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Sex Differences in Stress Regulation of Arousal and Cognition

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Abstract

There are sex differences in the prevalence and presentation of many psychiatric disorders. For example, posttraumatic stress disorder (PTSD) and major depression are more common in women than men, and women with these disorders present with more hyperarousal symptoms than men. In contrast, attention deficit hyperactivity (ADHD) and schizophrenia are more common in men than women, and men with these disorders have increased cognitive deficits compared to women. A shared feature of the aforementioned psychiatric disorders is the contribution of stressful events to their onset and/or severity. Here we propose that sex differences in stress responses bias females towards hyperarousal and males towards cognitive deficits. Evidence from clinical and preclinical studies is detailed. We also describe underlying neurobiological mechanisms. For example, sex differences in stress receptor signaling and trafficking in the locus coeruleus-arousal center are detailed. In learning circuits, evidence for sex differences in dendritic morphology is provided. Finally, we describe how evaluating sex-specific mechanisms for responding to stress in female and male rodents can lead to better treatments for stress-related psychiatric disorders.

Keywords

corticotropin releasing factor; glucocorticoids; memory; attention; norepinephrine; estrogen

1.1 Sex differences in psychiatric disorders

Many neuropsychiatric disorders affect women and men differently. There are differences in the rates at which some of these disorders occur. For example, women are more likely than men to be diagnosed with posttraumatic stress disorder (PTSD) and major depression [1–3], while men are more likely than women to be diagnosed with attention deficit hyperactivity disorder (ADHD) and schizophrenia [4–6]. There are also sex differences in the presentation of these disorders, such that women with depression suffer more from disrupted sleep than men [7, 8], and men with schizophrenia typically present with more negative symptoms than women (e.g., social withdraw, flattened affect) [6, 9–11]. Interestingly, the sex biased disorders that are known to have a greater impact on women share hyperarousal as a key feature. Hyperarousal comprises a specific cluster of PTSD symptoms [12] and is thought to contribute to the ruminations, sleep disturbance, and agitation symptoms observed in some patients with major depression [13–16]. In contrast, cognitive disruptions are a defining

feature of certain disorders that disproportionately affect men [12]. Thus, particular susceptibility to hyperarousal in females and cognitive deficits in males may contribute to these sex differences.

One environmental factor known to alter arousal and cognition is stress. In response to an acute or moderate stressor, increases in arousal and changes in cognition are thought to be adaptive [17, 18]. However, in response to a traumatic event or chronic stress, alterations in these processes can become disruptive, at least in some people [13, 18–20]. In fact, stress can precipitate and/or increase symptom severity of all the aforementioned disorders [12, 21–24]. Dysregulated stress hormones are also reported in patients. Abnormal levels of glucocorticoids are reported in PTSD, major depression, ADHD, and schizophrenia [24–29]. Additionally, hypersecretion of the stress-neuropeptide, corticotropin releasing factor (CRF), is thought to contribute to the pathophysiology of PTSD and depression [30–32].

The link between stressor exposure and disorders that occur differently in women and men has prompted studies investigating sex differences in stress responses. Data from preclinical models reveal sex differences in circuits, cells, and molecules that can lead to differences in the way females and males respond to stress (for review see [33–38]). Based on epidemiological and complementary preclinical data, here we propose that stressful life events increase the risk of hyperarousal in females and cognitive disruptions in males, effects that bias the sexes towards different pathology. We present data from human and non-human animal studies to support this idea, and highlight mechanisms by which stress can alter arousal and cognition differently in females and males. Finally, we detail how considering sex differences in stress responses can guide the development of better therapies for both women and men.

2.1 Female vulnerability to stress-induced hyperarousal: Evidence from human studies

Hyperarousal is a dysregulated state of persistently being “on-edge” that contributes to increased agitation, restlessness, lack of concentration, and sleep disruption. As noted, hyperarousal distinguishes a symptom cluster of PTSD and contributes to symptoms of depression [12]. Not only is there a female bias in these disorders [1–3], but, compared to men with PTSD and depression, women with the same disorders have greater hyperarousal symptoms, including disrupted sleep [7, 39–43]. Additionally, in depression, women ruminate more than men and ruminations are linked to high levels of arousal [44–46]. Collectively these epidemiological findings suggest that in clinical populations, women are more affected than men by dysregulated levels of arousal.

