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The biological mechanisms of sex difference of anxiety

ArmanNurlan [1], Renjie Qin [2], Man Li [1, 3, *]

[1] College of Acupuncture and Massage, Jiangxi University of Traditional Chinese Medicine, Nanchang 330004, China

[2] School of Basic Medicine, Tongji Medical College, Hubei key Laboratory of Drug Target Research and Pharmacodynamic Evaluation, Huazhong University of Science and Technology, Wuhan 430030, China

[3] Chengdu Center for Gender-specific Biology and Medicine, Chendu 611137, China

* Corresponding author: liman73@mails.tjmu.edu.cn

Abstract. The sex difference in anxiety has long been a subject of extensive research in neuroscience and psychology. This paper aims to explore the underlying biological mechanisms that contribute to the observed sex-specific differences in anxiety-related behaviors. We review evidence from multiple fronts, including genetic, hormonal, neuroanatomical, and neurochemical factors. Genetic studies have suggested the involvement of sex-linked genes in anxiety-related traits, while hormonal factors, particularly gonadal hormones, have been shown to modulate anxiety-like behaviors in both sexes. Neuroanatomical differences in brain regions associated with anxiety, such as the amygdala and hippocampus, also contribute to the sex difference in anxiety. Finally, neurochemical factors, including neurotransmitters and neuromodulators, play a crucial role in the regulation of anxiety-related neural circuits. The current paper discusses these mechanisms in detail and highlights the importance of considering sex as a biological variable in anxiety research. Understanding the biological mechanisms underlying sex differences in anxiety can help us develop more targeted and effective treatment strategies for anxiety disorders.

Keywords: Anxiety; Sex difference; Biological mechanisms; Genetics; Hormonal factors; Gonadal hormones; Neuroanatomical differences; Amygdala; Hippocampus; Neurochemical factors; Neurotransmitters; Neuromodulators; Anxiety research; Treatment strategies; anxiety disorders.

1. Introduction

Anxiety disorders vary between women and men, with women affected more. Elucidating sex biases in disease prevalence and severity can enhance our understanding of pathophysiology and guide treatment development. A significant sex difference in psychiatry is higher rates of mood and anxiety disorders in females [1].

Gender differences in anxiety presented in a variety of ways. Survivors of childhood sexual abuse frequently suffer from anxiety and depression. Key symptoms include worry, sadness, and low energy. It was found that these symptoms varied by gender. Males tend to link guilt with suicide, while females associate worry with suicidal thoughts. Tailored treatment should address guilt in males and worry in females to reduce suicide risk. PMID: 33888800. Anxiety and stress-related disorders are prevalent, characterized by excessive fear responses. There's a significant sex bias, with women disproportionately affected [2].

Factors like masculinity might protect against anxiety, while femininity might increase risk. Brain structures, genetics, and sexual hormone fluctuations could contribute to women's higher anxiety [3].

2. Sex difference in brain structure

Many vertebrate species, including primates and humans, exhibit sexual dimorphism in their brains [4]. Diverse research on this topic has revealed that males possess larger overall brain volume, more cortical surface area and gyrification, a higher proportion of white matter to gray matter, reduced gray

matter density, and thinner cortical thickness in comparison to females. Additional disparities exist in white matter organization, cerebral blood flow, caudate nucleus, and hippocampus size [5]. There is an ongoing debate surrounding the extent and impact of sex-specific differences in brain structure and function [6].

The human brain's local gray matter volume (GMV) exhibits sex-specific differences, and there is ongoing debate regarding the scale, location, and direction of these disparities [7]. Research has revealed that women possess greater GMV in specific regions, including the medial and lateral prefrontal areas, superior temporal sulcus, posterior insula, and orbitofrontal cortex. Conversely, men exhibit higher GMV in subcortical temporal structures such as the amygdala, hippocampus, temporal pole, fusiform gyrus, primary visual cortex, and motor areas, including the premotor cortex, putamen, and anterior cerebellum [8]. Ritchie et al [9]. further observed that males tend to have higher raw volumes, raw surface areas, and white matter fractional anisotropy, while females demonstrate thicker cortices and greater white matter tract complexity, with considerable overlap between the sexes [10].

