Mini-Symposium

Sex Differences in Risk and Resilience: Stress Effects on the Neural Substrates of Emotion and Motivation

Cara L. Wellman,[1] Debra A. Bangasser,[2] Justin L. Bollinger,[3] Laurence Coutellier,[4] Marian L. Logrip,[5] Kelly M. Moench,[1] and Kimberly R. Urban[6]

[1]Department of Psychological and Brain Sciences, Program in Neuroscience, and Center for the Integrative Study of Animal Behavior, Indiana University, Bloomington, Indiana 47405, [2]Psychology Department and Neuroscience Program, Temple University, Philadelphia, Pennsylvania 19122, [3]Department of Pharmacology and Systems Physiology, University of Cincinnati College of Medicine, Cincinnati, Ohio 45237, [4]Departments of Psychology and Neuroscience, Ohio State University, Columbus, Ohio 43210, [5]Department of Psychology, Indiana University-Purdue University Indianapolis, Indianapolis, Indiana 46202, and [6]Children's Hospital of Philadelphia, Abramson Research Center, Philadelphia, Pennsylvania 19104

Risk for stress-sensitive psychopathologies differs in men and women, yet little is known about sex-dependent effects of stress on cellular structure and function in corticolimbic regions implicated in these disorders. Determining how stress influences these regions in males and females will deepen our understanding of the mechanisms underlying sex-biased psychopathology. Here, we discuss sex differences in CRF regulation of arousal and cognition, glucocorticoid modulation of amygdalar physiology and alcohol consumption, the age-dependent impact of social stress on prefrontal pyramidal cell excitability, stress effects on the prefrontal parvalbumin system in relation to emotional behaviors, contributions of stress and gonadal hormones to stress effects on prefrontal glia, and alterations in corticolimbic structure and function after cessation of chronic stress. These studies demonstrate that, while sex differences in stress effects may be nuanced, nonuniform, and nonlinear, investigations of these differences are nonetheless critical for developing effective, sex-specific treatments for psychological disorders.

Key words: **corticolimbic regions; corticosterone; corticotropin releasing factor; parvalbumin; microglia**

Introduction

Risk for psychopathology differs markedly in men and women. For instance, men are at increased risk for disorders, such as attention deficit hyperactivity disorder and schizophrenia (Ramtekkar et al., 2010; Mendrek and Mancini-Marïe, 2016). Women are at increased risk for disorders such as depression and post-traumatic stress disorder (PTSD) (Breslau, 2009; Kessler et al., 2012), and often display more severe symptoms (de Graaf et al., 2002; Schoevers et al., 2003). One environmental factor linked to all of these disorders is stress. PTSD is precipitated by a traumatic event, and symptoms of depression, attention deficit hyperactivity disorder, and schizophrenia are exacerbated by stressor exposure (Newman and Bland, 1994; Hirvikoski et al., 2009). However, little is known about the sex-dependent effects of stress on corticolimbic regions implicated in these disorders (e.g., Bennett, 2011). Determining how stress influences corticolimbic functioning in males and females will deepen our knowledge of brain-behavior relationships and the mechanisms underlying sex-biased disorders. This understanding is critical to developing effective, sex-specific treatments for these disorders.

Here, we provide examples of new data demonstrating sex differences in the neurobiological effects of stress across several corticolimbic structures and cognitive and emotional processes. We conclude with a discussion of the important themes that emerge from these studies, emphasizing that sex differences in the effects of stress are nuanced, nonuniform, and nonlinear.

CRF regulation of arousal and cognition

CRF, a key orchestrator of the stress response, can directly regulate corticolimbic regions, including the PFC, to alter anxiety and working memory (Jaferi and Bhatnagar, 2007; Hupalo and Berridge, 2016). In addition, CRF can alter midbrain and hindbrain monoaminergic and cholinergic nuclei. One consequence of this regulation is that these neurotransmitter systems, in turn, affect corticolimbic regions, influencing a range of behaviors from stress coping strategies to decision making (Wood et al., 2013; Bryce and Floresco, 2016). Recent comparisons indicate that female rodents are more sensitive to CRF's effects on noradrenergic-mediated arousal, whereas male rodents are more sensitive to the effects of CRF on cholinergic-mediated cognition (Bangasser et al., 2018).

Stress activates the locus ceruleus (LC)-norepinephrine arousal system via CRF. Specifically, CRF increases the firing rate of LC neurons to cause norepinephrine release into corticolimbic regions to heighten arousal (Valentino and Van Bockstaele,

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Correspondence should be addressed to Dr. Cara L. Wellman, Department of Psychological and Brain Sciences, Program in Neuroscience, and Center for the Integrative Study of Animal Behavior, 1101 East 10th Street, Indiana University, Bloomington, IN 47405. E-mail: wellmanc@indiana.edu.

