the morphological changes produced in dendritic structure of the PFC, hippocampus, and AMY in males following chronic stress. Chronic stress produces substantial dendritic retraction in the CA3 region of the hippocampus and the PFC, with enhanced dendritic complexity in the AMY. Chronic stress also enhances the number of mature spines on the CA1 apical region (indicated with *circles*). The result is altered functional output as follows: impaired spatial ability (hippocampus), impaired behavioral flexibility (*PFC*), enhanced emotional arousal (*AMY*). *Bottom right*, Schematic of the morphological changes produced in the dendritic structure of the PFC, hippocampus, and amygdala in gonadally intact females following chronic stress. Chronic stress produces negligible dendritic changes in the CA3 region of the hippocampus, but enhanced dendritic hypertrophy in the PFC, with unknown changes in the AMY, although we predict dendritic hypertrophy based upon behavioral data. However, the *question mark* on the AMY represents the uncertainty of this outcome. Chronic stress also enhances the number of mature spines on the CA1 basal region (indicated with *circles*), while gonadal hormones such as 17β-estradiol increase apical dendritic spine density (indicated by *hatches*). The result is altered functional output as follows: functional spatial ability (hippocampus), altered behavioral flexibility (*PFC*), and altered emotional arousal (*AMY*). For connectivity, the *arrowhead* indicates the direction of information flow. *Bold and dashed lines* represent functionality, with *bold lines* representing enhanced influence and *dashed lines* representing weakened/altered influence

impacted by gonadal hormones and vice versa. The hippocampus, PFC, and amygdala are just three brain regions discussed that are highly interconnected, express sensitivity to stress and gonadal hormones, and influence a variety of cognitive abilities. In males, chronic stress-induced morphological changes in these brain structures parallel changes in cognition. Given the substantial morphological changes in males, it is not surprising that males show robust behavioral alterations following chronic stress. In contrast, chronic stress causes relatively moderate morphological changes and subsequent behavioral outcomes in gonadally intact, cycling females. Therefore, changes in behavior may reflect the corresponding changes in limbic morphology.

The neuromorphological and functional outcomes following chronic stress in males are represented in a schematic (Fig. 3). Chronic stress in males produces substantial CA3 and PFC neuronal dendritic retraction, while the amygdala shows dendritic hypertrophy. The consequence is a disruption of balance among these structures and behavioral outcomes reflecting impaired spatial ability from the hippocampus, reduced behavioral flexibility and executive function from the PFC, and elevated emotional arousal from the amygdala. Dashed arrows illustrate weakened/altered input, while bold arrows illustrate enhanced influence. Males also experience enhanced numbers of CA1 spine heads (mature synapses) following chronic stress. Notice that although the CA3 contribution to the CA1 region is mitigated by chronic stress, other inputs are still viable, including some cortical afferents (CC). Consequently, the combination of enhanced synaptic maturation on CA1 neurons and the maintenance of some connections to the CA1 makes it not too surprising that spatial ability can be resurrected in chronically stressed males under some circumstances [112, 134].

The neuromorphological and functional outcomes following chronic stress in females are also represented (Fig. 3). Chronic stress in gonadally intact, cycling females produces negligible CA3 dendritic retraction, PFC neuronal dendritic hypertrophy, with unknown morphological alterations in the amygdala. Behavior outcomes reflect intact spatial ability from the hippocampus, altered behavioral flexibility, and executive function from the PFC, and we predict reduced emotional arousal from the amygdala based upon our recent work. Moreover, the CA1 region expresses enhanced mature spines on apical and basal dendrites in response to gonadal hormones and chronic stress, respectively. These spines are proposed to allow the hippocampus to remain somewhat functional despite the chronic stress history. Consequently, the balance among the limbic brain regions is less skewed in females than in males following chronic stress. Therefore, chronic stress in gonadally intact females may allow them to maintain some behavioral outcomes, such as spatial ability, compared to their male counterparts. It should be noted that OVX produces substantial CA3 dendritic retraction (not illustrated), and yet OVX females show functional spatial ability. Understanding the changes in limbic brain structure beyond the hippocampus is hypothesized to yield insight into these functional outcomes.

While this review focused on changes in neuronal morphology of limbic structures, numerous other mechanisms likely contribute to sex differences observed in response to chronic stress. Such mechanisms include, but are certainly not restricted to, differences in corticosteroid receptor properties and sensitivity [176, 177, 258, 259] and alterations in neurochemistry, including changes in serotonin, dopamine, norepinephrine, and gamma-aminobutyric acid [12, 188, 260–263]. However, the structural changes described require substantial remodeling in order to restore these structures to their pre-stress condition. In some cases, these structural changes do not fully recover, even a month following the termination of the chronic stress paradigm [250]. Therefore, these structural changes are hypothesized to give rise to one's susceptibility to environmental influences, and in combination, these limbic regions can be damaged permanently (for review, see [264, 265]).

The frequency with which stress, sex, and gonadal hormones are implicated in a variety of human conditions emphasizes the importance of studying these variables, and it increases recognition of gender discrepancies in susceptibility and development of stress-related illness. As we begin to unravel the complexity of brain plasticity and function, which includes a variety of brain structures and behaviors, we increase the awareness of the neuromorphological and functional similarities among disorders such as MDD, PTSD, and Alzheimer's disease.

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## References

1. Hamann S, Canli T (2004) Individual differences in emotion processing. Curr Opin Neurobiol 14(2):233–238
2. Eichenbaum H, Yonelinas AP, Ranganath C (2007) The medial temporal lobe and recognition memory. Annu Rev Neurosci 30:123–152