A well-established sex difference in psychiatry is the higher incidence of mood and anxiety disorders in females. These disorders share stress as a potential etiological contributor and hyperarousal as a core symptom, suggesting that the distinction between sexes lies at the intersection of stress and arousal systems. The stress axis and the brain norepinephrine arousal system are a key point at which sex differences occur and are translated to differences in the expression of mood disorders, including a circuit designed to relay emotion-related information via the limbic corticotropin-releasing factor (CRF) system to the locus coeruleus (LC)-norepinephrine arousal system. Recent findings reveal sex differences in CRF receptor signaling and trafficking, leading to enhanced arousal and compromised stress adaptability in females. Additionally, sex differences in LC dendritic structure enhance females' ability to receive and process limbic information. These data suggest that the LC arousal system in females is poised to process more limbic information and respond in an enhanced manner compared to males [1].

Connectomics, a network-based framework for brain interconnectivity, offers a holistic understanding beyond regional analysis. Using MRI-derived connectomes, sex differences in resting-state connectivity were revealed. Initial findings show non-significant differences in the 22-25 age range, but these become significant in the 26-30 and 31-35 age groups. Diverging sex differences involve prefrontal cortex, temporal lobe, amygdala, hippocampus, inferior parietal lobule, posterior cingulate, and precuneus. They also identified sex-specific differences in self-reported inattention, hyperactivity, and anxiety, which interact with age and the basal configuration [11].

Neuroimaging studies have shown significant gender differences in emotional processing. Women respond more strongly to negative emotional stimuli, which is associated with increased risk of depression and anxiety. Meta-analysis revealed that women have higher activation in the left amygdala and other regions in response to negative emotions, while men have greater activation in the left amygdala and other regions in response to positive emotions. The amygdala is a key region for emotional processing, showing gender differences dependent on emotional valence. In conclusion, gender is an important factor regulating emotional processing, and individual differences need to be considered to understand the neurobiology of emotions [12].

It was found that the anxiety level of women was related to their speed in processing negative emotions, while there was no such relationship in men. In women, anxiety is negatively correlated with the activity of the medial prefrontal cortex, a region of the brain responsible for emotional regulation. This suggests that women's sensitivity to negative emotions may be influenced by dysfunction in the emotional regulation region of the brain. This helps us understand why women are more susceptible to emotional problems and may guide more personalized treatment approaches [13].

Aging and sex differentially impact anxiety-like behavior and the connection between the medial prefrontal cortex (mPFC) and medial amygdala (MeA) in rats. Old animals displayed less anxiety and stronger mPFC-MeA connectivity, while young females were less anxious and showed stronger

connections than males of the same age. The results suggest a negative relationship between anxiety levels and mPFC-MeA connectivity [14].

Experiments have shown that when women are under stress, the neuronal activity in the medial prefrontal cortex (mPFC) changes and affects learning, which is not the case for men. In particular, the prelimbic (PL) subregion of the mPFC plays a crucial role in women's learning during stress, rather than the infralimbic (IL) subregion. Experiments have demonstrated that PL activity under stress affects women's associative learning, while IL inactivation leads to impaired learning. These data suggest that the communication between PL and BLA plays a key role in women's stress experiences, which may explain the phenomenon of cognitive impairment in women after stressful life events [15].

Another study investigated sex differences in the relationship between neuroanatomical characteristics and the Behavioral Inhibition System (BIS) and Behavioral Activation System (BAS) in healthy young adults. Using voxel-based morphometry, it found that females showed negative correlation between BIS sensitivity and parahippocampal gyrus volume, while males exhibited the opposite pattern. Conversely, BAS sensitivity positively correlated with ventromedial prefrontal cortex and inferior parietal lobule volumes in females, but negatively in males. These findings suggest sex-related neuroanatomical differences in the processing of negative emotions and reward-related information linked to BIS and BAS, respectively, which may contribute to gender-specific vulnerabilities to affective and externalizing disorders [16].

Additionally, the observed sex difference in anxiety correlates with differences in low-frequency delta and theta oscillations in the nucleus accumbens [17].