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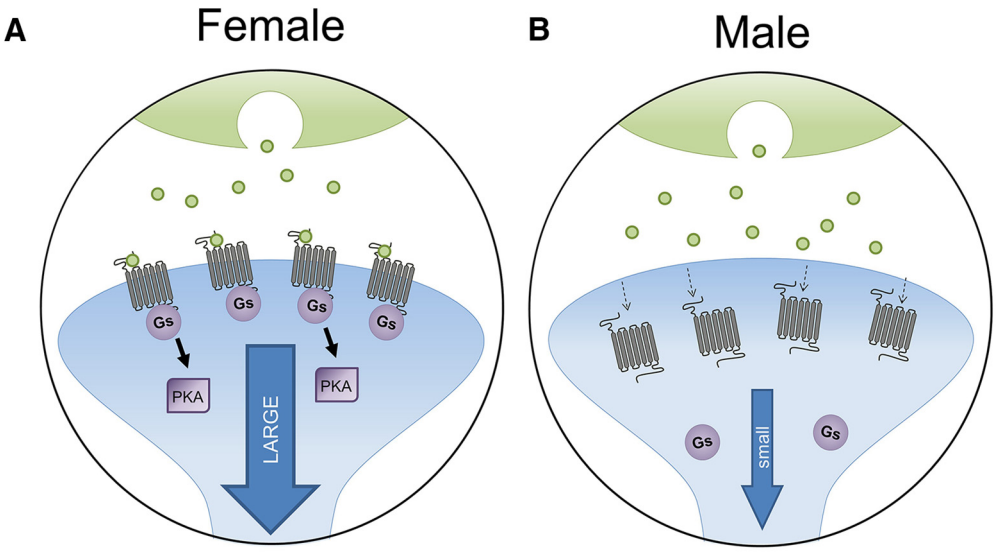

Figure 1. Sex differences in CRF_1 receptors in LC. ***A***, In females, CRF_1 receptors bind to Gs and signal more through the cAMP-PKA pathway, but they do not internalize following stress and CRF overexpression, leading to a large LC response to CRF. ***B***, In males, CRF_1 receptors in LC internalize following stress and CRF overexpression, resulting in a smaller response to CRF. Adapted with permission from Bangasser et al. (2018).

2005). There are sex differences in LC neuronal sensitivity to CRF, such that, compared with males, LC neurons in females respond to lower doses of CRF (Curtis et al., 2006; Bangasser et al., 2010). The LC contains CRF_1 receptors, which are G-protein (guanine-nucleotide binding protein) coupled receptors that preferentially bind Gs (a type of G-protein) to activate the cAMP-protein kinase A (PKA) signaling pathway (Grammatopoulos et al., 2001). CRF_1 receptor activation of the cAMP-PKA signaling pathway increases the firing rate of LC neurons (Jedema and Grace, 2004). In females, increased LC neuronal sensitivity to CRF results from greater CRF_1 receptor coupling to Gs and, consequently, more activation of the cAMP-PKA pathway in females than males (Fig. 1) (Bangasser et al., 2010; Bangasser and Wicks, 2017). There are also sex differences in CRF_1 receptor internalization, a process by which saturating concentrations of CRF cause receptors to be trafficked intracellularly, where they can no longer be activated. Stressor exposure and CRF hypersecretion induce CRF_1 receptor internalization in male, but not female, LC neurons (Bangasser et al., 2010, 2013). This lack of internalization in females may render their LC neurons less adaptable to conditions of CRF hypersecretion, which have been reported in patients with PTSD and depression (Bremner et al., 1997; Heuser et al., 1998). Collectively, these studies reveal sex differences in CRF_1 receptors in the LC that can bias females toward high arousal during stressful events. Hyperarousal symptoms, such as lack of concentration and sleep disturbance, are reported in PTSD and depression, disorders that are more common in women than men (Breslau, 2009; Kessler et al., 2012). Thus, if similar CRF_1 receptor sex differences in the LC occur in humans, they may contribute to this female vulnerability.

The basal forebrain cholinergic system is also regulated by CRF, and new findings are revealing sex differences in this regulation. One cognitive process mediated by this system is sustained attention, the ability to monitor situations for intermittent and unpredictable events (Sarter et al., 2001). Central administration of CRF disrupts sustained attention in both male and female rats (Cole et al., 2016). However, ovarian hormones modulate this effect, such that CRF impairs attention in females only when they are in estrous cycle stages with low levels of ovarian hormones. Thus, ovarian hormones appear to be protective against the impairing effect of CRF on attention. Unlike females, males, who lack surges in ovarian hormones, would never benefit from their protective effects. Bangasser et al. (2016) are beginning to investigate the effects of CRF on the medial septum (MS) cholinergic system, which is critical for regulating hippocampal-dependent learning. A low dose of CRF in the MS disrupts spatial learning only in males, whereas a high dose impairs learning in both sexes (Bangasser et al., 2016). Thus, the male MS is more sensitive to CRF than is the female MS. The mechanisms that establish sex differences in CRF regulation of the basal forebrain cholinergic system are not yet well understood. However, this male vulnerability to CRF-induced cognitive deficits could contribute, perhaps in part, to the higher rates of attention deficit hyperactivity disorder and schizophrenia in men than in women (Ramtekkar et al., 2010; Mendrek and Mancini-Marïe, 2016). These basic research studies highlight sex differences in CRF sensitivity that bias males and females toward different physiological responses to stress, and perhaps to different risks for psychiatric disorders in which symptoms are exacerbated by stress.