3. Lipton PA, Eichenbaum H (2008) Complementary roles of hippocampus and medial entorhinal cortex in episodic memory. Neural Plast 2008:1–8
4. Bird CM, Burgess N (2008) The hippocampus and memory: insights from spatial processing. Nat Rev Neurosci 9(3):182–194
5. Burgess N (2008) Spatial cognition and the brain. Ann N Y Acad Sci 1124:77–97
6. O'Keefe J, Nadel L (1978) The hippocampus as a cognitive map. Clarendon, Oxford

7. Kesner RP, Hopkins RO (2006) Mnemonic functions of the hippocampus: a comparison between animals and humans. Biol Psychol 73(1):3–18
8. Aggleton JP, Hunt PR, Rawlins JN (1986) The effects of hippocampal lesions upon spatial and non-spatial tests of working memory. Behav Brain Res 19:133–146
9. Kessels RP, de Haan EH, Kappelle LJ, Postma A (2001) Varieties of human spatial memory: a meta-analysis on the effects of hippocampal lesions. Brain Res Brain Res Rev 35 (3):295–303
10. Morris RGM, Garrud P, Rawlins JNP, O'Keefe J (1982) Place navigation impaired in rats with hippocampal lesions. Nature 297:681–683
11. McEwen BS, Milner TA (2007) Hippocampal formation: shedding light on the influence of sex and stress on the brain. Brain Res Rev 55(2):343–355
12. Luine V (2002) Sex differences in chronic stress effects on memory in rats. Stress 5(3):205–216
13. Luine VN, Beck KD, Bowman RE, Frankfurt M, Maclusky NJ (2007) Chronic stress and neural function: accounting for sex and age. J Neuroendocrinol 19(10):743–751
14. Ragozzino ME (2007) The contribution of the medial prefrontal cortex, orbitofrontal cortex, and dorsomedial striatum to behavioral flexibility. Ann N Y Acad Sci 1121:355–375
15. Dalley JW, Cardinal RN, Robbins TW (2004) Prefrontal executive and cognitive functions in rodents: neural and neurochemical substrates. Neurosci Biobehav Rev 28(7):771–784
16. Cahill L, McGaugh JL (1998) Mechanisms of emotional arousal and lasting declarative memory. Trends Neurosci 21:294–299
17. LeDoux J (2000) The amygdala and emotion: a view through fear. In: Aggleton JP (ed) The amygdala: a functional analysis. Oxford University Press, New York, pp 289–310
18. LeDoux JE (2000) Emotion circuits in the brain. Annu Rev Neurosci 23:155–184
19. Diamond DM, Campbell AM, Park CR, Halonen J, Zoladz PR (2007) The temporal dynamics model of emotional memory processing: a synthesis on the neurobiological basis of stress-induced amnesia, flashbulb and traumatic memories, and the Yerkes–Dodson law. Neural Past 2007:1–33
20. Quirk GJ, Russo GK, Barron JL, Lebron K (2000) The role of ventromedial prefrontal cortex in the recovery of extinguished fear. J Neurosci 20(16):6225–6231
21. Gao YJ, Ren WH, Zhang YQ, Zhao ZQ (2004) Contributions of the anterior cingulate cortex and amygdala to pain- and fear-conditioned place avoidance in rats. Pain 110(1–2):343–353
22. Phillips RG, LeDoux JE (1992) Differential contribution of amygdala and hippocampus to cued and contextual fear conditioning. Behav Neurosci 106(2):274–285
23. Conrad CD, Magariños AM, LeDoux JE, McEwen BS (1999) Repeated restraint stress facilitates fear conditioning independently of causing hippocampal CA3 dendritic atrophy. Behav Neurosci 113(5):902–913
24. Conrad CD, MacMillan DD II, Tsekhanov S, Wright RL, Baran SE, Fuchs RE (2004) Influence of chronic corticosterone and glucocorticoid receptor antagonism in the amygdala on fear conditioning. Neurobiol Learn Mem 81(3):185–199
25. Miracle AD, Brace MF, Huyck KD, Singler SA, Wellman CL (2006) Chronic stress impairs recall of extinction of conditioned fear. Neurobiol Learn Mem 85(3):213–218
26. Garcia R, Spennato G, Nilsson-Todd L, Moreau JL, Deschaux O (2008) Hippocampal low-frequency stimulation and chronic mild stress similarly disrupt fear extinction memory in rats. Neurobiol Learn Mem 89(4):560–566
27. Baran SE, Armstrong CE, Niren DC, Hanna JJ, Conrad CD (2009) Chronic stress and sex differences on the recall of fear conditioning and extinction. Neurobiol Learn Mem 91:323–332
28. Cahill L (2005) His brain, her brain. Sci Am 292(5):40–47
29. Cahill L (2006) Why sex matters for neuroscience. Nat Rev Neurosci 7(6):477–484
30. Amaral DG, Lavenex P (2007) Hippocampal neuroanatomy. In: Andersen P, Morris RG, Amaral DG, Bliss T, O'Keefe J (eds) The hippocampus book. Oxford University Press, New York, pp 37–114
31. Smith TC, Wingard DL, Ryan MA, Kritz-Silverstein D, Slymen DJ, Sallis JF (2008) Prior assault and posttraumatic stress disorder after combat deployment. Epidemiology 19(3):505–512
32. Weber K, Rockstroh B, Borgelt J, Awiszus B, Popov T, Hoffmann K, Schonauer K, Watzl H, Propster K (2008) Stress load during childhood affects psychopathology in psychiatric patients. BMC Psychiatry 8:63
33. Kendler KS, Prescott CA (1999) A population-based twin study of lifetime major depression in men and women. Arch Gen Psychiatry 56(1):39–44
34. Patten SB, Stuart HL, Russell ML, Maxwell CJ, Arboleda-Florez J (2003) Epidemiology of major depression in a predominantly rural health region. Soc Psychiatry Psychiatr Epidemiol 38 (7):360–365
35. Paykel ES (2003) Life events and affective disorders. Acta Psychiatr Scand Suppl 108(418):61–66
36. Bale TL (2006) Stress sensitivity and the development of affective disorders. Horm Behav 50(4):529–533
37. Hammen C, Kim EY, Eberhart NK, Brennan PA (2009) Chronic and acute stress and the prediction of major depression in women. Depress Anxiety (in press). doi:10.1002/da.20571
38. Gold PW, Chrousos GP (2002) Organization of the stress system and its dysregulation in melancholic and atypical depression: high vs low CRH/NE states. Mol Psychiatry 7(3):254–275
39. Breslau N, Davis GC, Andreski P, Peterson EL, Schultz LR (1997) Sex differences in posttraumatic stress disorder. Arch Gen Psychiatry 54(11):1044–1048
40. Chida Y, Hamer M (2008) Chronic psychosocial factors and acute physiological responses to laboratory-induced stress in healthy populations: a quantitative review of 30 years of investigations. Psychol Bull 134(6):829–885
41. Weber K, Rockstroh B, Borgelt J, Awiszus B, Popov T, Hoffmann K, Schonauer K, Watzl H, Propster K (2008) Stress load during childhood affects psychopathology in psychiatric patients. BMC Psychiatry 8:63–72
42. Agid O, Kohn Y, Lerer B (2000) Environmental stress and psychiatric illness. Biomed Pharmacother 54(3):135–141
43. De Bellis MD, Baum AS, Birmaher B, Keshavan MS, Eccard CH, Boring AM, Jenkins FJ, Ryan ND (1999) A.E. Bennett Research Award. Developmental traumatology. Part I: biological stress systems. Biol Psychiatry 45(10):1259–1270
44. De Bellis MD, Thomas LA (2003) Biologic findings of post-traumatic stress disorder and child maltreatment. Curr Psychiatry Rep 5(2):108–117
45. Reus VI, Wolkowitz OM (2001) Antiglucocorticoid drugs in the treatment of depression. Expert Opin Investig Drugs 10:1789–1796
46. Brown ES, Varghese FP, McEwen BS (2004) Association of depression with medical illness: does cortisol play a role? Biol Psychiatry 55(1):1–9