3. Sex difference Neurotransmitters and neurotrophic factors

Neurotransmitters and neurotrophic factors and their receptors are closely related to sex differences in anxiety. Females are more prone to depression and anxiety than males, making it a leading cause of disease-related disability among women. Given the role of the dopamine D1-D2 heteromer in depression- and anxiety-like behaviors, the potential involvement of this receptor complex in mediating sex differences in these behaviors and related biochemical signaling is intriguing. In non-human primates and rats, females exhibit a higher density of D1-D2 heteromer complexes and a greater number of neurons expressing them compared to males. Notably, this sex difference persists even when D1 receptor expression is lower in female rats, with no difference in D2 receptor expression. Analysis of signaling pathways further reveals that the sex difference in D1-D2 heteromer expression leads to distinct basal and heteromer-stimulated activities in key signaling pathways, such as BDNF/TrkB and Akt/GSK3/β-catenin. These findings suggest that the higher expression of D1-D2 heteromers in femalesmay significantly increase their predisposition to depressive-like and anxiety-like behaviors [17].

Pregnant mothers enduring severe adverse events may heighten the risk of anxiety disorders in their offspring, wherein glutamate receptors play a vital neurobiological role. Our study explored the anxiety-related behavioral impact of prenatal chronic mild stress (PCMS) using the elevated plus maze (EPM) and assessed the changes in glutamate receptors in distinct brain areas due to PCMS and/or anxiety-inducing conditions.

Our findings revealed that PCMS elevated anxiety-like behavior among both male and female offspring. Specifically, male EPM rats displayed notable reductions in mGluR2/3 in the prefrontal cortex, mGluR1 and mGluR2/3 in the hippocampus, along with increased levels of mGluR5, NR1, NR2B, and PSD95 in the amygdala. Conversely, female EPM rats exhibited decreased mGluR5 in the hippocampus, mGluR2/3 and mGluR5 in the prefrontal cortex, while NR2B and PSD95 levels rose in the amygdala.

Notably, PCMS appeared to have no significant effect on the baseline expression of glutamate receptors in adult offspring, but it triggered substantial alterations in response to anxiety-inducing

stimuli, exhibiting a sexual dimorphism. These observations strengthen the pathophysiological hypothesis linking prenatal stress as a risk factor in the development of anxiety disorders among offspring [18].

The excessive secretion of corticotropin-releasing factor (CRF) is linked to the pathophysiology of major depression and post-traumatic stress disorder, which are more prevalent in women than in men. Preclinical studies have identified gender differences in CRF receptors, with female rodents exhibiting increased neuronal sensitivity to CRF compared to males. These cellular gender differences suggest that CRF may regulate brain circuits and behaviors differently in males and females. To validate this, we assessed gender differences in anxiety-related behaviors induced by central CRF infusion. High doses of CRF increased self-grooming in female rats more than in males, and the effect was even greater during estrus (high ovarian hormones) compared to metestrus (low ovarian hormones), indicating ovarian hormones enhance CRF's anti-anxiety effect. Mapping brain regions associated with CRF-induced self-grooming using the neuronal activation marker cFOS revealed a positive correlation in females during estrus, but a negative one in both genders, indicating ovarian hormones alter the relationship between neuronal activation and behavior. Since CRF regulates many regions that work together to coordinate different aspects of stress response, we further examined gender differences in CRF-activated functional connectivity networks. Interestingly, hormonal status altered CRF-induced neuronal activation correlations across brain regions, with the most significant differences observed between estrous females and males, particularly in comparing neuronal activation between the prefrontal cortex and other forebrain areas. These findings suggest that ovarian hormones alter how brain regions respond to CRF, potentially driving different stress coping strategies in males and females. These gender differences in stress response may also contribute to women's vulnerability to psychiatric disorders characterized by excessive CRF secretion [19].

CRF receptors are implicated in psychiatry involve anxiety and depression, which are twice as common in women as men after puberty. compared CRF receptor binding in pre- and post-pubertal rats in eight. Distinct sex differences were observed in eight CRF receptor-expressing areas, indicating that sex differences pervade the CRF receptor system in rats. In the nucleus accumbens and olfactory tubercle, juveniles initially exhibited identical CRF1 binding levels, but this pattern shifted in adult females, who displayed higher binding. Within the piriform cortex, CRF1 binding patterns diverged, with an increase observed in females and a decrease in males, reflecting a sexual dimorphism. When it came to the anterior cingulate, CRF1 binding was consistently stronger in females than in males across both ages. Prior to puberty, CRF1 binding in CA3 was stronger in males, but during puberty, this binding decreased, effectively eliminating the sex-based difference. Conversely, CRF2 binding in the posterior bed nucleus of the stria terminalis was consistently greater in males, regardless of age. However, in each of the three subdivisions of the lateral septum, females demonstrated higher CRF2 binding than males, both as juveniles and as adults. Lastly, in the ventromedial hypothalamus, CRF2 binding levels were initially similar in juveniles, but these levels increased in males, ultimately leading to a sex difference in adults. Mechanisms controlling these differences are likely to be sex-, region-, and subtype-specific [20].