Glucocorticoid modulation of amygdala activity and alcohol responsiveness

Alcohol use disorder (AUD) is characterized by recidivism to alcohol use. While AUDs have historically been up to twice as prevalent in males relative to females (World Health Organization, 2014), this gender gap is narrowing (White et al., 2015). Stress is a prominent trigger for relapse (Sinha, 2013), and may, in part via the actions of glucocorticoids such as cortisol (corticosterone in rats), also accelerate the development of AUD (Blaine and Sinha, 2017). Importantly, women with AUD experience greater craving to drink following exposure to stressful images (Hartwell and Ray, 2013) and stronger relationships between past trauma severity and craving (Heffner et al., 2011), relative to men. Elucidating sex differences in neuronal responses to stressors and their impact on alcohol use is therefore crucial to developing novel treatments for both sexes.

Studies using females or both sexes to investigate stress-alcohol interactions in rodent models have been limited. Female

rodents may show increased (Cozzoli et al., 2014) or decreased (Chester et al., 2006, 2014) alcohol intake after stress, relative to males, which may vary based on stressor (Cozzoli et al., 2014) or age at stress exposure (Wille-Bille et al., 2017). Long-lasting effects of past stress on alcohol intake and relapse-like drinking have only been studied in males (Casey, 1960; Lynch et al., 1999; Logrip and Zorrilla, 2012; Logrip et al., 2014), although females display greater sensitivity to acute stress-induced reinstatement than do males (Bertholomey and Torregrossa, 2017). Females also show heightened sensitivity to corticosterone treatment throughout adolescence, which increased alcohol seeking in adulthood in both sexes but tended to affect females more (Bertholomey et al., 2016). Corticosterone may specifically regulate alcohol intake exacerbated by stress or anxiety, as glucocorticoid receptor antagonism blunted alcohol seeking or drinking in rats subsequent to stress or alcohol withdrawal (Simms et al., 2012; Vendruscolo et al., 2012). Importantly, blockade of corticosterone's actions only in the CeA replicated these effects (Simms et al., 2012; Vendruscolo et al., 2015).

Escalating alcohol intake over time shifts the motivation to drink toward alleviation of negative symptoms (Koob, 2015), and the CeA is integral to this transition. The CeA synthesizes inputs from amygdala subdivisions to regulate stress- and reward-related behavioral responses (Janak and Tye, 2015); thus, changes in the CeA and associated circuitry have a unique capacity to alter behavior. How the CeA differentially adapts to stressors, alcohol, and their co-occurrence in females versus males has been minimally explored. In males, alcohol acutely activates GABAergic and inhibits glutamatergic postsynaptic responses in the CeA, effects exacerbated during alcohol withdrawal (Roberto et al., 2003, 2004a,b). Stress similarly increases GABAergic responses in CeA of males (Ciccocioppo et al., 2014), suggesting overlap in the effects of alcohol and stress on CeA neurotransmission. Increased GABAergic and decreased glutamatergic responses should similarly alter the output of the CeA, implicating CeA neurons as a point of convergence for circuit adaptations to alcohol and stressors to produce maladaptive anxiety-like and alcohol-drinking behaviors. Yet these conclusions based on data collected in males fail to address possible sex differences in this circuitry.

Given the CeA's role in modulating anxiety-like and alcohol-drinking behavior and the stronger association between stress and alcohol intake in women, the CeA could be hypothesized as a site for greater synergistic adaptations to stress and alcohol in females. However, current data suggest that this is not the case. Instead, corticosterone and alcohol differentially altered glutamatergic EPSPs in response to activation of BLA inputs to the medial (CeM) and lateral (CeL) CeA in males versus females (Logrip et al., 2017). Alcohol acutely reduced BLA-evoked EPSP (BLA-EPSP) amplitudes in CeM and CeL neurons in males, whereas alcohol's effects on BLA-EPSPs were blunted in both subregions in females (Logrip et al., 2017; Kirson et al., 2018). BLA-EPSPs differed across estrous cycle phases in CeM neurons, indicating an interaction between hormonal status and alcohol responsiveness in females. Conversely, corticosterone treatment reduced BLA-EPSP amplitudes in CeL, but not CeM, in females, occluding the effects of alcohol coapplication in both subdivisions (Logrip et al., 2017). On the other hand, in males, corticosterone neither altered BLA-EPSPs nor changed alcohol's effects, as application of alcohol after corticosterone resulted in reductions in BLA-EPSP amplitudes similar to those produced by alcohol alone. These results demonstrate sex differences in sensitivity to corticosterone versus alcohol (as shown in Fig. 2) and highlight the necessity for understanding how stress and alcohol, as well as their interaction, differentially influence neuronal activity by sex in key nuclei regulating stress and drug responses.

Stress and PFC

Social stress and physiology of pyramidal neurons

The PFC regulates executive functions, including decision-making, judgment, behavioral inhibition, and cognitive flexibility (Goldman-Rakic, 1996; Arnsten and Li, 2005; Girotti et al., 2018). Impairments in executive function are symptoms of many stress-related psychological disorders (e.g., schizophrenia, depression, PTSD), implicating pathophysiology in the PFC in these disorders (e.g., Negrón-Oyarzo et al., 2016). Indeed, in males, chronic stress impairs performance on many tasks involving PFC, including fear extinction, behavioral flexibility, and working memory (Holmes and Wellman, 2009; Maren and Holmes, 2016).