47. Swaab DF, Bao AM, Lucassen PJ (2005) The stress system in the human brain in depression and neurodegeneration. Ageing Res Rev 4(2):141–194
48. Gomez RG, Fleming SH, Keller J, Flores B, Kenna H, Debattista C, Solvason B, Schatzberg AF (2006) The neuropsychological profile of psychotic major depression and its relation to cortisol. Biol Psychiatry 60:472–478
49. Reppermund S, Zihl J, Lucae S, Horstmann S, Kloiber S, Holsboer F, Ising M (2007) Persistent cognitive impairment in

depression: the role of psychopathology and altered hypothalamic–pituitary–adrenocortical (HPA) system regulation. Biol Psychiatry 62(5):400–406
50. Beck AT (2008) The evolution of the cognitive model of depression and its neurobiological correlates. Am J Psychiatry 165(8):969–977
51. Pardon MC, Rattray I (2008) What do we know about the long-term consequences of stress on ageing and the progression of age-related neurodegenerative disorders? Neurosci Biobehav Rev 32(6):1103–1120
52. Sotiropoulos I, Cerqueira JJ, Catania C, Takashima A, Sousa N, Almeida OF (2008) Stress and glucocorticoid footprints in the brain—the path from depression to Alzheimer's disease. Neurosci Biobehav Rev 32(6):1161–1173
53. Willner P (1997) Validity, reliability and utility of the chronic mild stress model of depression: a 10-year review and evaluation. Psychopharmacology 134:319–329
54. McEwen BS, Weiss JM, Schwartz LS (1968) Selective retention of corticosterone by limbic structures in rat brain. Nature 220:911–912
55. McEwen BS, Weiss JM, Schwartz LS (1969) Uptake of corticosterone by rat brain and its concentration by certain limbic structures. Brain Res 16:227–241
56. Sapolsky RM (2000) Glucocorticoids and hippocampal atrophy in neuropsychiatric disorders. Arch Gen Psychiatry 57:925–935
57. Bremner JD, Elzinga B, Schmahl C, Vermetten E (2008) Structural and functional plasticity of the human brain in posttraumatic stress disorder. Prog Brain Res 167:171–186
58. Bremner JD (2006) The relationship between cognitive and brain changes in posttraumatic stress disorder. Ann N Y Acad Sci 1071:80–86
59. Karl A, Schaefer M, Malta LS, Dörfel D, Rohleder N, Werner A (2006) A meta-analysis of structural brain abnormalities in PTSD. Neurosci Biobehav Rev 30:1004–1031
60. Gilbertson MW, Shenton ME, Ciazewski A, Kasai K, Lasko NB, Orr SP, Pitman RK (2002) Smaller hippocampal volume predicts pathological vulnerability to psychological trauma. Nat Neurosci 5:1242–1247
61. Lindauer RJ, Vlieger EJ, Jalink M, Olff M, Carlier IV, Majoie CB, den Heeten GJ, Gersons BP (2004) Smaller hippocampal volume in Dutch police officers with posttraumatic stress disorder. Biol Psychiatry 56(5):356–363
62. Wignall EL, Dickson JM, Vaughan P, Farrow TF, Wilkinson ID, Hunter MD, Woodruff PW (2004) Smaller hippocampal volume in patients with recent-onset posttraumatic stress disorder. Biol Psychiatry 56(11):832–836
63. Brown ES, Rush AJ, McEwen BS (1999) Hippocampal remodeling and damage by corticosteroids: implications for mood disorders. Neuropsychopharmacology 21:474–484
64. Bremner JD, Narayan M, Anderson ER, Staib LH, Miller HL, Charney DS (2000) Hippocampal volume reduction in major depression. Am J Psychiatry 157(1):115–117
65. Sheline YI, Gado MH, Kraemer HC (2003) Untreated depression and hippocampal volume loss. Am J Psychiatr 160(8):1516–1518
66. Campbell S, Marriott M, Nahmias C, MacQueen GM (2004) Lower hippocampal volume in patients suffering from depression: a meta-analysis. Am J Psychiatry 161(4):598–607
67. Lange C, Irle E (2004) Enlarged amygdala volume and reduced hippocampal volume in young women with major depression. Psychol Med 34(6):1059–1064
68. Vasic N, Walter H, Hose A, Wolf RC (2008) Gray matter reduction associated with psychopathology and cognitive dysfunction in unipolar depression: a voxel-based morphometry study. J Affect Disord 109(1–2):107–116
69. Sheline YI, Wang PW, Gado MH, Csernansky JC, Vannier MW (1996) Hippocampal atrophy in recurrent major depression. Proc Natl Acad Sci U S A 93:3908–3913
70. Vakili K, Pillay SS, Lafer B, Fava M, Renshaw PF, Bonello-Cintron CM, Yurgelun-Todd DA (2000) Hippocampal volume in primary unipolar major depression: a magnetic resonance imaging study. Biol Psychiatry 47(12):1087–1090
71. von Gunten A, Fox NC, Cipolotti L, Ron MA (2000) A volumetric study of hippocampus and amygdala in depressed patients with subjective memory problems. J Neuropsychiatry Clin Neurosci 12(4):493–498
72. Frodl T, Meisenzahl EM, Zetzsche T, Born C, Groll C, Jager M, Leinsinger G, Bottlender R, Hahn K, Moller HJ (2002) Hippocampal changes in patients with a first episode of major depression. Am J Psychiatry 159(7):1112–1118
73. Keller J, Shen L, Gomez RG, Garrett A, Solvason HB, Reiss A, Schatzberg AF (2008) Hippocampal and amygdalar volumes in psychotic and nonpsychotic unipolar depression. Am J Psychiatr 165(7):872–880
74. Sheline YI, Mittler BL, Mintun MA (2002) The hippocampus and depression. Eur Psychiatry 17(Suppl 3):300–305
75. Frodl TS, Koutsouleris N, Bottlender R, Born C, Jager M, Scupin I, Reiser M, Moller HJ, Meisenzahl EM (2008) Depression-related variation in brain morphology over 3 years: effects of stress? Arch Gen Psychiatry 65(10):1156–1165
76. Ahima RS, Harlan RE (1990) Charting of type II glucocorticoid receptor-like immunoreactivity in the rat central nervous system. Neuroscience 39(3):579–604
77. Ahima RS, Harlan RE (1991) Differential corticosteroid regulation of type II glucocorticoid receptor-like immunoreactivity in the rat central nervous system: topography and implications. Endocrinology 129(1):226–236
78. Ahima R, Krozowski Z, Harlan R (1991) Type I corticosteroid receptor-like immunoreactivity in the rat CNS: distribution and regulation by corticosteroids. J Comp Neurol 313(3):522–538
79. Herman JP, Figueiredo H, Mueller NK, Ulrich-Lai Y, Ostrander MM, Choi DC, Cullinan WE (2003) Central mechanisms of stress integration: hierarchical circuitry controlling hypothalamo-pituitary-adrenocortical responsiveness. Front Neuroendocrinol 24(3):151–180
80. Bremner JD, Vythilingam M, Vermetten E, Nazeer A, Adil J, Khan S, Staib LH, Charney DS (2002) Reduced volume of orbitofrontal cortex in major depression. Biol Psychiatry 51 (4):273–279
81. Coryell W, Nopoulos P, Drevets W, Wilson T, Andreasen NC (2005) Subgenual prefrontal cortex volumes in major depressive disorder and schizophrenia: diagnostic specificity and prognostic implications. Am J Psychiatry 162(9):1706–1712
82. Konarski JZ, McIntyre RS, Kennedy SH, Rafi-Tari S, Soczynska JK, Ketter TA (2008) Volumetric neuroimaging investigations in mood disorders: bipolar disorder versus major depressive disorder. Bipolar Disord 10(1):1–37
83. Brown ES, Woolston DJ, Frol AB (2008) Amygdala volume in patients receiving chronic corticosteroid therapy. Biol Psychiatry 63(7):705–709