This study found sex differences in the effects of chronic variable stress (CVS) on corticotropin-releasing factor receptor 1 (CRFR1) cells in mice. Female mice exhibited increased CRFR1-GFP cell numbers and CRFR1/pCREB co-expression in the AVPV/PeN after CVS, while males showed a male-specific reduction in CRFR1/c-Fos cells in the PVN. These sex-specific effects of CVS on CRFR1 populations may contribute to gender disparities in stress-induced mood disorders [21].

In addition to neurotransmitters, neurotrophic factors have also been linked to sex differences in anxiety. This study examined the long-term impacts of noxious stimuli on nociceptive and anxiety-like behaviors, hippocampal function, and neurogenesis in adolescent rats. Noxious stimulation, via intra-plantar injection of Complete Freund's adjuvant (CFA), was administered at different developmental stages (P1, P8, or P21). Hypoalgesia and reduced anxiety-like behaviors were observed, particularly in female adolescents. Maximum cell proliferation in the dentate gyrus was

seen in P8 rats, with males showing higher proliferation than females on P1 and P8. BDNF levels were positively correlated with proliferation, while plasma corticosterone was inversely related. Sex differences were evident in manganese-enhanced MRI signal, being more prominent in P1 females. This research marks the initial inquiry into the cellular mechanisms underlying sex-dependent long-term effects of nociceptive stimuli in newborns [22].

4. Sex difference in Hormones

The prevalence of affective disorders is higher in women than men, potentially due to hormonal and environmental influences during critical developmental periods. Gonadal hormones play a role in brain formation, influencing stress responsivity. In mice, testosterone propionate (TP) administered postnatally and during puberty had distinct effects on female stress responses. Activational TP reduced sex differences in the hypothalamic-pituitary-adrenal axis stress response, while organizational TP increased anxiety-like behaviors. These findings suggest that sex differences in stress responsivity may be partially attributed to the absence of testosterone in females [23].

Previous studies have found that prepubertal hormone changes affect adult stress responses, especially in the brain's stress center. Androgen treatment during puberty can reduce stress effects in adulthood. Hormones during puberty are key in shaping stress responses later on [24].

Gender differences in stress-induced affective disorders such as depression and anxiety are more prevalent in women than in men. Male resilience to these conditions may be attributed to the presence of androgens, which are known to suppress stress responses and reduce anxiety-like behaviors. However, the neurobiological mechanisms underlying this gender disparity remain unclear. Given that the corticotropin-releasing hormone receptor 2 (CRHR2) is associated with the regulation of anxiety-like behaviors and is expressed in stress-reactive brain regions that also contain androgen receptors (AR), we hypothesized that androgens may exert their effects through actions on CRHR2. Our study examined the regulation of CRHR2 mRNA and receptor binding in the forebrain of male rats following androgen administration. Gonadectomized (GDX) young adult male Sprague/Dawley rats were treated with non-dramatizable androgen, dihydrotestosterone propionate (DHTP), using hormone-filled silicone rubber capsules. Control animals received empty capsules. CRHR2 mRNA levels in dissected brain regions were determined using quantitative real-time RT-PCR. Compared to vehicle-treated controls, DHTP treatment significantly increased CRHR2 mRNA expression in the hippocampus, hypothalamus, and lateral septum ($p<0.01$). A similar trend was observed in the amygdala ($p=0.05$). Additionally, in vitro autoradiography showed significantly elevated CRHR2 binding in the lateral septum of androgen-treated males, with the most significant differences observed in the ventral subregion. The regulation of CRHR2 mRNA by AR was also examined using in vitro methods. Hippocampal neurons from E17-18 rat fetuses, containing high levels of AR, were harvested and maintained in primary cultures for 14 days. Neurons were then treated with dihydrotestosterone (DHT; 1nM), DHT plus flutamide (an androgen receptor antagonist), or vehicle for 48 hours. CRHR2 mRNA levels were measured using quantitative real-time RT-PCR. Consistent with the in vivo study, DHT significantly increased CRHR2 mRNA expression in hippocampal neurons compared to vehicle-treated controls ($p<.02$). Flutamide treatment blocked the effects of DHT on CRHR2 mRNA, indicating that DHT's influence on CRHR2 expression is mediated by AR. In conclusion, the CRHR2 gene appears to be a target of AR regulation, suggesting a potential mechanism for how androgens may alter emotional and anxiety-related behaviors [25].