Dendritic retraction and spine atrophy, neurochemical and physiological changes, and impairment of PFC-mediated behaviors are well-documented sequelae of chronic restraint or chronic variable stress in adult males (Farrell et al., 2013; Moench and Wellman, 2015). However, for humans, stressors are often of a social nature (i.e., bullying); thus, rodent social stressors (i.e., resident-intruder defeat) may provide better translational validity than restraint or shock stress. Social stress is particularly damaging during adolescence, as this is a period of dynamic growth and restructuring in the PFC (Lewis, 1997; Lenroot and Giedd, 2006; Koss et al., 2010, 2014). Social stress impaired strategy-shifting of adolescent males only when they were tested as adults (Snyder and Valentino, 2015). Female adolescents were better at the task than adults, but stress impaired their reversal learning, indicating age- and sex-specific effects of social stress (Snyder et al., 2015).

Urban and Valentino (2017) used the resident-intruder stress paradigm to examine the effects of chronic social stress in male and female rats in early adolescence (PD 30–36), mid-adolescence/puberty (PD 42–46), or adulthood (PD 69–76). Stress impacts in mPFC were most striking at mid-adolescence, regardless of sex. Social stress reduced intrinsic excitability, measured as response to injected current, and also increased interspike interval, in mid-adolescents of both sexes, indicating slowed kinetics and reduced potassium channel function. In addition, social stress reduced the amplitude, but not frequency, of EPSPs, indicating reduced synaptic transmission via reduction of postsynaptic glutamate receptors (AMPAR and NMDAR). In addition, there were sex-dependent stress effects. For instance, social stress reduced intrinsic excitability and increased interspike interval in adult females, but not adult males. Sex-specific effects of stress were also noted in mid-adolescents. Stress increased input resistance, but lowered threshold to fire, in male mid-adolescents, but it increased the amplitude of afterhyperpolarization in female mid-adolescents. Stress also selectively reduced the amplitude of action potentials only in male mid-adolescents. These sex-specific effects implicate potassium channel alterations and suggest that social stress impacts potassium channel function differently in males and females, but these effects lead to the same outcome of reduced neuronal excitability. These results suggest reduced mPFC activity following social stress in mid-adolescents of both sexes and female adults but show that adult male mPFC is largely impervious to social stress. Given previous studies showing stronger impairments in PFC-mediated tasks following social stress in adolescence, the neuronal changes noted in this study

provide a likely cellular correlate of impaired executive function that would allow for greater amygdalar drive and enhance the likelihood of psychiatric disorders in stressed adolescents.

These data suggest that mid-adolescence is a time of particular vulnerability to the effects of social stress on mPFC function. This vulnerability persists in females into adulthood but disappears in males. Given the likely role of layer V pyramidal neurons in behavioral flexibility and working memory (Wang et al., 2008), decreased excitability and synaptic transmission in these neurons could contribute to impairment of executive functions. Indeed, previous studies have shown that stress in adolescence impairs working memory and strategy-shifting in males, but only when tested in adulthood (Novick et al., 2013, 2016; Snyder and Valentino, 2015). Given that immediate stress-induced changes are seen on a cellular level in adolescent males but cognitive impacts appear later, adolescent rats may engage different brain circuits to complete these tasks while mPFC is still developing. Alternatively, immediate stress-induced changes in neuronal physiology may alter developmental trajectory, resulting in later emergence of deficits.