There is further evidence from healthy human subjects for sex differences in arousal following exposure to aversive stimuli that elicit stress responses. Electroencephalography (EEG), which integrates electrical activity of cortical areas, changes with arousal states. Exposure to negative stimuli alters EEG measures revealing increased arousal in both sexes [47, 48]. However, compared to men, women have faster frontal cortical EEG responses to negative stimuli [48]. Additionally, unpleasant pictures enhance negative Event-Related Potentials, an averaged EEG signal, in women more than men, particularly when the stimuli

are highly arousing [47]. These findings indicate that, at the electrophysiological level, women are more attuned to negative stimuli, and respond to them more rapidly than men.

Compared to EEG, which reflects cortical activity, functional magnetic resonance imaging (fMRI) uses changes in blood flow as an indices of activity throughout the brain, and fMRI studies are revealing sex differences arousal circuits that include cortical and subcortical structures. A recent meta-analysis of fMRI data, identified sex differences in brain regions activated by emotional stimuli [49]. In particular, a major brain arousal center, the noradrenergic locus coeruleus (LC), was more activated in women than in men during emotion-evoking tasks [49], suggesting that a stressful event would elicit a greater LC-mediated arousal response in women than in men. Sex differences in functional connectivity, or the functional coupling of brain regions in a circuit, are reported for circuits that include the LC. Surprisingly, resting-state functional connectivity of the LC with the midbrain, hippocampus, parahippocampus, and middle temporal gyrus is greater in men than in women [50]. Whether or not functional connectivity with the LC changes during stress and whether there would be a sex difference in this change has not been directly assessed. However, following exposure to an aversive visceral stimulus, women with irritable bowel syndrome—a stress-related condition that is more common in women than in men [51]—had greater functional connectivity within an emotional-arousal circuit comprised of the LC, amygdala, and anterior cingulate than did men with the same condition [52]. Taken together these studies suggest that stressful events would cause a greater increase in the arousal network of women than men, because women have lower resting state LC functional connectivity, but greater activation of LC circuits following aversive stimuli. Beyond functional differences, there is structural evidence that the LC contains more neurons in females than males, an effect consistent in humans and certain rat strains [53–59]. Collectively, these studies provide support for the idea that stress-inducing negative stimuli would have a greater impact on arousal in women than in men.

2.2 Female vulnerability to stress-induced hyperarousal: Evidence from animal studies

Animal studies have revealed further sex differences in the LC and its regulation by stress (for review see [60]). In addition to its larger size in females than males of certain rat strains [55, 56], we found that dendrites of LC neurons are longer and more complex in female compared to male rats [61] (Fig. 1a,b). LC dendrites are present within the nuclear core of the LC but they also extend into the ventromedial and dorsolateral pericoerulear (peri-LC) regions [62, 63]. Inputs into the LC are topographically organized such that certain regions project to the core, while others project to the peri-LC (Fig. 1)[64, 65]. Afferents to the core carry autonomic information from the nucleus paragigantocellularis (PGi), dorsal cap of the paraventricular hypothalamic nucleus (PVN), and Barrington's nucleus (Bar.) [66, 67]. Because these afferents synapse on dendrites close to LC cell bodies, even the short dendrites of males would be expected to adequately receive this type of input. In contrast, longer LC dendrites in females would increase their connections with afferents that project to the peri-LC region, including the nucleus of the solitary tract (NTS) and periaqueductal gray (PAG) that project to the ventromedial peri-LC, as well as the central nucleus of the

amygdala (CeA), bed nucleus of the stria terminalis (BNST), and paraventricular hypothalamic nucleus (PVN) that project to the dorsolateral peri-LC [65, 68–71]. In support of this idea, female rats have increased labeling of the synaptic marker, synaptophysin, in the peri-LC relative to male rats [61]. Of relevance to affective disorders, this dendritic structure would increase the limbic input to the dorsolateral peri-LC of females. Thus, an emotional event would be more likely to induce LC-mediated arousal in females than males.