A prospective study found that women had a higher risk of developing non-remitting PTSD after trauma compared to men. Female trauma survivors showed lower proinflammatory cytokines and higher cortisol and progesterone levels, while testosterone levels were similar. Proinflammatory cytokines mediated the gender difference in PTSD risk, with higher levels in men associated with lower risk. Estradiol buffered this effect, suggesting that higher estradiol levels after trauma may protect men from developing non-remitting PTSD. The findings indicate gender differences in

inflammatory response to trauma exposure contribute to PTSD risk, and estradiol levels may modulate this risk in men [26].

Male rats carrying the testicular feminization mutation (Tfm-affected males) are insensitive to androgens, resulting in a female-typical peripheral phenotype despite possession of inguinal testes that are androgen secretory. Androgen-dependent neural and behavioral processes may likewise show atypical sexual differentiation. Interestingly, these mutant rats display elevated serum corticosterone, suggesting a chronic anxiety phenotype and dysregulated hypothalamic-pituitary-adrenal axis. In order to understand if elevated anxiety-like behavior is a possible mediating variable affecting the display of certain androgen-dependent behaviors, compared the performance of Tfm-affected males to wild type males and females in the elevated plus maze (EPM). They found that Tfm-affected male rats, insensitive to androgens, display a female-typical phenotype and elevated corticosterone levels, suggesting chronic anxiety. Tfm-affected males spent less time on open arms, indicating increased anxiety, without a global reduction in exploratory behavior. These findings implicate androgen receptor-mediated functions in anxiety behaviors, potentially providing insights into depression pathogenesis [27].

In addition to androgens, estrogen is also involved in gender differences in anxiety. found that women with high estradiol levels exhibited less deactivation in limbic regions and less subjective distress during stress compared to women with low estradiol levels. These findings suggest that ovarian hormone fluctuations may modulate the brain's response to psychosocial stress, potentially influencing risk for affective disorders in women [28].

Women are more prone to anxiety and depression than men, which may be related to gender differences in brain arousal systems and chronic stress regulation. Social isolation, as a form of early life stress, can trigger neurobiological changes, leading to increased anxiety and depressive-like behaviors. investigated the effects of post-weaning social isolation on acute stress sensitivity and behavior in rats. The results showed that social isolation reduced the levels of neuroactive steroid allopregnanolone in the brain and plasma corticosterone in both male and female rats. After acute stress, the plasma corticosterone level increased more significantly in male rats that were socially isolated. Female rats showed no change in allopregnanolone levels after acute stress, possibly due to higher physiological levels of this hormone in women. Accordingly, elevating allopregnanolone concentrations in male rats attenuated their reaction to foot-shock stress. Male rats that were socially isolated exhibited depressive-like behaviors and increased hippocampal brain-derived neurotrophic factor (BDNF), while ovarian steroids may buffer the adverse effects on these parameters in women. Additionally, dexamethasone suppression tests indicated increased abundance of glucocorticoid receptors in the hippocampus. In conclusion, isolation affects neuroendocrine responses to stress, plasticity, and sexual dimorphism in emotions [29].

The hippocampus, involved in cognitive and emotional responses, exhibits sex differences relevant to depressive and anxiety disorders. Male rats' hippocampi are slightly larger than females. Studies often focus on estradiol's effects on volumetric sex differences, neglecting androgens. explored the impact of both estradiol and androgens on new cells in developing rat hippocampi. Male neonates had more BrdU+ cells than females. Both testosterone and dihydrotestosterone increased BrdU+ cells in females, blocked by the androgen receptor antagonist. Only testosterone significantly increased neuronal nuclear antigen+ neurons. Estradiol also increased BrdU+ cells but not neuron numbers, instead promoting glial cell genesis. No sex difference in cell death was observed, suggesting gonadal steroids promote cell genesis [30].

Ghrelin is an important gastric hormone that not only promotes eating, controls energy homeostasis, and regulates blood sugar, but also has anti-anxiety and antidepressant effects. Studies have shown that female rats may be more sensitive to ghrelin compared to males. Female rats have higher levels of ghrelin in their serum, which is related to estradiol levels. Additionally, female rats express higher levels of ghrelin receptors in brain regions, especially in the amygdala after fasting. In behavioral tests, female rats showed stronger anti-anxiety responses to fasting and ghrelin. These gender

differences are partially regulated by gonadal steroids, particularly estradiol.It suggested that ghrelin plays an important role in regulating anxiety-like behavior in female rats [31].