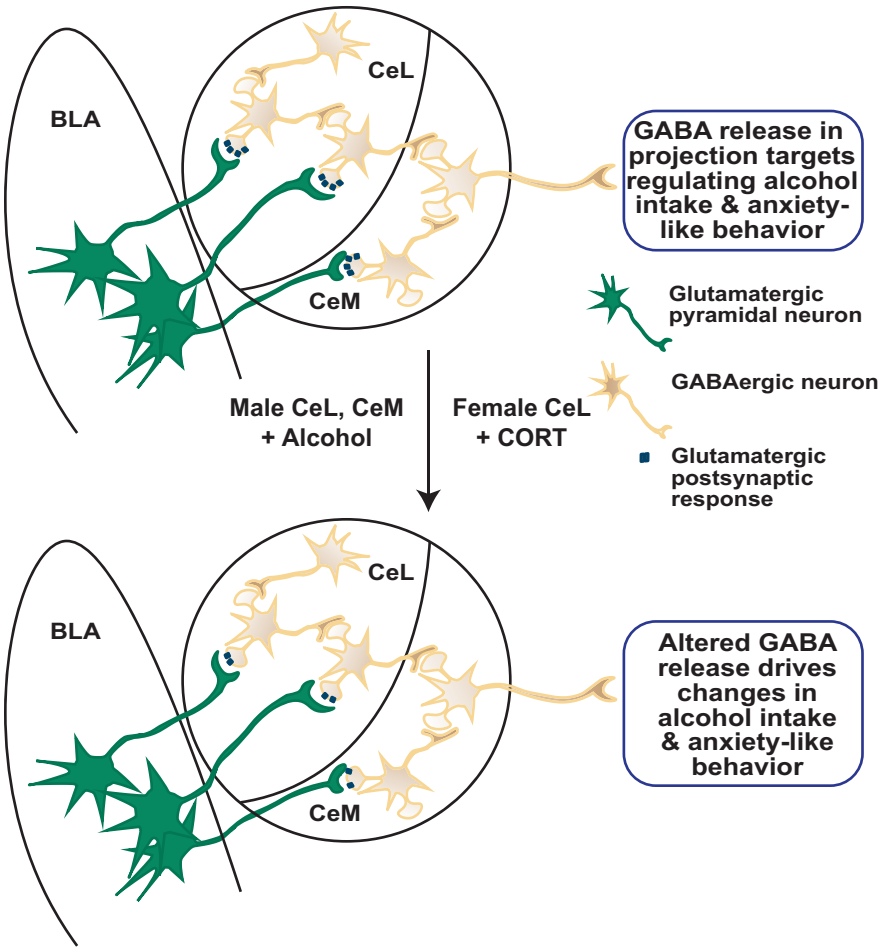

Figure 2. Model of alterations in basolateral-central amygdala circuit activity by alcohol and stress. Neurons of the CeL and CeM in males and females display similar basal glutamatergic postsynaptic responses to stimulation of BLA inputs (top). Given similar baseline single-neuron responses, male and female CeM projection neurons may similarly release GABA in downstream targets. However, after acute exposure to alcohol or the stress hormone corticosterone (CORT), the magnitude of the CeA response to BLA stimulation is dampened in a sexually divergent fashion (bottom). Specifically, alcohol, but not CORT, reduces postsynaptic response magnitude in both CeL and CeM neurons in males, whereas CORT, but not alcohol, reduces response magnitude in only CeL neurons in females. At the circuit level, these reductions in BLA excitation of CeA, measured *ex vivo* at the single-neuron level, are predicted to combine to produce similar alterations in GABA release by CeM projection neurons, resulting in altered alcohol intake and anxiety-like behavior in both sexes.

Sensitivity of the parvalbumin (PV) system to stress

Research in mouse models of stress-related disorders supports sex-specific vulnerability: exposure to subchronic variable stress increases anxiety- and depressive-like behaviors in female but not male mice (Hodes et al., 2015). Similar sex-specific findings were observed after exposure to 4 weeks of unpredictable chronic mild stress, whereby female, but not male, mice developed anxiety-like behaviors (Shepard et al., 2016; Shepard and Coutellier, 2018). Identifying the molecular mechanisms underlying this sex-specific vulnerability to stress is critical, as this information can improve the diagnosis and prevention of stress-related mood disorders.

Evidence suggest that resilience or vulnerability to stress-induced emotional dysregulation may be modulated by prefrontal neuronal activity (Vialou et al., 2014; Labonté et al., 2017). The mPFC contains a heterogeneous population of excitatory pyramidal and inhibitory GABAergic neurons. Prefrontal GABAergic interneurons are the primary regulators of pyramidal neurons' spiking activity and are highly sensitive to modulation by stress (Maguire, 2014; Fuchikami et al., 2015). Their dysregulation during and following chronic stress likely affects mPFC activity and thereby emotional behaviors. GABAergic interneurons in the cortex form distinct subpopulations of inhibitory neurons based on their firing properties and molecular characteristics. Studies in rodents provide evidence for a strong effect of stress on all types of inhibitory neurons in the PFC. For instance, chronic stress reduces expression of somatostatin (Banasr et al., 2017), and somatostatin-expressing GABAergic neurons have long been thought to be involved in depression (Fee et al., 2017). Others have shown that mPFC activity during chronic social stress, regulated by cholecystokinin-GABA neurons, mediates the effects of chronic social defeat stress on social avoidance and sucrose preference in male mice (e.g., Vialou, 2014). Finally, findings from the L.C. laboratory and others showed that chronic stress impacts prefrontal PV-GABA interneurons (McKlveen et al., 2016; Shepard et al., 2016; Shepard and Coutellier, 2018). Specifically, 4 weeks of exposure to unpredictable chronic mild stress increases levels of PV mRNA in the ventral mPFC of female but not male mice. Increases in PV mRNA were positively correlated with increased emotionality in females only (Shepard et al., 2016), and was also associated with reduced cFos expression in non-PV cells, indicative of reduced prefrontal activity. Moreover, chronic stress increased the number of PV neurons expressing cFos, reflecting hyperactivity of this specific interneuronal population even after cessation of chronic stress. Recently, using a chemogenetic approach, we further supported the idea of a causal relation-

