

Sex differences in anxiety and emotional behavior

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Abstract Research has elucidated causal links between stress exposure and the development of anxiety disorders, but due to the limited use of female or sex-comparative animal models, little is known about the mechanisms underlying sex differences in those disorders. This is despite an overwhelming wealth of evidence from the clinical literature that the prevalence of anxiety disorders is about twice as high in women compared to men, in addition to gender differences in severity and treatment efficacy. We here review human gender differences in generalized anxiety disorder, panic disorder, posttraumatic stress disorder and anxiety-relevant biological functions, discuss the limitations of classic conflict anxiety tests to measure naturally occurring sex differences in anxiety-like behaviors, describe sex-dependent manifestation of anxiety states after gestational, neonatal, or adolescent stressors, and present animal models of chronic anxiety states induced by acute or chronic stressors during adulthood. Potential mechanisms underlying sex differences in stress-related anxiety states include emerging evidence supporting the existence of two anatomically and functionally distinct serotonergic circuits that are related to the modulation of conflict anxiety and panic-like anxiety, respectively. We discuss how these serotonergic circuits may be controlled by reproductive steroid hormone-dependent modulation of *crfr1* and *crfr2* expression in the midbrain dorsal raphe nucleus and by estrous stage-dependent alterations of γ -aminobutyric acid (GABAergic) neurotransmission in the periaqueductal gray, ultimately leading to sex differences in emotional behavior.

Keywords Anxiety · Gender/sex · Stress · Panic disorder · PTSD · Estrous cycle

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Human gender differences in anxiety and emotional disorders

Similar to the increased prevalence of depression in women [194, 197, 387] the US National Institute of Mental Health reports that the lifetime prevalence of an anxiety disorder is 60 % higher in women than in men [198, 215, 247, 269] and that the onset, severity, clinical course, and treatment response of anxiety disorders differ significantly in women [293]. According to the current Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision (DSM-IV-TR), anxiety disorders are categorized into generalized anxiety disorder (GAD), panic disorder with or without agoraphobia, agoraphobia without history of panic disorder, posttraumatic stress disorder (PTSD), acute stress disorder, obsessive–compulsive disorder, social anxiety disorder (social phobia), anxiety secondary to a medical condition, substance-induced anxiety disorder, and stimulus-specific phobias [16, 189]. For this review, GAD, panic disorder, PTSD, and to a certain extent, acute stress disorder are of particular relevance because acute, repeated, or chronic stress exposures are common triggers for these psychiatric disorders [273, 286], because women may have an inherently increased stress vulnerability, and because key symptoms of these disorders have been successfully modeled in animals.

Generalized anxiety disorder

GAD is characterized by constant, nonspecific, often irrational worry and increased arousal in generally safe situations or interactions, resulting in significant impairment of everyday functionality. In developed, but not in developing, countries, women are two to three times more likely than men to suffer from GAD and have higher self-reported anxiety scores [90, 138, 215, 396]. In light of evolution, different rates of gametogenesis, number of gamete availability, and partner selection

may have predestined females to display a “more carefully assessing,” selective, or anxious behavioral spectrum than men, with the exception of pregnancy, peripartum period, and lactation, times when more aggressive and less anxious behaviors are beneficial in order to protect the offspring [265]. Accordingly, naturally higher anxiety scores in females commonly disappear during the peripartum period and lactation in both women [254, 280, 360] and rodents [49, 265].

Panic disorder

Panic disorder patients suffer from sudden brief periods of intense fear, hypervigilance, and distress, including autonomic symptoms like tachycardia, difficulty breathing, or nausea, without significant hypothalamic–pituitary–adrenal (HPA) axis stress responses [135]. Panic attacks can be, but do not have to be, triggered by specific stimuli, and the prevalence for panic disorder is two to three times as high in women as in men [127, 199, 396]. Also, in an 8-year longitudinal study Yonkers et al. [396] reported a threefold higher incidence of relapse in women compared to men. Kelly et al. [192] found that, among healthy test subjects, both men and women exposed to 20 % CO₂, a stimulus that elicits responses comparable to a spontaneous panic attack in panic patients, display similar autonomic responses (heart rate, electrodermal response, and frontalis muscle tension), while the subjective experience of fear and panic is far greater in women, indicating differences in how a panicogenic stimulus is perceived or processed in the female brain. To dissect such gender differences, research must also take the estrous cycle stage into account. The female brain must have mechanisms in place to cope with the monthly fluctuations of sex steroids, many of which are neuroactive [157, 252, 325], and it is probably only when such adaptive mechanisms are disturbed that psychiatric diseases manifest themselves. Anxiety sensitivity, e.g., the fearful belief that certain bodily sensations or the experience of anxiety itself may indicate undetected illness [248], is an established cognitive risk factor for the development of panic disorder [233, 268, 323]. During the premenstrual phase (days 24–28) both women with panic disorder and women with high anxiety sensitivity scores display a greater electrodermal response magnitude to auditory anxiety-provoking stimuli than healthy controls, while baseline recordings (in the absence of auditory stimulation) are the same among all groups and estrous phases [333, 334]. Similarly, women suffering from panic disorder are more likely to experience a panic attack after a laboratory CO₂ challenge during their premenstrual phase (days 23–28), compared to their intermenstrual phase (days 8–22) or healthy controls in either phase. The fact that a panicogenic challenge with CO₂ [132, 196] or intravenous sodium lactate [113, 318] causes premenstrual dysphoric disorder (PMDD) patients to display panic attacks at about the same rate as in panic disorder patients