A study investigated the role of guanylate cyclase C (GC-C) in anxiety levels, focusing on sex differences and the influence of estrous cycle and feeding in female animals. GC-C expression in the amygdala was found to be regulated by feeding, and activation of GC-C abolished sex differences in anxiety-related behavior tests. Additionally, GC-C mRNA expression increased after a meal only in female animals, leading to changes in anxiety levels. Therefore, attention should be paid to both estrous cycle and feeding time when studying anxiety in female animals. The results suggest that sex differences in anxiety disorders in humans could be GC-C dependent [32].

5. Sex difference in genetics

These sexual dimorphisms might be rooted in distinct gene regulation and expression patterns [33]. Genetic changes are strongly linked to sex differences in anxiety. The occurrence of anxiety and depressive disorders is generally twice as frequent among women as compared to men, with the gender disparity in prevalence typically manifesting during the adolescent period. Hormonal fluctuations during menstrual cycle, postpartum, and perimenopausal periods raise the risk for anxiety and depression. Decreased brain-derived neurotrophic factor (BDNF) is linked to affective pathology in humans and animals. A BDNF gene variant (Val66Met) reducing BDNF availability has been identified in humans and associated with neuropsychiatric disorders. It was found that Mice homozygous for the BDNF Val66Met SNP begin to exhibit increased anxiety-like behaviors over prepubertal and early adult development, show significant fluctuations in anxiety-like behaviors over the estrous cycle, and, as adults, differ from wild-type mice by showing significant fluctuations in anxiety-like behaviors over the estrous cycle-specifically, more anxiety-like behaviors during the estrus phase. These findings have implications regarding the potential role of this SNP in contributing to the anxiety and depressive disorders in women [34].

Sex-specific differences exist in psychiatric disorders, but preclinical models often focus on males, leaving the molecular mechanisms underlying these differences unclear. Our study identified over 3000 differentially expressed genes (DEGs) in the NAcS of male and female rats, with 303 conserved in humans. These DEGs are related to blood vessel morphogenesis and cell migration. Single nuclei RNA sequencing revealed sex-dependent expression patterns, with female-upregulated genes enriched in synaptic function. Notably, these female-upregulated genes in astrocytes, Drd3+MSNs, and oligodendrocytes are also enriched in psychiatric GWAS. Our data suggest an intrinsic molecular basis for sex-based differences in psychiatric disorders, implicating the NAcS [35].

Epigenetic changes have also been linked to sex differences in anxiety. Stressors, both chemical and psychological, can lead to lasting changes in brain function and behavior. DNA methylation alterations, especially in the amygdala, are crucial in mediating such changes, particularly for anxiety and stress responses. Our research found sex differences in Dnmt1 expression in the central amygdala of adult California mice, with females having higher levels. Social defeat stress reduced Dnmt1 and Dnmt3a expression in females' amygdala, while perinatal exposure to estrogens eliminated sex differences in Dnmt1 expression. These findings highlight the sensitivity of Dnmt1 expression to both stressors, suggesting future studies should explore its role in behavioral plasticity [36].

Deficiencies in the adaptive immune system are associated with anxiety-like behaviors and stress reactivity. Mice lacking T lymphocytes due to knockout of TCR β and δ chains exhibited exaggerated stress-related gene expression and higher baseline corticosterone levels after repeated restraint stress compared to wild-type mice. Moreover, sexual dimorphism in stress responses was abolished in these knockout mice. These findings suggest that T cell-brain interactions modulate sex differences in stress reactivity and CNS stress circuitry [37].

The role of Plant Genome Research Network (PGRN) in sex differences in anxiety was investigated. Female wild-type mice displayed higher anxiety than males in the elevated plus maze, while this

difference was absent in PGRN-deficient mice. Castration and testosterone/cholesterol treatment did not affect anxiety. The volume of the(LC), an anxiety-related brain region, was larger in males and PGRN-deficient miceNo significant differences were observed in the paraventricular nucleus (PVN). These results suggest PGRN's role in LC organization modulating anxiety [38].