84. Sheline YI, Gado MH, Price JL (1998) Amygdala core nuclei volumes are decreased in recurrent major depression. NeuroReport 9(9):2023–2028
85. Yoshikawa E, Matsuoka Y, Yamasue H, Inagaki M, Nakano T, Akechi T, Kobayakawa M, Fujimori M, Nakaya N, Akizuki N, Imoto S, Murakami K, Kasai K, Uchitomi Y (2006) Prefrontal cortex and amygdala volume in first minor or major depressive episode after cancer diagnosis. Biol Psychiatry 59(8):707–712
86. Frodl T, Meisenzahl E, Zetzsche T, Bottlender R, Born C, Groll C, Jager M, Leinsinger G, Hahn K, Moller HJ (2002)

Enlargement of the amygdala in patients with a first episode of major depression. Biol Psychiatry 51(9):708–714
87. Ramel W, Goldin PR, Eyler LT, Brown GG, Gotlib IH, McQuaid JR (2007) Amygdala reactivity and mood-congruent memory in individuals at risk for depressive relapse. Biol Psychiatry 61 (2):231–239
88. Kemp AH, Felmingham K, Das P, Hughes G, Peduto AS, Bryant RA, Williams LM (2007) Influence of comorbid depression on fear in posttraumatic stress disorder: an fMRI study. Psychiatry Res 155(3):265–259
89. Shin LM, Rauch SL, Pitman RK (2006) Amygdala, medial prefrontal cortex, and hippocampal function in PTSD. Ann N Y Acad Sci 1071:67–79
90. Shin LM, Wright CI, Cannistraro PA, Wedig MM, McMullin K, Martis B, Macklin ML, Lasko NB, Cavanagh SR, Krangel TS, Orr SP, Pitman RK, Whalen PJ, Rauch SL (2005) A functional magnetic resonance imaging study of amygdala and medial prefrontal cortex responses to overtly presented fearful faces in posttraumatic stress disorder. Arch Gen Psychiatry 62(3):273–281
91. Woon FL, Hedges DW (2008) Hippocampal and amygdala volumes in children and adults with childhood maltreatment-related posttraumatic stress disorder: a meta-analysis. Hippocampus 18(8):729–736
92. Becker JB, Arnold AP, Berkley KJ, Blaustein JD, Eckel LA, Hampson E, Herman JP, Marts S, Sadee W, Steiner M, Taylor J, Young E (2005) Strategies and methods for research on sex differences in brain and behavior. Endocrinology 146:1650–1673
93. Olff M, Langeland W, Draijer N, Gersons BP (2007) Gender differences in posttraumatic stress disorder. Psychol Bull 133 (2):183–204
94. Richter R, Flowers T (2008) Gendered dimensions of disaster care: critical distinctions in female psychosocial needs, triage, pain assessment, and care. Am J Disaster Med 3(1):31–37
95. Heller W (1993) Gender differences in depression: perspectives from neuropsychology. J Affect Disord 29(2–3):129–143
96. Kessler RC, McGonagle KA, Swartz M, Blazer DG, Nelson CB (1993) Sex and depression in the National Comorbidity Survey. I: Lifetime prevalence, chronicity and recurrence. J Affect Disord 29(2-3):85–96
97. Weissman MM, Bland R, Joyce PR, Newman S, Wells JE, Wittchen HU (1993) Sex differences in rates of depression: cross-national perspectives. J Affect Disord 29(2–3):77–84
98. Gao S, Hendrie HC, Hall KS, Hui S (1998) The relationships between age, sex, and the incidence of dementia and Alzheimer disease: a meta-analysis. Arch Gen Psychiatry 55(9):809–815
99. Azad NA, Al Bugami M, Loy-English I (2007) Gender differences in dementia risk factors. Gend Med 4(2):120–129
100. Altemus KL, Almi CR (1997) Neonatal hippocampal damage in rats: long-term spatial memory deficits and associations with magnitude of hippocampal damage. Hippocampus 7:403–414
101. Parry BL, Javeed S, Laughlin GA, Hauger R, Clopton P (2000) Cortisol circadian rhythms during the menstrual cycle and with sleep deprivation in premenstrual dysphoric disorder and normal control subjects. Biol Psychiatry 48(9):920–931
102. Kajantie E, Phillips DI (2006) The effects of sex and hormonal status on the physiological response to acute psychosocial stress. Psychoneuroendocrinology 31(2):151–178
103. Young EA, Altemus M (2004) Puberty, ovarian steroids, and stress. Ann N Y Acad Sci 1021:124–133
104. Endicott J (1993) The menstrual cycle and mood disorders. J Affect Disord 29(2–3):193–200
105. Goldstein JM, Jerram M, Poldrack R, Ahern T, Kennedy DN, Seidman LJ, Makris N (2005) Hormonal cycle modulates arousal circuitry in women using functional magnetic resonance imaging. J Neurosci 25(40):9309–9316
106. Protopopescu X, Pan H, Altemus M, Tuescher O, Polanecsky M, McEwen B, Silbersweig D, Stern E (2005) Orbitofrontal cortex activity related to emotional processing changes across the menstrual cycle. Proc Natl Acad Sci U S A 102(44):16060–16065
107. Genazzani AR, Pluchino N, Luisi S, Luisi M (2007) Estrogen, cognition and female ageing. Hum Reprod Update 13(2):175–187
108. Garcia-Bueno B, Caso JR, Leza JC (2008) Stress as a neuro-inflammatory condition in brain: damaging and protective mechanisms. Neurosci Biobehav Rev 32(6):1136–1151
109. Buynitsky T, Mostofsky DI (2009) Restraint stress in biobehavioral research: recent developments. Neurosci Biobehav Rev 33:1089–1098
110. Conrad CD, Galea LAM, Kuroda Y, McEwen BS (1996) Chronic stress impairs rat spatial memory on the Y-maze, and this effect is blocked by tianeptine pretreatment. Behav Neurosci 110(6):1321–1334
111. Wright RL, Conrad CD (2005) Chronic stress leaves novelty-seeking intact while impairing spatial recognition memory in the Y-maze. Stress 8(2):151–154
112. Wright RL, Lightner EN, Harman JS, Meijer OC, Conrad CD (2006) Attenuating corticosterone levels on the day of memory assessment prevents chronic stress-induced impairments in spatial memory. Eur J NeuroSci 24:595–605
113. Kleen JK, Sitomer MT, Killeen PR, Conrad CD (2006) Chronic stress impairs spatial memory and motivation for reward without disrupting motor ability and motivation to explore. Behav Neurosci 120(4):842–851
114. Bellani R, Luecken L, Conrad CD (2006) Peripubertal anxiety profile can predict spatial memory impairments following chronic stress. Behav Brain Res 166(2):263–270
115. Duman RS (2004) Depression: a case of neuronal life and death? Biol Psychiatry 56(3):140–145
116. Dranovsky A, Hen R (2006) Hippocampal neurogenesis: regulation by stress and antidepressants. Biol Psychiatry 59 (12):1136–1143
117. Vyas A, Mitra R, Shankaranarayana Rao BS, Chattarji S (2002) Chronic stress induces contrasting patterns of dendritic remodeling in hippocampal and amygdaloid neurons. J Neurosci 22:6810–6818
118. McLaughlin KJ, Gomez JL, Baran SE, Conrad CD (2007) The effects of chronic stress on hippocampal morphology and function: an evaluation of chronic restraint paradigms. Brain Res 1161:56–64
119. Magariños AM, McEwen BS, Flügge G, Fuchs E (1996) Chronic psychosocial stress causes apical dendritic atrophy of hippocampal CA3 pyramidal neurons in subordinate tree shrews. J Neurosci 16:3534–3540
120. Cook SC, Wellman CL (2004) Chronic stress alters dendritic morphology in rat medial prefrontal cortex. J Neurobiol 60 (2):236–248
