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Sex differences and chronic stress effects on the neural circuitry underlying fear conditioning and extinction

Mollee R. Farrell *, Dale R. Sengelaub, Cara L. Wellman

Department of Psychological & Brain Sciences, Program in Neuroscience, and Center for the Integrative Study of Animal Behavior, Indiana University, Bloomington, IN 47405, United States

HIGHLIGHTS

- Expression and rates of stress-dependent psychopathology are sex-dependent.
- Remodeling of fear circuits may contribute to sex differences in psychopathology.
- Sex and stress alter medial prefrontal cortex dendritic morphology.
- There are sex-dependent stress effects on fear conditioning and extinction.
- Dendritic remodeling may underlie sex and stress effects on emotional learning.

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ABSTRACT

There are sex differences in the rates of many stress-sensitive psychological disorders such as posttraumatic stress disorder (PTSD). As medial prefrontal cortex and amygdala are implicated in many of these disorders, understanding differential stress effects in these regions may shed light on the mechanisms underlying sex-dependent expression of disorders like depression and anxiety. Prefrontal cortex and amygdala are key regions in the neural circuitry underlying fear conditioning and extinction, which thus has emerged as a useful model of stress influences on the neural circuitry underlying regulation of emotional behavior. This review outlines the current literature on sex differences and stress effects on dendritic morphology within medial prefrontal cortex and basolateral amygdala. Such structural differences and/or alterations can have important effects on fear conditioning and extinction, behaviors that are mediated by the basolateral amygdala and prefrontal cortex, respectively. Given the importance of extinction-based exposure therapy as a treatment for anxiety disorders such as PTSD, understanding the neural mechanisms by which stress differentially influences fear learning and extinction in males and females is an important goal for developing sex-appropriate interventions for stress-related disorders.

1. Chronic stress, psychopathology, and corticolimbic structure and function

Women are more susceptible than men to stress-related mental illness and twice as likely to experience depression [1,2]. There is also a greater incidence of most types of anxiety disorders, such as social anxiety, phobias, and posttraumatic stress disorder (PTSD), among women compared to men [3]. However, after women experience menopause, a stage of life marked by a pronounced decline in ovarian hormones, this sex difference diminishes [4,5]. In women, depression is also more likely to occur during periods of hormonal fluctuation, such as prior to menses, immediately after pregnancy, and during and after menopause [6,7]. Thus, there may be a role for the cyclic release of ovarian hormones in exacerbating the high incidence of stress-sensitive psychological disorders in women.

Chronic stress is linked to cognitive and emotional dysfunctions. For instance, stressful life events play a role in precipitating episodes of major depression, and can trigger posttraumatic stress disorder [8,9]. Chronic stress also has detrimental effects on many behaviors. For instance, several studies have demonstrated stress-induced deficits on a variety of cognitive tasks, including fear conditioning and retrieval of extinction, attentional set-shifting, spatial learning and recognition, and working memory [reviewed in 10–13]. However, it is not well understood how stress acts on the brain to contribute to the development of psychopathology.

Several stress-related disorders, including anxiety [14], depression [15], PTSD [16], and schizophrenia [17], have been associated with changes in the volume of prefrontal cortex and amygdala, implicating these regions as important targets for investigating stress effects in the brain. In fact, both prefrontal cortex and amygdala contain

* Corresponding author at: 1101 E. 10th Street, Indiana University, Bloomington, IN 47405, United States. Tel.: +1 812 855 4922; fax: +1 812 855 4691.
E-mail address: mrfarrel@indiana.edu (M.R. Farrell).

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corticosteroid receptors and are involved in the regulation of hypothalamic–pituitary–adrenal axis activity [18–20]. Further, there is interconnectivity between prefrontal cortex and amygdala [21], allowing for prefrontal inhibition of amygdala activity [22–25]. Connections between these two regions are critical modulators of a useful model of the regulation of emotional behavior, fear conditioning and extinction.

Fear conditioning and extinction provide an excellent model system for examining how stress-induced changes in corticolimbic morphology are related to stress-induced changes in neural function and behavior, as the neural circuitry underlying this behavior is well characterized, and involves both medial prefrontal cortex and basolateral amygdala. During fear conditioning, an animal is placed in an operant chamber and acquires a learned fear response to a neutral stimulus, such as a tone, that is paired with an aversive unconditioned stimulus, such as a shock. Repeated pairings of the tone with the shock result in a conditioned fear response to the conditioned stimulus (CS) tone. In a rodent model, a common measure of the conditioned fear response (CR) is the animal's freezing during the tone, which is defined as absence of all movements except that due to breathing. Time away from the operant chamber (typically ranging from 1 to 24 h) is necessary for consolidation of the fear memory. The animal is then placed back in the operant chamber for subsequent presentations of the CS in the absence of the unconditioned stimulus. Multiple presentations of the CS will result in extinction of the fear response—the animal learns that the tone no longer predicts the shock, and no longer freezes in response to presentation of the tone [12,26]. Memory for extinction of conditioned fear can be measured by presentation of the CS on subsequent days. High levels of freezing during the CS indicate poor retrieval of the extinction memory.

Variations in the ability to consolidate and/or retrieve the extinction memory could contribute to disorders such as PTSD [27,28], which makes stress effects on retrieval of extinction an especially important topic of study. Patients with PTSD have impairments in both the ability to extinguish an aversive conditioned response [29,30] and later retrieval of the extinction memory [27]. These extinction deficits could be responsible for the persistence of traumatic memories in the absence of the trauma-inducing stimulus, a hallmark of PTSD [28,31].