Women are more likely to suffer from anxiety, and there are significant gender differences in stress responses between women and men. Elucidating the mechanisms underlying sex biases in the prevalence and severity of diseases can advance our understanding of their pathophysiological basis and serve as a guide for developing treatments.

However, sex differences are species-specific and often do not replicate human brain-related diseases. Human sex/gender disparities have a strong sociocultural component, challenging to model in animals. We support research exploring sex-related variables but caution against policies that overemphasize sex analysis, as it may distort research and overlook social, psychological, and cultural contributors to neurobehavioral health gaps. Both biological and psychosocial factors are needed to understand gender differences in anxiety, emphasizing the need for a biopsychosocial model and gender perspective (Figure 1).

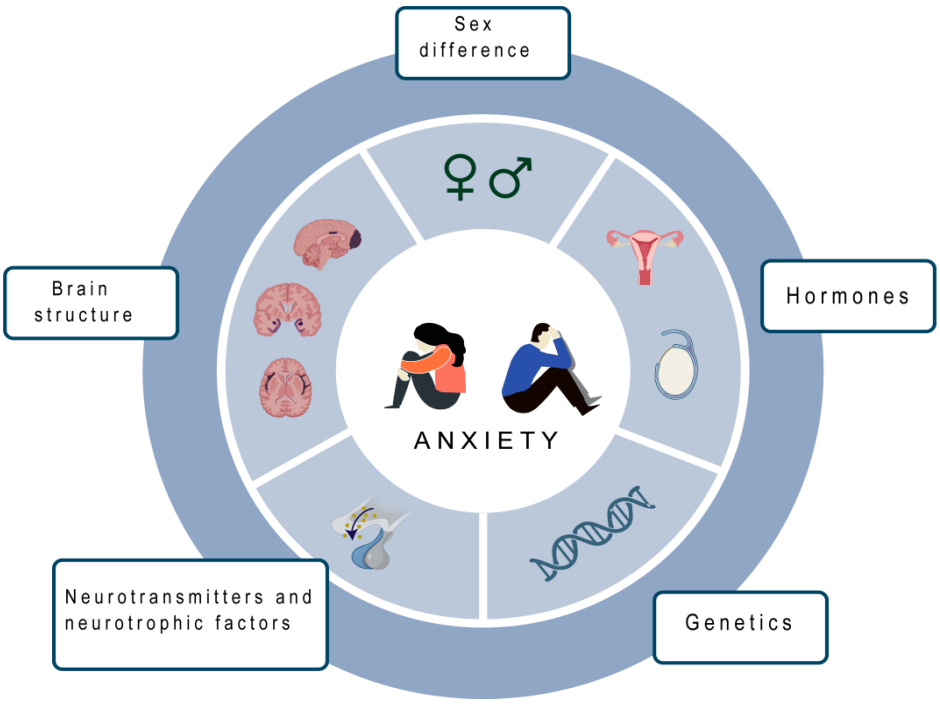

Figure 1. Gender differences in anxiety

6. Conclusion and Outlook

The biological mechanisms underlying sex differences in anxiety remain a complex and intriguing field of research. Emerging studies suggest that a combination of genetic, hormonal, and neurobiological factors contribute to these differences, which are often observed in both the prevalence and manifestation of anxiety disorders.

In terms of genetic factors, research indicates that specific genes may play a role in the sex-specific expression of anxiety. For instance, the X chromosome, which females have two copies of and males have one, harbors genes that have been linked to anxiety-related traits. Additionally, the role of sex hormones, such as estrogen and testosterone, in modulating anxiety is well-documented. Estrogen, for example, has been shown to influence the amygdala, a key brain region involved in emotional processing and anxiety.

From a neurobiological perspective, differences in brain structure and function between males and females may contribute to sex differences in anxiety. For instance, the amygdala and hippocampus,

which are involved in emotional regulation and memory, have been found to differ in size and connectivity between sexes. These structural differences may underlie the different ways that males and females respond to and process anxiety-provoking stimuli.

Future research in this area is likely to focus on elucidating the complex interplay between genetic, hormonal, and neurobiological factors in shaping sex differences in anxiety. This will involve using cutting-edge techniques, such as genomics, epigenetics, and neuroimaging, to gain a deeper understanding of the biological mechanisms underlying these differences. Ultimately, this knowledge may help develop more targeted and effective treatments for anxiety disorders, taking into account the unique needs of both male and female patients.

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