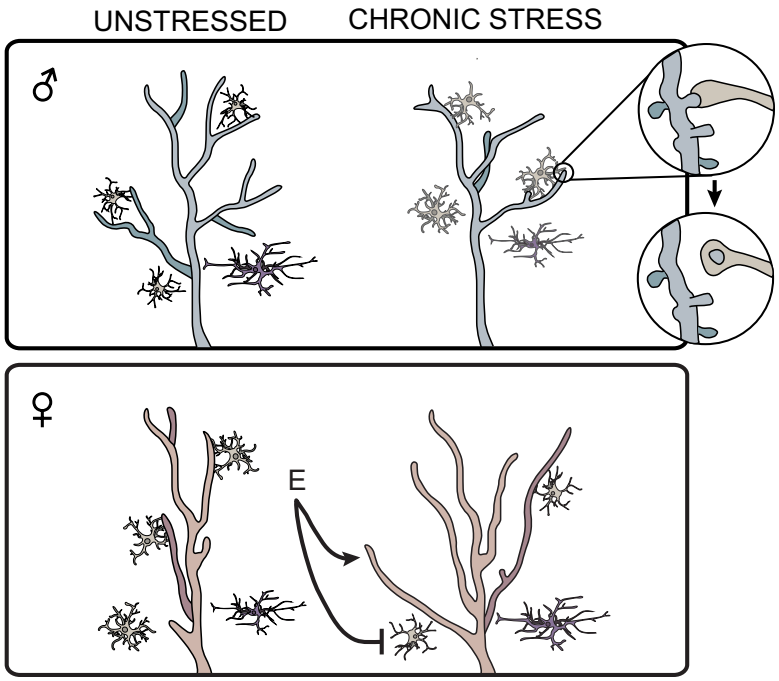

Figure 3. Hormonal contributions to sex-dependent stress effects on neuronal and glial morphology, and glia-neuron interaction in mPFC. Males (blue) exhibit increased apical dendritic complexity in pyramidal cells (red), increased astroglial ramification (purple), and reduced microglial activation (tan) compared with females. In males, chronic stress increases microglial activation, microglia-neuron interaction, and microglia-mediated synaptic pruning, decreases astroglial coverage, and reduces dendritic arborization. In females, chronic stress reduces microglial density and activation and increases astroglial coverage and dendritic complexity in mPFC. Estradiol (E) is necessary for stress-induced microglial deactivation in females and the stress-linked dendritic remodeling reported by Garrett and Wellman (2009).

ship between dysregulation of prefrontal PV-expressing neurons and anxiety-like phenotype in female mice. Importantly, such a link between PV-expressing neurons and anxiety was not observed in males, suggesting a sex-specific pathway in the regulation of anxiety-like behaviors (L.C. et al., unpublished data). These novel findings showing changes in PV-expressing cells in the PFC after chronic stress are very important for our understanding of prefrontal activity changes in stress-related disorders. PV-expressing interneurons form synapses onto the cell body and the axon initial segment of pyramidal cells. They are thus well positioned to provide strong inhibition of excitatory cells, much more so than, for instance, somatostatin-expressing neurons that regulate integration of dendritic input on pyramidal cells. Even small changes in the functioning of PV-expressing neurons might have important consequences for overall circuit activity.

Although cholecystokinin- and somatostatin-expressing neurons likely also regulate emotional behaviors (Freund, 2003; Sibille, 2017), our findings (Shepard et al., 2016; Shepard and Coutellier, 2018) suggest an important contribution of prefrontal PV-expressing neurons to sex-specific vulnerabilities to stress-induced emotional dysregulation. While many studies support the idea that different subpopulations of GABAergic neurons are sensitive to stress, electrophysiological studies indicating that hippocampal PV-expressing neurons are more vulnerable to the effects of stress than cholecystokinin-expressing cells (Hu et al., 2010). Such findings support the idea that increased plasticity of the prefrontal PV-expressing neurons in response to chronic stress might heighten vulnerability to emotional dysregulation, which could contribute to the increased risk for anxiety and depressive disorders in females. Elucidating the molecular mechanisms for this sex-specific neuronal sensitivity to stress could identify sex-specific targets for treatment for stress-sensitive disorders.

Stress effects on glia

Recent findings suggest glial contributions to stress-linked mood disorders, including depression (Miguel-Hidalgo et al., 2000; Holmes et al., 2018). For instance, microglial morphological activation and astroglial atrophy are observed in the mPFC in postmortem tissue from depressed patients (Miguel-Hidalgo et al., 2000; Torres-Platas et al., 2014), and markers of heightened neuroimmune activity in anterior cingulate cortex correlate with depressive symptom severity (Setiawan et al., 2015). Consistent with these data, preclinical models of depression demonstrate stress-induced alterations in microglia (Tynan et al., 2013), astrocytes (Banasr and Duman, 2008), and inflammatory priming (Frank et al., 2007) in numerous corticolimbic brain regions. Upon sensing a perturbation in the microenvironment, microglial processes thicken and reorient toward neuronal and astroglial signals (Ransohoff and Perry, 2009). Activated microglia can modulate neurotransmission, prune synapses and dendritic elements (Paolicelli et al., 2011), stimulate dendritic spine outgrowth (Weinhard et al., 2018), and potentially reshape dendritic architecture (Rappert et al., 2004; Salter and Beggs, 2014). Likewise, astrocytes are crucial in maintaining synaptic plasticity and function, including glutamatergic neurotransmission, regulate the neuroimmune milieu (Rossi, 2015), and likely contribute to depressive-like behaviors (Banasr and Duman, 2008).

In males, stress induces microglial morphological remodeling and inflammatory factor expression in mPFC (Hinwood et al., 2013), which contribute to stress-induced deficits in mPFC function (Hinwood et al., 2012; Kreisel et al., 2014; Wohleb et al., 2018). Chronic stress also reduces astroglial complexity and communication in mPFC, and astroglial atrophy in mPFC, produced by an astrocyte-specific toxin, is sufficient to induce a depressive-like phenotype (Banasr and Duman, 2008). Thus, glia may contribute to stress-induced alterations in synaptic function and behavior.