121. Brown SM, Henning S, Wellman CL (2005) Mild, short-term stress alters dendritic morphology in rat medial prefrontal cortex. Cereb Cortex 15(11):1714–1722
122. Radley JJ, Sisti HM, Hao J, Rocher AB, McCall T, Hof PR, McEwen BS, Morrison JH (2004) Chronic behavioral stress induces apical dendritic reorganization in pyramidal neurons of the medial prefrontal cortex. Neuroscience 125:1–6
123. Vyas A, Jadhav S, Chattarji S (2006) Prolonged behavioral stress enhances synaptic connectivity in the basolateral amygdala. Neuroscience 143(2):387–393
124. Cui H, Sakamoto H, Higashi S, Kawata M (2008) Effects of single-prolonged stress on neurons and their afferent inputs in the amygdala. Neuroscience 152(3):703–712
125. Colla M, Kronenberg G, Deuschle M, Meichel K, Hagen T, Bohrer M, Heuser I (2007) Hippocampal volume reduction and

HPA-system activity in major depression. J Psychiatry Res 41 (7):553–560
126. Watanabe Y, Gould E, Daniels DC, Cameron H, McEwen BS (1992) Tianeptine attenuates stress-induced morphological changes in the hippocampus. Eur J Pharmacol 222:157–162
127. Luo L, Tan RX (2001) Fluoxetine inhibits dendrite atrophy of hippocampal neurons by decreasing nitric oxide synthase expression in rat depression model. Acta Pharmacol Sin 22 (10):865–870
128. Bao AM, Meynen G, Swaab DF (2008) The stress system in depression and neurodegeneration: focus on the human hypothalamus. Brain Res Rev 57:531–553
129. Purves D, Lichtman JW (1985) Geometrical differences among homologous neurons in mammals. Science 228(4697):298–302
130. Schaefer AT, Larkum ME, Sakmann B, Roth A (2003) Coincidence detection in pyramidal neurons is tuned by their dendritic branching pattern. J Neurophysiol 89(6):3143–3154
131. Spruston N (2008) Pyramidal neurons: dendritic structure and synaptic integration. Nat Rev Neurosci 9(3):206–221
132. Cove J, Blinder P, Baranes D (2009) Contacts among non-sister dendritic branches at bifurcations shape neighboring dendrites and pattern their synaptic inputs. Brain Res 1251:30–41
133. Martinez JL Jr, Barea-Rodriguez EJ (1997) How the brain stores information: Hebbian mechanisms. In: Lueer G, Lass U (eds) Erinnern und Behalten Wege zur Erforschung des menschlichen gedaechtnisses. Vandenhoeck & Ruprecht, Goettingen, pp 39–59
134. Conrad CD (2006) What is the functional significance of chronic stress-induced CA3 dendritic retraction within the hippocampus? Behav Cogn Neurosci Rev 5(1):41–60
135. Pittenger C, Duman RS (2008) Stress, depression, and neuroplasticity: a convergence of mechanisms. Neuropsychopharmacology 33(1):88–109
136. Calabrese F, Molteni R, Racagni G, Riva MA (2009) Neuronal plasticity: a link between stress and mood disorders. Psychoneuroendocrinology (in press). doi:10.1016/j.psyneuen.2009.05.014
137. Grossman AW, Churchill JD, McKinney BC, Kodish IM, Otte SL, Greenough WT (2003) Experience effects on brain development: possible contributions to psychopathology. J Child Psychol Psychiatry 44(1):33–63
138. Fiala JC, Spacek J, Harris KM (2002) Dendritic spine pathology: cause or consequence of neurological disorders? Brain Res Rev 39(1):29–54
139. Sjostrom PJ, Rancz EA, Roth A, Hausser M (2008) Dendritic excitability and synaptic plasticity. Physiol Rev 88(2):769–840
140. Viau V (2002) Functional cross-talk between the hypothalamic–pituitary–gonadal and –adrenal axes. J Neuroendocrinol 14 (6):506–513
141. Aloisi AM, Bonifazi M (2006) Sex hormones, central nervous system and pain. Horm Behav 50(1):1–7
142. Altemus M, Redwine L, Leong Y, Yoshikawa T, Yehuda R, Detera-Wadleigh S, Murphy DL (1997) Reduced sensitivity to glucocorticoid feedback and reduced glucocorticoid receptor mRNA expression in the luteal phase of the menstrual cycle. Neuropsychopharmacology 17:100–109
143. Viau V, Meaney MJ (1991) Variations in the hypothalamic–pituitary–adrenal response to stress during the estrous cycle in the rat. Endocrinology 129(5):2503–2511
144. Atkinson HC, Waddell BJ (1997) Circadian variation in basal plasma corticosterone and adrenocorticotropin in the rat: sexual dimorphism and changes across the estrous cycle. Endocrinology 138(9):3842–3848
145. Haim S, Shakhar G, Rossene E, Taylor AN, Ben-Eliyahu S (2003) Serum levels of sex hormones and corticosterone throughout 4- and 5-day estrous cycles in Fischer 344 rats and their simulation in ovariectomized females. J Endocrinol Invest 26(10):1013–1022
146. Conrad CD, Jackson JL, Wieczorek L, Baran SE, Harman JS, Wright RL, Korol DL (2004) Acute restraint stress impairs spatial memory in male but not female rats: influence of estrous cycle. Pharmacol Biochem Behav 78(3):569–579
147. Dalla C, Antoniou K, Drossopoulou G, Xagoraris M, Kokras N, Sfikakis A, Papadopoulou-Daifoti Z (2005) Chronic mild stress impact: are females more vulnerable? Neuroscience 135(3):703–714
148. McEwen BS, Conrad CD, Kuroda Y, Frankfurt M, Magariños AM, McKittrick C (1997) Prevention of stress-induced morphological and cognitive consequences. Eur Neuropsychopharm 7: S323–S328
149. McEwen BS, Magariños AM (1997) Stress effects on morphology and function of the hippocampus. Ann N Y Acad Sci 821:271–284
150. McEwen BS (2005) Glucocorticoids, depression, and mood disorders: structural remodeling in the brain. Metabolism 54 (5 Suppl 1):20–23
151. Lambert KG, Buckelew SK, Staffiso-Sandoz G, Gaffga S, Carpenter W, Fisher J, Kinsely CH (1998) Activity-stress induces atrophy of apical dendrites of hippocampal pyramidal neurons in male rats. Physiol Behav 65:43–49
152. Sousa N, Lukoyanov NV, Madeira MD, Almeida OFX, Paula-Barbosa MM (2000) Reorganization of the morphology of hippocampal neurites and synapses after stress-induced damage correlates with behavioral improvement. Neuroscience 97:253–266
153. Woolley CS, Gould E, McEwen BS (1990) Exposure to excess glucocorticoids alters dendritic morphology of adult hippocampal pyramidal neurons. Brain Res 531:225–231
154. Magariños AM, McEwen BS (1995) Stress-induced atrophy of apical dendrites of hippocampal CA3c neurons: comparison of stressors. Neuroscience 69(1):83–88
155. Sandi C, Davies HA, Cordero MI, Rodriquez JJ, Popov VI, Stewart MG (2003) Rapid reversal of stress induced loss of synapses in CA3 of rat hippocampus following water maze training. Eur J NeuroSci 17:2447–2456
156. Fuchs E, Uno H, Flügge G (1995) Chronic psychosocial stress induces morphological alterations in hippocampal pyramidal neurons of the tree shrew. Brain Res 673(2):275–282
157. Conrad CD, McLaughlin KJ, Harman JS, Foltz C, Wieczorek L, Lightner E, Wright RL (2007) Chronic glucocorticoids increase hippocampal vulnerability to neurotoxicity under conditions that produce CA3 dendritic retraction but fail to impair spatial recognition memory. J Neurosci 27(31):8278–8285
158. Luine VN, Spencer RL, McEwen BS (1993) Effects of chronic corticosterone ingestion on spatial memory performance and hippocampal serotonergic function. Brain Res 616:65–70