There are also sex differences in the way the LC is regulated by CRF. Unlike its role as a hormone in initiating the hypothalamic pituitary adrenal (HPA) axis, CRF acts as a neuromodulator in the LC [72]. CRF is released into the LC during stress, which causes LC neurons to increase their firing rate (i.e., the rate at which action potentials are generated) [73–75]. In turn, this faster LC firing rate increases norepinephrine release throughout the brain, heightening arousal [73–76]. There is a sex difference in CRF regulation of LC neuronal firing. A low dose of CRF that has no effect on the firing rate of LC neurons in males, actually increases the firing rate of LC neurons in females [77, 78]. In fact, the CRF dose-response curve for LC activation is shifted to the left in females relative to males, indicating enhanced sensitivity of female LC neurons to CRF [77, 78]. This sex difference in LC neuronal sensitivity to CRF is attributed to sex differences in the CRF₁ receptor, the receptor subtype present in the LC [78]. CRF₁ receptors are G-protein coupled receptors that preferentially bind to the Gs protein to initiate signaling through the cyclic adenosine monophosphate (cAMP)/protein kinase A (PKA) signaling pathway [79, 80]. We found that the CRF₁ receptor is more highly coupled to Gs (Fig. 2a,b) and signals more through the cAMP/PKA pathway in females compared to males [78, 82]. Because CRF activation of the cAMP/PKA pathway is the mechanism by which CRF increases LC neuronal firing [81], the enhanced CRF-induced cAMP/PKA signaling in females explains their increased LC firing rate in response to CRF compared to males.

In contrast to the increased Gs coupling of the CRF₁ receptor in females, the CRF₁ receptor of male rats preferentially binds to β arrestin2 following stressor exposure (15 min of forced swimming), an effect not observed in female rats (Fig. 2a,b)[78]. β arrestin2 can initiate its own suite of signaling cascades, which are often distinct from the pathways activated by G-proteins [83, 84]. Using CRF overexpressing mice to maximize receptor activation, a phosphoproteomic analysis revealed increased signaling through β arrestin2 in male, but not female mice [82]. Collectively, these findings reveal that signaling of the CRF₁ receptor is sex biased and signals more through Gs-mediated pathways in females and β arrestin2-mediated pathways in males [85, 86]. Aside from changes in electrophysiology, this sex biased signaling could result in other cellular changes that drive females and males towards different pathological states.

β arrestin2 also initiates receptor internalization, a process by which CRF₁ receptors are trafficked from the membrane to the cytoplasm, where they can no longer respond to CRF [80, 87–89]. This internalization is thought to be compensatory and help moderate the potentially disruptive effect of high levels of CRF release. Using an immunoelectron microscopy approach, we confirmed that CRF₁ receptors internalize following stress in male, but not female rats (Fig. 2a,b) [78, 90]. A lack of internalization in females relative to males could render females vulnerable to conditions of CRF hypersecretion. To test this

idea, we used CRF overexpressing mice that express similarly high levels of CRF in the LC in both sexes, and these CRF levels are much higher than those found in wild type mice [91]. Much like stressed rats, the CRF₁ receptor in LC neurons is internalized in male, but not female CRF overexpressing mice [91]. This sex difference in trafficking translates into physiological differences such that female CRF overexpressing mice have LC neurons that fire at a faster rate than wild type controls of both sexes [91]. Yet LC neurons of male CRF overexpressing mice fire at wild type levels, despite the fact that excess CRF is found in the LC, an effect that highlights the compensatory properties of CRF₁ internalization.

When considered together, the various CRF₁ receptor sex differences result in greater sensitivity to CRF in females compared to males. Increased CRF₁ receptor-Gs coupling and cAMP/PKA signaling in females renders their LC neurons more sensitive to even low levels of CRF, while a lack of CRF₁ receptor internalization renders their neurons less adaptable to conditions of excess CRF relative to males. Although these effects may help females become alert during acute or moderate stressors, under conditions of CRF hypersecretion, females may be more likely to suffer from hyperarousal than males. CRF hypersecretion is thought to contribute to the etiology of PTSD and depression [30, 31], disorders which, as noted, have hyperarousal as a key feature. Thus, if these sex differences in LC CRF₁ receptors are present in humans, they could help account for the higher rates of PTSD and depression in women relative to men.