Patients with PTSD have reduced ventral medial prefrontal cortex activity and increased activity in the amygdala [32–34], and alterations in prefrontal and amygdalar activity are associated with extinction deficits in these patients [27]. Indeed, connections between medial prefrontal cortex and amygdala are important for fear conditioning and extinction. Basolateral amygdala is a key site of convergence for unconditioned and conditioned stimuli, a critical requirement for the neuroplasticity necessary for learning of fear conditioning [35], and the acquisition of fear conditioning is mediated by amygdala [36,37]. Basolateral amygdala is specifically involved in mediating the initial acquisition of extinction, as either temporary inactivation [38] or blockade of glutamatergic transmission [39,40] in basolateral amygdala prevented or attenuated extinction.

Medial prefrontal cortex contributes to both acquisition and retrieval of extinction of conditioned fear [41]. Male rats with infralimbic cortex lesions showed normal acquisition of fear conditioning and initial extinction, but deficits in the ability to retrieve extinction memory [42]. Likewise, stimulation [43] or pharmacological activation [44] of infralimbic cortex facilitated extinction retrieval, while blockade of infralimbic cortex activity impaired extinction retrieval [45]. Further, neurons in infralimbic cortex showed an increase in firing in response to the CS during extinction retrieval [46]. This evidence suggests that infralimbic cortex is necessary for inhibiting fear responses during extinction [47].

Prelimbic cortex, on the other hand, seems to be involved in the expression of conditioned fear [47]. Temporary inactivation of prelimbic cortex during extinction disrupted conditioned fear expression [48], while stimulation of prelimbic cortex during extinction increased fear expression and slowed extinction of the fear memory [49]. Neural activity in prelimbic cortex is associated with freezing during extinction [50]. Thus, there is a regional specificity in the involvement of medial prefrontal cortex in the modulation of fear conditioning and extinction: prelimbic cortex facilitates fear expression while infralimbic cortex is involved in fear extinction.

The different output targets of infralimbic cortex and prelimbic cortex are the key to the differential effects of each region on fear expression. Although a small percentage of infralimbic neurons innervate basolateral amygdala [51], infralimbic cortex neurons also heavily innervate the intercalated cells of the amygdala and the lateral division of the central nucleus of the amygdala [21,52]. These regions contain GABAergic neurons that inhibit output neurons of the medial division of central amygdala to inhibit fear [53]. Lesion of intercalated cells impaired extinction [22], while activation of intercalated cells facilitated extinction [54]. On the other hand, prelimbic cortex targets basolateral amygdala. Basolateral amygdala connects via excitatory projections to output neurons of central amygdala [24,55], and these neurons trigger midbrain and hypothalamic structures, resulting in the expression of fear [56]. Further, basolateral amygdala provides projections to both prelimbic cortex and infralimbic cortex [57,58]. The presence of these reciprocal connections highlights the importance of investigating multiple structures within the circuit.

Not only is this corticolimbic circuit linked to psychopathology, it also is involved in the regulation of stress response [20], and plays a role in emotion regulation [59]. Its involvement in fear conditioning and extinction is well documented, and thus provides a neural substrate to address questions of stress effects on behavior. However, despite the sex differences in the rates and expression of stress-related psychological disorders, most of the research on the neurobiological mechanisms underlying stress effects on emotional behavior focuses on males. Thus, research into the mechanisms underlying potential stress-induced plasticity of corticolimbic structures in females may provide the groundwork necessary to develop sex-specific treatment for stress-related psychopathology. In this review, we will focus on sex differences and potential differential effects of chronic stress on morphology of basolateral amygdala and medial prefrontal cortex and fear conditioning and extinction in rodents.

2. Chronic stress effects on neuronal morphology

As in primates, prefrontal cortex in rodents can be subdivided into several major subregions. Medial prefrontal cortex includes anterior cingulate, prelimbic, and infralimbic cortex. This region is functionally homologous to the primate dorsolateral and ventromedial prefrontal cortices, and plays a role in autonomic and HPA axis regulation, emotion regulation [e.g., prelimbic cortex plays a role in expression of conditioned fear, while infralimbic cortex plays a role in retrieval of extinction, see 60 and above], and working memory. Orbitofrontal cortex, which includes the medial, ventral, and lateral orbitofrontal subregions, is functionally homologous to primate orbitofrontal cortex and appears to play a role in modulating behavioral responses based on changing incentive values of reward-related stimuli [13].

Medial prefrontal cortex is involved in cognitive tasks that are influenced by chronic stress [as reviewed in 13], is a target for stress hormones like corticosterone [61], and helps regulate HPA axis activity [62]. In male rats, chronic restraint stress produced retraction of apical dendrites of pyramidal neurons in male prelimbic cortex [63–70], an effect that was mimicked with chronic corticosterone administration [71–73]. A similar pattern of stress-induced retraction was seen for apical dendritic branches of neurons within the infralimbic region of medial prefrontal cortex [74,75]. Finally, even shorter, milder episodes of stress were sufficient to produce dendritic atrophy. Ten minutes of stress for 10 days [76] or 3 weeks of vehicle injection alone [71] reduced dendritic arborization within medial prefrontal cortex, again with retraction occurring only in distal portions of the apical arbor.