159. Luine V, Villegas M, Martinez C, McEwen BS (1994) Repeated stress causes reversible impairments of spatial memory performance. Brain Res 639:167–170
160. Park CR, Campbell AM, Diamond DM (2001) Chronic psychosocial stress impairs learning and memory and increases sensitivity to yohimbine in rats. Biol Psychiatry 50:994–1004
161. Gerges NZ, Alzoubi KH, Park CR, Diamond DM, Alkadhi KA (2004) Adverse effect of the combination of hypothyroidism and chronic psychosocial stress on hippocampus-dependent memory in rats. Behav Brain Res 155(1):77–84
162. Srivareerat M, Tran TT, Alzoubi KH, Alkadhi KA (2009) Chronic psychosocial stress exacerbates impairment of cognition and long-term potentiation in beta-amyloid rat model of Alzheimer's disease. Biol Psychiatry 65(11):918–926
163. Sunanda, Shankaranarayana Rao BS, Raju TR (2000) Chronic restraint stress impairs acquisition and retention of spatial memory task in rats. Curr Sci 79:14581–1584
164. Ohl F, Fuchs E (1999) Differential effects of chronic stress on memory processes in the tree shrew. Cogn Brain Res 7:379–387

165. Venero C, Tilling T, Hermans-Borgmeyer I, Schmidt R, Schachner M, Sandi C (2002) Chronic stress induces opposite changes in the mRNA expression of the cell adhesion molecules NCAM and L1. Neuroscience 115(4):1211–1219
166. Wright RL, Conrad CD (2008) Enriched environment prevents chronic stress-induced spatial learning and memory deficits. Behav Brain Res 187(1):41–47
167. Ma WP, Cao J, Tian M, Cui MH, Han HL, Yang YX, Xu L (2007) Exposure to chronic constant light impairs spatial memory and influences long-term depression in rats. Neurosci Res 59(2):224–230
168. Song L, Che W, Min-Wei W, Murakami Y, Matsumoto K (2006) Impairment of the spatial learning and memory induced by learned helplessness and chronic mild stress. Pharmacol Biochem Behav 83(2):186–193
169. Walesiuk A, Trofimiuk E, Braszko JJ (2005) Gingko biloba extract diminishes stress-induced memory deficits in rats. Pharmacol Rep 57(2):176–187
170. Watanabe Y, Gould E, Cameron HA, Daniels DC, McEwen BS (1992) Phenytoin prevents stress- and corticosterone-induced atrophy of CA3 pyramidal neurons. Hippocampus 2(4):431–436
171. Lathe R (2001) Hormones and hippocampus. J Endocrinol 169:205–231
172. Galea LAM, McEwen BS, Tanapat P, Deak T, Spencer RL, Dhabhar FS (1997) Sex differences in dendritic atrophy of CA3 pyramidal neurons in response to chronic restraint stress. Neuroscience 81(3):689–697
173. McLaughlin KJ, Wilson JO, Harman J, Wright RL, Wieczorek L, Gomez J, Korol DL, Conrad CD (2009) Chronic 17β-estradiol or cholesterol prevents stress-induced hippocampal CA3 dendritic retraction in ovariectomized females: possible correspondence between CA1 spine properties and spatial acquisition. Hippocampus (in press)
174. McLaughlin KJ, Baran SE, Wright RL, Conrad CD (2005) Chronic stress enhances spatial memory in ovariectomized female rats despite CA3 dendritic retraction: possible involvement of CA1 neurons. Neuroscience 135(4):1045–1054
175. Bowman RE, Zrull MC, Luine VN (2001) Chronic restraint stress enhances radial arm maze performance in female rats. Brain Res 904:279–289
176. Kitraki E, Kremmyda O, Youlatos D, Alexis MN, Kittas C (2004) Gender-dependent alterations in corticosteroid receptor status and spatial performance following 21 days of restraint stress. Neuroscience 125:47–55
177. Kitraki E, Kremmyda O, Youlatos D, Alexis M, Kittas C (2004) Spatial performance and corticosteroid receptor status in the 21-day restraint stress paradigm. Ann N Y Acad Sci 1018:323–327
178. Conrad CD, Grote KA, Hobbs RJ, Ferayorni A (2003) Sex differences in spatial and non-spatial Y-maze performance after chronic stress. Neurobiol Learn Mem 79:32–40
179. Bowman RE, Ferguson D, Luine VN (2002) Effects of chronic restraint stress and estradiol on open field activity, spatial memory, and monoaminergic neurotransmitters in ovariectomized rats. Neuroscience 113:401–410
180. McEwen BS, Alves SE (1999) Estrogen actions in the central nervous system. Endocr Rev 20(3):279–307
181. Lee SJ, McEwen BS (2001) Neurotrophic and neuroprotective actions of estrogens and their therapeutic implications. Annu Rev Pharmacol Toxicol 41:569–591
182. Loy R, Gerlach JL, McEwen BS (1988) Autoradiographic localization of estradiol-binding neurons in the rat hippocampal formation and entorhinal cortex. Brain Res 467(2):245–251
183. Blurton-Jones M, Tuszynski MH (2002) Estrogen receptor-beta colocalizes extensively with parvalbumin-labeled inhibitory neurons in the cortex, amygdala, basal forebrain, and hippocampal formation of intact and ovariectomized adult rats. J Comp Neurol 452(3):276–287
184. Kretz O, Fester L, Wehrenberg U, Zhou L, Brauckmann S, Zhao S, Prange-Kiel J, Naumann T, Jarry H, Frotscher M, Rune GM (2004) Hippocampal synapses depend on hippocampal estrogen synthesis. J Neurosci 24(26):5913–5921
185. Cornil CA, Ball GF, Balthazart J (2006) Functional significance of the rapid regulation of brain estrogen action: where do the estrogens come from? Brain Res 1126(1):2–26
186. Conrad CD, Jackson JL, Wise L (2004) Chronic stress enhances ibotenic acid-induced damage selectively within the hippocampal CA3 region of male, but not female rats. Neuroscience 125 (3):759–767
187. Takuma K, Matsuo A, Himeno Y, Hoshina Y, Ohno Y, Funatsu Y, Arai S, Kamei H, Mizoguchi H, Nagai T, Koike K, Inoue M, Yamada K (2007) 17β-Estradiol attenuates hippocampal neuronal loss and cognitive dysfunction induced by chronic restraint stress in ovariectomized rats. Neuroscience 146(1):60–68
188. Bowman RE, Beck KD, Luine VN (2003) Chronic stress effects on memory: sex differences in performance and monoaminergic activity. Horm Behav 43:48–59
189. Brun VH, Otnass MK, Molden S, Steffenach HA, Witter MP, Moser MB, Moser EI (2002) Place cells and place recognition maintained by direct entorhinal–hippocampal circuitry. Science 296(5576):2243–2246
190. Vago DR, Bevan A, Kesner RP (2007) The role of the direct perforant path input to the CA1 subregion of the dorsal hippocampus in memory retention and retrieval. Hippocampus 17(10):977–987
191. Brun VH, Leutgeb S, Wu HQ, Schwarcz R, Witter MP, Moser EI, Moser MB (2008) Impaired spatial representation in CA1 after lesion of direct input from entorhinal cortex. Neuron 57 (2):290–302
192. Kajiwara R, Wouterlood FG, Sah A, Boekel AJ, Baks-te Bulte LT, Witter MP (2008) Convergence of entorhinal and CA3 inputs onto pyramidal neurons and interneurons in hippocampal area CA1—an anatomical study in the rat. Hippocampus 18(3):266–280
193. Poirier GL, Amin E, Aggleton JP (2008) Qualitatively different hippocampal subfield engagement emerges with mastery of a spatial memory task by rats. J Neurosci 28:1034–1045