3.1 Male vulnerability to stress-induced cognitive deficits: Evidence from human studies

Schizophrenia and ADHD are chiefly characterized by disruptions in cognition. These disorders affect men more frequently than women, and there are also sex differences in symptomatology [6, 92, 93]. In patients with schizophrenia, most studies indicate that men have greater cognitive deficits than women [6, 94–96]. Sex differences in verbal memory deficits in schizophrenia patients are linked to distinct structural changes in the brains of men versus women [97]. Unlike female patients, male patients have volumetric reductions in all regions that comprise a verbal memory circuit. For two regions within this circuit, the hippocampus and prefrontal cortex (PFC), their reduced size in males was associated with poor memory [97]. In contrast, female schizophrenia patients have a smaller anterior cingulate gyrus than healthy female controls, but the potential cognitive effects of this volumetric change appear to be mitigated by the recruitment of the inferior parietal lobule during the memory task in female patients [97]. In addition to assessing cognition, a recent fMRI study examined how stress alters the activity of brain regions within a stress circuit in female and male patients with psychosis [98]. During the stress challenge, women with psychosis had increased activity in the hippocampus and amygdala, but decreased activity in the orbital and medial prefrontal cortices compared to control women [98]. In contrast, men with psychosis had increased activation in all the stress-responsive brain regions assessed compared to their same sex control group. Activity in the hypothalamus and anterior cingulate was significantly correlated with stress-induced cortisol levels, but only in men with psychosis [98]. Collectively, these studies reveal that in patients with schizophrenia

symptoms, cognition and stress responsivity are associated with structural and functional differences between the female and male brain.

Sex differences are also reported in ADHD [93]. A meta-analysis revealed that boys with ADHD have greater attention deficits than girls [99]. Yet, females with ADHD are more frequently diagnosed with the inattentive subtype of the disorder, relative to other subtypes [93, 100]. These seemingly contradictory findings may be due to the fact that female ADHD patients present with lower levels of hyperactivity and impulsivity than males [93, 99, 101, 102], so inattention is their prominent feature. In addition to differences in symptoms, there are structural sex differences reported in brains of children with ADHD [93]. Both sexes show cerebellar reductions compared to healthy controls, but boys with ADHD have a smaller right anterior frontal region and right striatum than boys without ADHD, an effect not reported in girls [93, 103, 104]. Functional neuroimaging studies that are disambiguated by sex and/or powered to detect sex differences in ADHD are rare. A study on working memory did compare the sexes and found working memory impairments in ADHD patients, regardless of sex, but only males showed reduced activation of the right frontal, temporal, and subcortical regions, as well as left occipital and cerebellar regions during the working memory task [105]. Interestingly, brain activation during the working memory task was negatively correlated with hyperactive symptoms for men and inattentive symptoms for women, suggesting that circuits related to different symptoms of ADHD can differ by sex [105]. Although the data comparing the sexes in ADHD is very limited, collectively these studies suggest that, compared to females, males with ADHD have more structural and functional changes in forebrain regions that are critical for cognition. How stress impacts these effects and whether it does so to a greater degree in males than females with ADHD remains unexplored. However, data from healthy human subjects and animal models suggests that, in general, stress does alter cognition more in males than in females.

Most of the studies assessing sex differences in cognitive processes following stressor exposure in healthy humans employ acute manipulations of stress. In men, acute stressors, such as the Trier Social Stress Test (TSST) and the cold pressor stress task, enhance the encoding or consolidation of recognition memory, declarative memory, and working memory [106–110]. However, administration of these stressors prior to memory retrieval impairs recall in men [111]. In contrast, there are reports that in women these same stressors have no effect on recognition memory, declarative memory, working memory, or recall [106–109, 112]. There are, however, some exceptions to this pattern wherein, rather than showing a lack of response in comparison to men, women show the opposite effect of stress on cognition. For example, a modified TSST disrupts the acquisition of fear conditioning in women, while enhancing acquisition in men [113]. Similarly, in one report, working memory was impaired following the TSST in women, but improved following the TSST in men [110], but see [107]. These seemingly conflicting results in women may be linked to age, hormonal status, timing of the stressor and task, or the type of mnemonic process assessed. Further research is required to fully understand these factors. Yet, collectively these studies reveal a general pattern of sensitivity to the influence of stress on cognition in men which is not observed in women.