There are sex differences in microglial morphology in numerous stress-sensitive brain regions (e.g., Schwarz et al., 2012), including mPFC (Bollinger et al., 2016). However, few researchers have addressed sex-dependent stress effects on glia. In an initial report, acute restraint stress increased microglial morphological activation state in mPFC in males but decreased activation state in females. Microglial morphology returned to baseline following 10 d of daily restraint in males, whereas microglial deactivation persisted in females (Bollinger et al., 2016). These findings demonstrate sex-specific temporal patterns of stress-induced microglial remodeling in mPFC. Additional studies report sex-dependent stress effects on microglial morphology (Bollinger et al., 2017) and inflammatory priming (Fonken et al., 2018) in other corticolimbic structures that interact extensively with mPFC (e.g., orbitofrontal cortex, hippocampus).

Recent unpublished data (J.L.B. and C.L.W.) also suggest sex differences in, and sex-dependent stress effects on, morphology of astrocytes in mPFC. Males exhibit heightened astroglial coverage compared with females. Moreover, chronic stress induces atrophy of astrocytes in mPFC in males (Tynan et al., 2013) but may produce astroglial hypertrophy in females (J.L.B. and C.L.W., unpublished data).

Astrocytes and microglia can express estrogen and androgen receptors (Azcoitia et al., 1999; Sierra et al., 2008; Johnson et al., 2012). Therefore, gonadal hormones could contribute to sex differences in glial biology. Indeed, preliminary data suggest that ovariectomy prevents chronic stress-induced microglial deactivation in mPFC, and estradiol replacement may restore

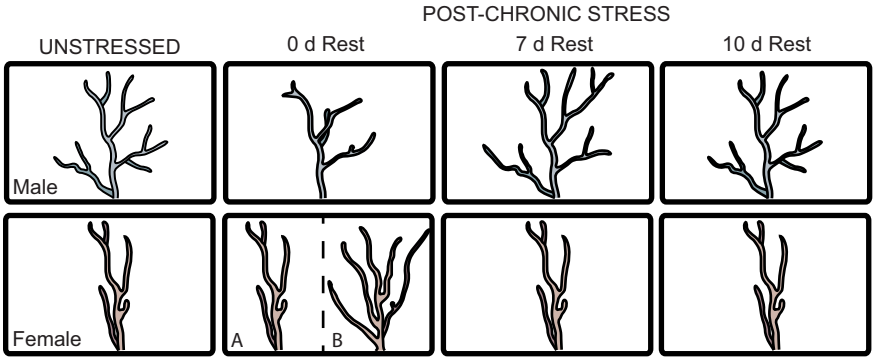

Figure 4. Sex differences in dendritic remodeling following CRS. Following CRS, males show initial retraction, overgrowth, and then retraction; immediately after cessation of CRS, females show either minimal remodeling (***A***) or growth (***B***), which may be dependent on mPFC subregion or duration of chronic stress, and no dynamic post-stress remodeling.

These sex-, stress-, and hormone-dependent alterations in neuroimmune and glial activation could influence corticolimbic structure and functioning (Fig. 3). For instance, divergent microglial and astroglial patterns align with sex differences in dendritic morphology (Garrett and Wellman, 2009b; Shansky et al., 2010): unstressed females have reduced apical dendritic arbors on mPFC pyramidal neurons relative to males, which could be due to increased pruning of spines and branches by the more-activated microglia in females. Similarly, the stress-induced decreases in microglial activity could either permit the dendritic growth in mPFC of stressed females that has been reported (Garrett and Wellman, 2009) or underlie the maintenance of normal dendritic lengths in stressed females reported previously (Moench and Wellman, 2017). Conversely, the stress-induced dendritic retraction seen in males could be driven by their increased microglial activity (Fig. 3). Supporting this hypothesis, stress induces microglia-neuron interaction and synaptic pruning in mPFC in males, but not females, and pharmacological inactivation of microglia during stress prevents stress-induced reductions in spine density in males (Wohleb et al., 2018). Moreover, reports demonstrate opposite molecular signatures in men and women with depression, which parallel patterns of stress-induced glial and neuronal remodeling in preclinical work. This includes heightened microglia-associated and reduced synapse-associated gene expression in PFC in postmortem tissue from depressed males, and reduced microglia-associated and heightened synapse-associated gene expression in depressed females (Seney et al., 2018). Together, these findings suggest a role for sex-dependent glial mechanisms in stress-linked psychopathology.

Lasting effects of chronic stress on corticolimbic structure and function

Immediately following chronic restraint stress (CRS), male rats have dendritic retraction in the prelimbic (PL) subregion of mPFC and deficits in behaviors mediated by mPFC (Holmes and Wellman, 2009). Chronically stressed female rats typically do not show deficits in many of these same behaviors (Wei et al., 2014; Snyder et al., 2015), and have either no dendritic remodeling (Moench and Wellman, 2017) or dendritic outgrowth (Garrett and Wellman, 2009) in mPFC. The discrepancy in chronic stress-induced dendritic remodeling in mPFC in females in these two studies is likely due to stressor duration (10 d vs 7 d) and/or the specific subregions analyzed (PL only vs PL and anterior cingulate cortex, respectively). Regardless, what is consistent across these studies is that chronic stress results in sex-specific dendritic remodeling and behavioral changes in rats. A similar pattern of results is found in dorsal hippocampus, such that CRS induces dendritic retraction and behavioral deficits in males but not females (Bowman et al., 2003; Conrad et al., 2003, 2004; McLaughlin et al., 2009). Together, these studies suggest that male rats may be more susceptible to the detrimental effects of prolonged stress exposure, whereas female rats appear to have some level of resiliency. This is paradoxical given women's increased susceptibility to several stress-linked psychopathologies. Investigation of the long-term effects of CRS may resolve this apparent paradox.