194. Vago DR, Kesner RP (2008) Disruption of the direct perforant path input to the CA1 subregion of the dorsal hippocampus interferes with spatial working memory and novelty detection. Behav Brain Res 189(2):273–283
195. Goodrich-Hunsaker NJ, Hunsaker MR, Kesner RP (2008) The interactions and dissociations of the dorsal hippocampus subregions: how the dentate gyrus, CA3, and CA1 process spatial information. Behav Neurosci 122(1):16–26
196. Hoang LT, Kesner RP (2008) Dorsal hippocampus, CA3, and CA1 lesions disrupt temporal sequence completion. Behav Neurosci 122(1):9–15
197. Hunsaker MR, Lee B, Kesner RP (2008) Evaluating the temporal context of episodic memory: the role of CA3 and CA1. Behav Brain Res 188(2):310–315
198. Okada K, Okaichi H (2009) Functional differentiation and cooperation among the hippocampal subregions in rats to effect spatial memory processes. Behav Brain Res 200(1):181–191
199. Nakazawa K, Sun LD, Quirk MC, Rondi-Reig L, Wilson MA, Tonegawa S (2003) Hippocampal CA3 NMDA receptors are crucial for memory acquisition of one-time experience. Neuron 38(2):305–315
200. Gold AE, Kesner RP (2005) The role of the CA3 subregion of the dorsal hippocampus in spatial pattern completion in the rat. Hippocampus 15(6):808–814
201. Lee I, Jerman TS, Kesner RP (2005) Disruption of delayed memory for a sequence of spatial locations following CA1- or

CA3-lesions of the dorsal hippocampus. Neurobiol Learn Mem 84(2):138–147
202. Maclusky NJ, Hajszan T, Prange-Kiel J, Leranth C (2006) Androgen modulation of hippocampal synaptic plasticity. Neuroscience 138:957–965
203. Cunningham RL, Claiborne BJ, McGinnis MY (2007) Pubertal exposure to anabolic androgenic steroids increases spine densities on neurons in the limbic system of male rats. Neuroscience 150(3):609–615
204. Hajszan T, MacLusky NJ, Leranth C (2008) Role of androgens and the androgen receptor in remodeling of spine synapses in limbic brain areas. Horm Behav 53(5):638–646
205. Prange-Kiel J, Rune GM (2006) Direct and indirect effects of estrogen on the rat hippocampus. Neuroscience 138:765–772
206. Woolley CS (2007) Acute effects of estrogen on neuronal physiology. Annu Rev Pharmacol Toxicol 47:657–680
207. McLaughlin KJ, Bimonte-Nelson HA, Neisewander JL, Conrad CD (2008) Assessment of estradiol influence on spatial tasks and hippocampal CA1 spines: evidence that the duration of hormone deprivation after ovariectomy compromises 17β-estradiol effectiveness in altering CA1 spines. Horm Behav 54(3):386–395
208. Woolley CS, Gould E, Frankfurt M, McEwen BS (1990) Naturally occurring fluctuation in dendritic spine density on adult hippocampal pyramidal neurons. J Neurosci 10:4035–4039
209. Woolley CS, McEwen BS (1992) Estradiol mediates fluctuation in hippocampal synapse density during the estrous cycle in the adult rat. J Neurosci 12(7):2549–2554
210. Woolley CS (1998) Estrogen-mediated structural and functional synaptic plasticity in the female rat hippocampus. Horm Behav 34:140–148
211. Garza-Meilandt A, Cantu RE, Claiborne BJ (2006) Estradiol's effects on learning and neuronal morphology vary with route of administration. Behav Neurosci 120(4):905–916
212. Wallace M, Luine V, Arellanos A, Frankfurt M (2006) Ovariectomized rats show decreased recognition memory and spine density in the hippocampus and prefrontal cortex. Brain Res 1126(1):176–182
213. Sandstrom NJ, Williams CL (2001) Memory retention is modulated by acute estradiol and progesterone replacement. Behav Neurosci 115:384–393
214. Sandstrom NJ, Williams CL (2004) Spatial memory retention is enhanced by acute and continuous estradiol replacement. Horm Behav 45(2):128–135
215. Donohue HS, Gabbott PLA, Davies HA, Rodriguez JJ, Cordero MI, Sandi C, Medvedev NI, Popov VI, Colyer FM, Peddie CJ, Stewart MG (2006) Chronic restraint stress induces changes in synapse morphology in stratum lacunosum-moleculare CA1 rat hippocampus: a stereological and three-dimensional ultrastructural study. Neuroscience 140(2):597–606
216. Shors TJ (2006) Significant life events and the shape of memories to come: a hypothesis. Neurobiol Learn Mem 85:103–115
217. Dalla C, Whetstone AS, Hodes GE, Shors TJ (2009) Stressful experience has opposite effects on dendritic spines in the hippocampus of cycling versus masculinized females. Neurosci Lett 449(1):52–56
218. Diamond DM, Campbell AM, Park CR, Woodson JC, Conrad CD, Bachstetter AD, Mervis R (2006) Influence of predator stress on the consolidation versus retrieval of long-term spatial memory and hippocampal spinogenesis. Hippocampus 16:571–576
219. Cerqueira JJ, Almeida OF, Sousa N (2008) The stressed prefrontal cortex. Left? Right!. Brain Behav Immun 22(5):630–638
220. Holmes A, Wellman CL (2009) Stress-induced prefrontal reorganization and executive dysfunction in rodents. Neurosci Biobehav Rev 33(6):773–783
221. Singewald N (2007) Altered brain activity processing in high-anxiety rodents revealed by challenge paradigms and functional mapping. Neurosci Biobehav Rev 31(1):18–40
222. Del Arco A, Segovia G, Garrido P, de Blas M, Mora F (2007) Stress, prefrontal cortex and environmental enrichment: studies on dopamine and acetylcholine release and working memory performance in rats. Behav Brain Res 176(2):267–273
223. Mizoguchi K, Yuzurihara M, Ishige A, Sasaki H, Chui DH, Tabira T (2000) Chronic stress induces impairment of spatial working memory because of prefrontal dopaminergic dysfunction. J Neurosci 20(4):1568–1574
224. Moghaddam B (1993) Stress preferentially increases extraneuronal levels of excitatory amino acids in the prefrontal cortex: comparison to hippocampus and basal ganglia. J Neurochem 60:1650–1557
225. Miner LH, Jedema HP, Moore FW, Blakely RD, Grace AA, Sesack SR (2006) Chronic stress increases the plasmalemmal distribution of the norepinephrine transporter and the coexpression of tyrosine hydroxylase in norepinephrine axons in the prefrontal cortex. J Neurosci 26(5):1571–1578
226. Herman JP, Ostrander MM, Mueller NK, Figueiredo H (2005) Limbic system mechanisms of stress regulation: hypothalamo-pituitary-adrenocortical axis. Prog Neuropsychopharmacol Biol Psychiatry 29(8):1201–1213
227. Liston C, Miller MM, Goldwater DS, Radley JJ, Rocher AB, Hof PR, Morrison JH, McEwen BS (2006) Stress-induced alterations in prefrontal cortical dendritic morphology predict selective impairments in perceptual attentional set-shifting. J Neurosci 26(30):7870–7874
228. Garrett JE, Wellman CL (2009) Chronic stress effects on dendritic morphology in medial prefrontal cortex: sex differences and estrogen dependence. Neuroscience 162(1):195–207
229. Izquierdo A, Wellman CL, Holmes A (2006) Brief uncontrollable stress causes dendritic retraction in infralimbic cortex and resistance to fear extinction in mice. J Neurosci 26(21):5733–5738
230. Seib LM, Wellman CL (2003) Daily injections alter spine density in rat medial prefrontal cortex. Neurosci Lett 337(1):29–32