Stress regulation of cognition in men, but not in women, is closely tied to cortisol levels. Unlike in women, men's cortisol levels are positively associated with the acquisition of fear conditioning [114], a sex difference that is still observed when a stressor precedes training on the fear conditioning task [113]. For other cognitive tasks, however, the relationship between cortisol and performance reverses in men. For instance, one study found a negative correlation between cortisol levels and declarative memory following the TSST in men, but not in women [115]. Additionally, cortisol levels were negatively associated with performance on a social memory task in men, although women were not included in the study [116]. Thus in men, cortisol appears to enhance the acquisition of fear conditioning, while impairing declarative and social memory. This may indicate that cortisol differentially alters learning versus memory in men. Alternatively, cortisol's effects may be region specific in men, with cognitive processes that engage different brain regions being differentially altered by cortisol levels. Importantly, these relationships between cortisol and cognition are not reported in women.

The relationship between stress and cognition in women appears to be modulated more by circulating ovarian hormones than cortisol. Studies that track women's menstrual cycles repeatedly conclude that women in phases of the cycle with higher estradiol levels are protected from the effect of stress on cognition [112, 121, 122]. Women who underwent TSST before memory retrieval only showed a cortisol response to the stressor and a subsequent retrieval impairment when they were in the follicular phase of the menstrual cycle, which is characterized by low levels of circulating estradiol and progesterone [121]. Consistent with these data, the TSST had no effect on memory retrieval in a sample comprised solely of naturally cycling women in the luteal phase, which is characterized by elevated levels of ovarian hormones [112]. Estrogens play a role in modulating fear conditioning as well, which is arguably a stressful procedure. Women on hormonal contraceptives, who have lower overall estradiol levels, showed poorer fear extinction recall than naturally cycling women, who have higher overall estradiol levels [123]. Another study reported a significant positive correlation between estradiol levels and extinction retention in a fear conditioning task [122]. Together, these studies suggest that estrogens modulate the effects of stress on cognition in women, with higher levels of estrogens promoting resilience to stress regulation of cognitive processes.

In summary, men and women seem to rely on different mechanisms for mediating the effects of stress on cognition in both patient and healthy populations. In patient populations, cognitive deficits are related to greater changes in forebrain structures in men than women. In healthy controls, mnemonic processes are more greatly affected by stress in men than women and cortisol is linked to these effects in men. In contrast, estrogens appear to mitigate the effect of stress on cognition in women. These differences in how stress affects cognition in males and females are important for understanding sex differences in susceptibility to psychiatric disorders. In particular, this pattern of cognitive sensitivity to stress in men may be a risk factor for their higher rates of psychiatric disorders defined by cognitive deficits and their greater presentation of cognitive symptoms.

3.2 Male vulnerability to stress-induced mnemonic deficits: Evidence from animal studies

Many studies have investigated how stress affects learning and memory in animal models, and some have considered sex differences. A portion of this literature focuses on prenatal or perinatal stress, and, generally, exposure to chronic stress early in development alters cognitive processes more in male than female rodents [34, 124–126]. In addition to early life stress, other studies have focused on how exposure to an acute stressor alters learning and memory in both sexes. For example, work from Shors and colleagues demonstrated that an acute stressful event improves classical eyeblink conditioning in male rats, while it impairs conditioning in female rats, effects that are, in part, related to sex differences in underlying circuits [127–132]. This mirrors some of the human literature that reports opposing effects of acute stress on learning in men versus women [110, 113]. While the impact of early life stress and acute stress on cognition in males and females is very important, here we focus on the immediate effects of chronic stress on mnemonic processes, as this is the type of stress typically associated with exacerbating symptoms in patients with ADHD and schizophrenia [21, 24].

In male rats, chronic restraint stress in adulthood impairs performance on a number of spatial memory tasks [38, 133–137]. In contrast, chronic restraint stress improves spatial memory in female rats [38, 136, 138–140]. A similar sex difference has been reported following chronic unpredictable stress, although this finding is less consistent, perhaps due to differences in unpredictable stress procedures [141, 142]. Sex differences in the effect of chronic stress on mnemonic processes are not limited to spatial memory. Recognition memory is also impaired by chronic stress in male rats [139, 143, 144]. However, chronic stress does not alter recognition memory in female rats [139, 143, 144]. Notably, when the sexes are directly compared, memory is comparable in male and female unstressed rats [38, 140, 141, 143], so the lack of a stress-induced impairment in females is not due to their inability to adequately perform memory tasks. One exception to this pattern is cognitive flexibility, which is impaired by chronic stress in female, but not male rats [145]. When considered together, similar to human studies, the majority of animal studies reveal that mnemonic processes are more broadly affected by stress in male compared to female rats. In the rodent literature, chronic stress reliably impairs spatial and recognition memory in males, but not females. The basis of this sex difference is not fully understood, but there is some evidence that estradiol in females may be protective against the negative effect of stress on spatial and reference memory [38, 143, 146], which again is similar to the protective effect of estrogens in humans.