CRS-induced dendritic atrophy in CA3 of males is ameliorated following a 10 day rest period (Conrad et al., 1999), and behavioral deficits are reversed following a poststress rest period (Sousa et al., 2000). Dendritic retraction in PL of CRS male rats is also ameliorated following a 21 day rest period (Radley et al., 2005). However, this process occurs more rapidly and is quite dynamic. CRS-induced dendritic retraction is absent following a 10 day rest period; and, surprisingly, dendritic outgrowth beyond unstressed lengths is present after a 7 day rest period, indicating that "recovery" from stress may not involve a simple return to baseline. Instead, changes during the poststress period likely involve the recruitment of important neuroadaptive mechanisms, resulting in a new functional state distinct from both stress-naive and chronically stressed rats, as was highlighted in a recent review by Ortiz and Conrad (2018). In contrast to the dynamic pattern of dendritic reorganization in male rats during the post-stress rest period, females show minimal dendritic remodeling in mPFC during this poststress period (Fig. 4) (Moench and Wellman, 2017), suggesting that in the days following chronic stress PL of females may be less plastic than that of males.

If so, then subsequent stress during the post-CRS rest period, a second hit, may have novel effects on the function of stress-sensitive brain regions, and these effects may be sex-dependent. Indeed, in male rats exposed to chronic variable stress, exposure to a novel acute stressor produces reductions in cFos mRNA expression in several brain regions (Ostrander et al., 2006, 2009). Similarly, in the paraventricular nucleus of the hypothalamus, mPFC, and hippocampal CA1 and dentate gyrus, cFos expression assessed via immunohistochemistry is reduced in male rats exposed to a novel acute stressor the day following CRS, and partially ameliorated when acute stress occurs after a 7 day rest period (K.M.M. et al., manuscript under review). In contrast, in females, prior CRS does not blunt novel acute stress-induced

neuronal activation, regardless of whether acute stress occurs before or after a recovery period. Notably, CRS followed by a rest period increased neuronal activation in the paraventricular nucleus of the hypothalamus and BLA following acute stress (K.M.M. et al., manuscript under review). These findings suggest that males may show initial buffering after CRS, followed by reemergence of a more typical acute stress response, whereas CRS females may have an exaggerated neuroendocrine response to subsequent stressors.

This raises the possibility that CRS-induced changes in male rats may protect against subsequent stressors, whereas female rats may be more susceptible to two-hit stress. Preliminary data support this hypothesis, demonstrating that, despite immediate chronic stress-induced deficits in behavioral flexibility (Nikiforuk and Popik, 2014), reflected in performance on the attentional set-shifting task (Birrell and Brown, 2000), male rats do not appear to have deficits after two-hit stress (K.M.M. and C.L.W., unpublished data). Conversely, females do not appear to have deficits in behavioral flexibility immediately after chronic stress, but exposure to a novel acute stressor after a recovery period may induce deficits in behavioral flexibility (K.M.M. and C.L.W., unpublished data). Understanding this potential female-biased vulnerability to multiple stressors may begin to elucidate mechanisms underlying increased risk for stress-linked psychological disorders in women.

Discussion

Together, these studies illustrate several important emerging themes in sex-dependent stress effects on the neural circuitry underlying emotion, motivation, and cognition. First, sex differences in the effects of stress are nuanced. Just as sex differences in risk for psychopathology include both male-biased and female-biased disorders, sex differences in stress effects include examples of male vulnerability (e.g., CRF's effects on cholinergic processing) as well as female vulnerability (e.g., CRF's effects on noradrenergic processing). Second, sex-dependent effects of stress may be nonlinear, as in the dynamic dendritic remodeling seen in mPFC of males subsequent to CRS, and the late emergence of deleterious effects of CRS in mPFC of females. Third, sex differences in stress effects can be quite variable, depending on the animal model used (e.g., unpredictable chronic mild stress in mice vs CRS in rats), the timing of stress and testing (e.g., different patterns of persistence of the effects of adolescent social stress on physiology of mPFC in males vs females), and brain regions examined (e.g., sex differences in glucocorticoid modulation of activity in CeL but not CeM). Finally, given the extensive interactions among the brain regions highlighted in this brief review, studies of mechanisms underlying sex differences will need to take into account not just neuronal mechanisms, but also circuit-level interactions, as well as potential contributions of non-neuronal pathways involving neuron-glia interactions. While such mechanistic studies are still in their infancy, elucidating the mechanisms contributing to sex-dependent effects of stress on corticolimbic physiology can reveal the basis of sex differences in psychopathology, and inform the development of better treatments for these disorders in men and women.

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