231. Czéh B, Perez-Cruz C, Fuchs E, Flügge G (2008) Chronic stress-induced cellular changes in the medial prefrontal cortex and their potential clinical implications: does hemisphere location matter? Behav Brain Res 190(1):1–13
232. Cerqueira JJ, Pego JM, Taipa R, Bessa JM, Almeida OF, Sousa N (2005) Morphological correlates of corticosteroid-induced changes in prefrontal cortex-dependent behaviors. J Neurosci 25(34):7792–7800
233. Cerqueira JJ, Mailliet F, Almeida OF, Jay TM, Sousa N (2007) The prefrontal cortex as a key target of the maladaptive response to stress. J Neurosci 27(11):2781–2787
234. Grootendorst J, de Kloet ER, Vossen C, Dalm S, Oitzl MS (2001) Repeated exposure to rats has persistent genotype-dependent effects on learning and locomotor activity of apolipoprotein E knockout and C57Bl/6 mice. Behav Brain Res 125(1–2):249–259
235. Grootendorst J, de Kloet ER, Dalm S, Oitzl MS (2001) Reversal of cognitive deficit of apolipoprotein E knockout mice after repeated exposure to a common environmental experience. Neuroscience 108(2):237–247
236. Schwabe L, Dalm S, Schachinger H, Oitzl MS (2008) Chronic stress modulates the use of spatial and stimulus-response learning strategies in mice and man. Neurobiol Learn Mem 90(3):495–503
237. Wellman CL (2001) Dendritic reorganization in pyramidal neurons in medial prefrontal cortex after chronic corticosterone administration. Brain Res 828:127–134
238. Cerqueira JJ, Taipa R, Uylings HB, Almeida OF, Sousa N (2007) Specific configuration of dendritic degeneration in pyramidal neurons of the medial prefrontal cortex induced by differing corticosteroid regimens. Cereb Cortex 17(9):1998–2006

239. Wang VC, Sable HJ, Ju YH, Allred CD, Helferich WG, Korol DL, Schantz SL (2008) Effects of chronic estradiol treatment on delayed spatial alternation and differential reinforcement of low rates of responding. Behav Neurosci 122(4):794–804
240. Cahill L, Babinsky R, Markowitsch HJ, McGaugh JL (1995) The amygdala and emotional memory. Nature 377:295–296
241. Sarter M, Markowitsch HJ (1985) Involvement of the amygdala in learning and memory: a critical review, with emphasis on anatomical relations. Behav Neurosci 99(2):342–380
242. McGaugh JL, Roozendaal B (2002) Role of adrenal stress hormones in forming lasting memories in the brain. Curr Opin Neurobiol 12:205–210
243. Roozendaal B (2002) Stress and memory: opposing effects of glucocorticoids on memory consolidation and memory retrieval. Neurobiol Learn Mem 78:578–595
244. Roozendaal B, Portillo-Marquez G, McGaugh JL (1996) Basolateral amygdala lesions block glucocorticoid-induced modulation of memory for spatial learning. Behav Neurosci 110(5):1074–1083
245. Roozendaal B, McGaugh JL (1997) Basolateral amygdala lesions block the memory-enhancing effect of glucocorticoid administration in the dorsal hippocampus of rats. Eur J NeuroSci 9:76–83
246. Rodriguez Manzanares PA, Isoardi NA, Carrer HF, Molina VA (2005) Previous stress facilitates fear memory, attenuates GABAergic inhibition, and increases synaptic plasticity in the rat basolateral amygdala. J Neurosci 25(38):8725–8734
247. Roozendaal B, McReynolds JR, McGaugh JL (2004) The basolateral amygdala interacts with the medial prefrontal cortex in regulating glucocorticoid effects on working memory impairment. J Neurosci 24(6):1385–1392
248. Anglada-Figueroa D, Quirk GJ (2005) Lesions of the basal amygdala block expression of conditioned fear but not extinction. J Neurosci 25(42):9680–9685
249. Conrad CD, Mauldin-Jourdain ML, Hobbs RJ (2001) Metyrapone reveals that previous chronic stress differentially impairs hippocampal-dependent memory. Stress 4(4):305–318
250. Vyas A, Pillai AG, Chattarji S (2004) Recovery after chronic stress fails to reverse amygdaloid neuronal hypertrophy and enhanced anxiety-like behavior. Neuroscience 128(4):667–673
251. Jackson ED, Payne JD, Nadel L, Jacobs WJ (2006) Stress differentially modulates fear conditioning in healthy men and women. Biol Psychiatry 59(6):516–522
252. Zorawski M, Blanding NQ, Kuhn CM, LaBar KS (2006) Effects of stress and sex on acquisition and consolidation of human fear conditioning. Learn Mem 13(4):441–450
253. Shors TJ, Weiss C, Thompson RF (1992) Stress-induced facilitation of classical conditioning. Science 257:537–539
254. Bangasser DA, Shors TJ (2004) Acute stress impairs trace eyeblink conditioning in females without altering the unconditional response. Neurobiol Learn Mem 82:57–60
255. Wood GE, Shors TJ (1998) Stress facilitates classical conditioning in males, but impairs classical conditioning in females through activational effects of ovarian hormones. Proc Natl Acad Sci U S A 95(7):4066–4071
256. Shors TJ (2001) Acute stress rapidly and persistently enhances memory formation in the male rat. Neurobiol Learn Mem 75:10–29
257. Waddell J, Bangasser DA, Shors TJ (2008) The basolateral nucleus of the amygdala is necessary to induce the opposing effects of stressful experience on learning in males and females. J Neurosci 28(20):5290–5294
258. Turner BB (1997) Influence of gonadal steroids on brain corticosteroid receptors: a minireview. Neurochem Res 22 (11):1375–1385
259. Karandrea D, Kittas C, Kitraki E (2000) Contribution of sex and cellular context in the regulation of brain corticosteroid receptors following restraint stress. Neuroendocrinology 71:343–353
260. Alves SE, Hoskin E, Lee SJ, Brake WG, Ferguson D, Luine V, Allen PB, Greengard P, McEwen BS (2002) Serotonin mediates CA1 spine density but is not crucial for ovarian steroid regulation of synaptic plasticity in the adult rat dorsal hippocampus. Synapse 45(2):143–151
261. Beck KD, Luine VN (2002) Sex differences in behavioral and neurochemical profiles after chronic stress: role of housing conditions. Physiol Behav 75:661–673
262. Inoue T, Li XB, Abekawa T, Kitaichi Y, Izumi T, Nakagawa S, Koyama T (2004) Selective serotonin reuptake inhibitor reduces conditioned fear through its effect in the amygdala. Eur J Pharmacol 497(3):311–316
263. Mitsushima D, Yamada K, Takase K, Funabashi T, Kimura F (2006) Sex differences in the basolateral amygdala: the extracellular levels of serotonin and dopamine, and their responses to restraint stress in rats. Eur J NeuroSci 24(11):3245–3254
264. Conrad CD (2008) Chronic stress-induced hippocampal vulnerability: the glucocorticoid vulnerability hypothesis. Rev Neurosci 19(6):395–412
265. Conrad CD, Wright RL, McLaughlin KJ (2009) Stress and vulnerability to brain damage. In: Squire LR (ed) Encyclopedia of neuroscience. Academic, Oxford, pp 481–488
266. Foy MR, Baudry M, Briton RD, Thompson RF (2008) Estrogen and hippocampal plasticity in rodent models. J Alzheim Dis 15:589–603
267. Foy MR, Baudry M, Foy JG, Thompson RF (2008) 17b-estradiol modifies stress-induced and age-related changes in hippocampal synaptic plasticity. Behav Neurosci 122(2):301–309