At a cellular level, changes in the morphology of dendrites are thought to contribute to the effects of chronic stress on memory. The deficits in spatial memory observed following chronic stress in male rats prompted investigations of alterations in dendrites in the hippocampus, a structure required for spatial processes. Chronic stress reduces dendritic complexity of pyramidal neurons in the CA3 region of the hippocampus in male rats [147–149]. Administering an antidepressant during chronic stress in males prevents this dendritic atrophy [150, 151], along with stress-induced spatial deficits [152], which suggests a causal

role for morphological changes of CA3 neurons in mediating the negative effect of chronic stress on spatial memory in males. In contrast, chronic stress does not induce dendritic retraction in CA3 in female rats [149, 153]. This resilience to dendritic remodeling in females may explain the failure of chronic stress to impair their spatial memory.

Changes in dendrites following chronic stress have also been observed in the medial PFC (mPFC), which mediates cognitive processes and is engaged in recognition memory tasks [143]. Similar to findings in CA3, chronic stress reduces apical dendrites in mPFC pyramidal neurons in male rats [154–156]. For females, this effect is opposite; chronic restraint stress increases apical dendrites [154]. The same effect on morphology is observed in ovariectomized females with estradiol replacement, but not in ovariectomized females without estradiol replacement, highlighting a role for estrogens in this sex difference [154]. Interestingly, these stress-induced dendritic alterations occur in different circuits within the mPFC depending on sex. Dendritic hypertrophy induced by chronic stress is observed specifically in basolateral amygdala-projecting mPFC neurons in females that were ovariectomized and replaced with estrogen, but not those without estrogen replacement [157]. In contrast, these basolateral amygdala-projecting mPFC neurons in males were resistant to the dendritic retraction that was observed on other populations of mPFC neurons [158]. The structures receiving input from the mPFC neurons on which dendritic remodeling due to stress occurred in males remain unidentified [158], however this work highlights how stress-induced changes in dendritic morphology can be sex- and circuit-specific, as well as regulated by ovarian hormones. It is likely that chronic stress has cellular and molecular effects beyond inducing morphology changes that also bias males, but not females towards impaired mnemonic processes. However, the above studies do highlight that changes in dendrites, which would alter connections in learning circuits, are an important mechanism contributing to sex-specific effects of chronic stress on cognition.

3.3 Gonadal hormone regulation of stress effects on attention: Evidence from animal studies

Many studies investigating sex differences in the effects of stress on cognition have focused on mnemonic processes. Recently, our laboratory has been interested in whether stress alters attention in female and male rats. Given our previous studies exploring sex differences in CRF sensitivity, we first wanted to determine whether CRF altered attention. A previous study found that central administration of CRF altered selective and divided attention in male rats [159], but we wanted to specifically determine the effect of CRF on sustained attention, the ability to monitor a situation for intermittent and unpredictable events, in both sexes. To this end, we employed a well characterized sustained attention task, where rats are trained to discriminate between signal trials (where a brief light is presented) and non-signal trials [160]. Accurate signal detection in this task requires the prefrontal release of acetylcholine from neurons originating in the nucleus basalis of Meynert (NBM) within the basal forebrain [161–164]. We found that central administration of CRF disrupted performance—as measured by a vigilance index that takes into account accuracy on both signal and non-signal trials—in a dose-dependent manner in both sexes [165]. Although a significant sex difference was not found, the effects of CRF on sustained attention were

modulated by ovarian hormone status in female rats. Attention was similarly disrupted by central CRF in males and females in the diestrous phase of their cycle, which is characterized by lower levels of ovarian hormones. In contrast, females in the proestrous and estrous phases of their cycle (combined for this analysis), which are characterized by higher levels of ovarian hormones, were resistant to the disruptive effect of CRF on sustained attention (Fig. 3a)[165].

How ovarian hormones regulate the effects of CRF on attention are still under investigation. Yet results from a functional connectivity analysis assessing CRF-activated networks between male and cycling female rats revealed differences in functional connectivity between the NBM and mPFC, the key regions in the attention circuitry, following central administration of CRF [166]. Specifically, central CRF increases cFOS, a marker of neuronal activation, in the NBM and infralimbic region of the PFC in female and male rats, regardless of cycle phase [166]. However, correlations for neuronal activation between these regions differed in females in the proestrous phase relative to males and females in the diestrous phase (Fig. 3b). This result suggests that ovarian hormones regulate how the sustained attention circuits coordinate to respond to CRF. The mechanism by which ovarian hormones regulate this circuit remains unknown, but direct regulation of this circuit is possible because ovarian hormone receptors are present in the NBM and PFC [167–169]. Perhaps activation of these receptors promotes some downstream process that mitigates the effect of CRF in these regions. There remains much more to investigate with regards to how stress differentially regulates attention in males and females. However, the results thus far support the pattern observed with other stress effects on mnemonic processes in rats and healthy humans; namely, that ovarian hormones protect against potentially disrupting effects of stress on cognition.

4.1 Implications and conclusions

The processes that underlie psychiatric disorders and cause sex differences therein are complex. The data presented here highlight that one contributing factor is sex differences in responses to stress. This emerging research suggests that stress biases females towards hyperarousal and males towards altered cognition. These data suggest that interventions designed to mitigate the effects of stress would be helpful in treating certain psychiatric disorders. Although such interventions have been a focus for PTSD and depression [170, 171], the therapeutic benefits of mitigating stress to improve symptoms of ADHD and schizophrenia have received less attention, and therefore could present a novel avenue to treatment development. Additionally, the similarities between animal and human findings suggest that employing both sexes in preclinical stress research can lead to discoveries relevant to human health. For example, the work on sex differences in CRF₁ receptors in the LC suggest that increased CRF₁ receptor binding to β arrestin2 in males confers protection against stress-induced hyperarousal. Biased ligands that switch signaling from G-protein to β arrestin-mediated signaling have been developed for other receptors [172–174]. If a similar compound is developed for the CRF₁ receptor, it may reduce stress-induced hyperarousal and be particularly effective in females [86, 175, 176]. Notably, if only male rodents were included in these studies, as is typically the case in animal studies [177], the protective effects of β arrestin2 and their potential benefits for treatment would not have been

discovered. Thus, comparing how stress differentially affects the sexes will likely lead to novel treatments for sex biased psychiatric disorders, improving outcomes for both female and male patients.

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Figure 1.

Schematics depict a sex difference in LC dendrites and how this could affect the processing of inputs. Dendrites of female LC neurons (A) are longer and more complex than dendrites of male LC neurons (B), which would increase the input from regions that project to the dorsolateral (green) and ventromedial (orange) peri-LC regions in females compared to males. Bar., Barrington's nucleus; BNST, bed nucleus of the stria terminalis; CeA, central amygdala; NTS, solitary nucleus; PAG, periaqueductal gray; PGI, nucleus paragigantocellularis; PVN, paraventricular nucleus

Figure 2.

Images illustrate sex differences in CRF₁ receptors. In females, CRF₁ receptors bind to Gs and CRF₁ receptors do not internalize following stress and CRF overexpression, which leads to a large response to CRF (A). In males, CRF₁ receptors associate with β arrestin2 (β arr) and CRF₁ receptors internalize following stress and CRF overexpression, which results in a smaller response to CRF (B).

Figure 3.

Ovarian hormones regulate the effect of CRF on sustained attention. (A) The vigilance index, an overall measure of attentional performance, is disrupted by CRF (0.5 μ g, i.c.v.) in male and diestrus female rats, but not in proestrus/estrous females. Reproduced with permission [165]. (B) Sustained attention circuitry comprised of the nucleus basalis of Meynert (NBM) and infralimbic cortex (IL) is activated by CRF in all groups, but the correlation for neuronal activation between these regions, as assessed with Fisher's z-tests, is significantly different in proestrus female rats compared to males and diestrus females (Bangasser et al., 2015). * $p < 0.05$. Reproduced with permission [33].