further indicates a common underlying psychobiology [368]. Rodent as well as human research [190, 260, 274, 333] now proposes a three-factor interaction between (a) the rate at which progesterone and its anxiolytic metabolite allopregnanolone drop during the late luteal phase (humans) or during late diestrus (comparable phase in rodents) [221, 222, 314], (b) γ -aminobutyric acid (GABA)_A receptor sensitivity, kinetics, and subunit assembly in stress-coping circuitries including the amygdala and the periaqueductal gray (PAG) [143, 147], and (c) external stressors [94, 95, 340] as a model of sex-dependent predisposition for panic disorder [268].

Posttraumatic stress disorder

According to Olf [275], Breslau [60, 62], and Cohen and Yehuda [80], women are also more likely than men to develop acute stress disorder or PTSD, but controversy exists on whether this is due to inherently increased stress vulnerability or an earlier average age of trauma exposure, different types of PTSD-inducing events (e.g., sexual vs. combat-related assaults), or increased societal victimization of women combined with a different perception of the PTSD-inducing event [80, 275]. In contrast to GAD, PTSD diagnosis requires the experience of one or a series of psychologically traumatic events that result in flashback memories and nightmares as well as avoidance of stimuli associated with that event, in combination with typical anxiety symptoms such as hypervigilance. HPA axis dysfunction in PTSD is proposed for both genders [395], but a recent meta-analysis revealed that especially female PTSD patients appear to have lower circulating cortisol concentrations, compared to healthy controls [251].

Anxiety-relevant physiological and psychological gender differences

In healthy individuals, research over the past decade has identified several physiological and neurological gender differences that are relevant to stress responsiveness and anxiety. In the Trier Social Stress Test (TSST) [205], an anxiogenic, social-evaluative laboratory setting that reliably activates the human HPA axis, many studies report lower salivary cortisol responses in women compared to men [186, 212, 213, 324], while others find no difference [193, 388], yet women report overall more irritability and distress after the test [193]. Overall, these human HPA axis response results are puzzling because rodent studies robustly find the opposite sex difference, meaning higher increases of corticosterone secretion in females following various types of stressors [156, 327, 365, 381]. Because estrogens have been shown to positively regulate the expression of the human corticotropin-releasing factor (*CRF*) gene [363], which does not only orchestrate HPA axis activity, but is also expressed in

anxiety-related brain circuits [139, 216, 335, 375] and facilitates anxiety-like behaviors and lasting anxiety states [107, 328], differences in central actions of CRF may be more relevant to the female bias in anxiety disorders. This notion is supported by recent animal studies [28, 244, 346].

Imaging studies have now revealed several structural or functional gender differences in anxiety-relevant brain regions, such as the prefrontal cortex (PFC), hippocampus, and extended amygdala complex [348]. For example, the central part of the bed nucleus of the stria terminalis (BNST) is smaller in women compared to men [399], and a meta-analysis found that negative emotions were consistently associated with a stronger activation of the left central amygdala (CE) in women, whereas positive emotions activated the left CE more in men compared to women [348].

Interestingly, women have greater pain sensitivity than men [119, 142], a phenomenon that is due to thalamocortical processing or emotional appraisal of the stimulus, not spinal nociceptive activity [130], and that disappears when trait anxiety is controlled for [130, 300]. This likely depends on an interaction of sex steroid fluctuation and stress exposure because rodent studies have demonstrated that such sex-dependent hyperalgesia only occurs after a mild anxiogenic stressor during late diestrus, but not during other estrous stages [93].

Thus, while some gender discrepancies in emotional disorders might be skewed by the fact that women tend to report and seek help more readily than men [43, 199, 235], understanding the true biological determinants of anxiety disorders in both women and men is of therapeutic and economic importance.

Significance and socioeconomic impact of gender differences in anxiety

In Western civilizations, the lifetime prevalence for anxiety disorders amounts to approximately 18 % of the population [198], the average onset age for anxiety disorders is 11 years of age [269], and while the overall costs of anxiety disorders in the USA were an estimated \$42 billion/year during the 1990s [141], mental health care costs, including those for anxiety disorders, are currently outgrowing those of heart disease and cancer [270]. In women, more so than in men, anxiety disorders are also often identified as a preexisting condition before the onset of a major depressive episode [63, 64, 163, 281, 282], and anxiety often remains a major comorbidity with depression [61, 77, 106, 246, 258]. Recent studies have also shown that anxiety disorders occurring as early as childhood and adolescence are strong predictors of later depressive episodes [20] and, in girls, of later suicide attempts [65]. Generally, anxiety disorders are much more common in girls than in boys [20, 267], and adolescent

anxiety is associated with increased rumination in girls but not in boys [158]. This highlights the ethical and socioeconomic need to prevent or treat anxiety disorders as early as possible under the reasonable assumption that preventing the manifestation of an early anxiety disorder may also reduce the risk of later affective disorders.

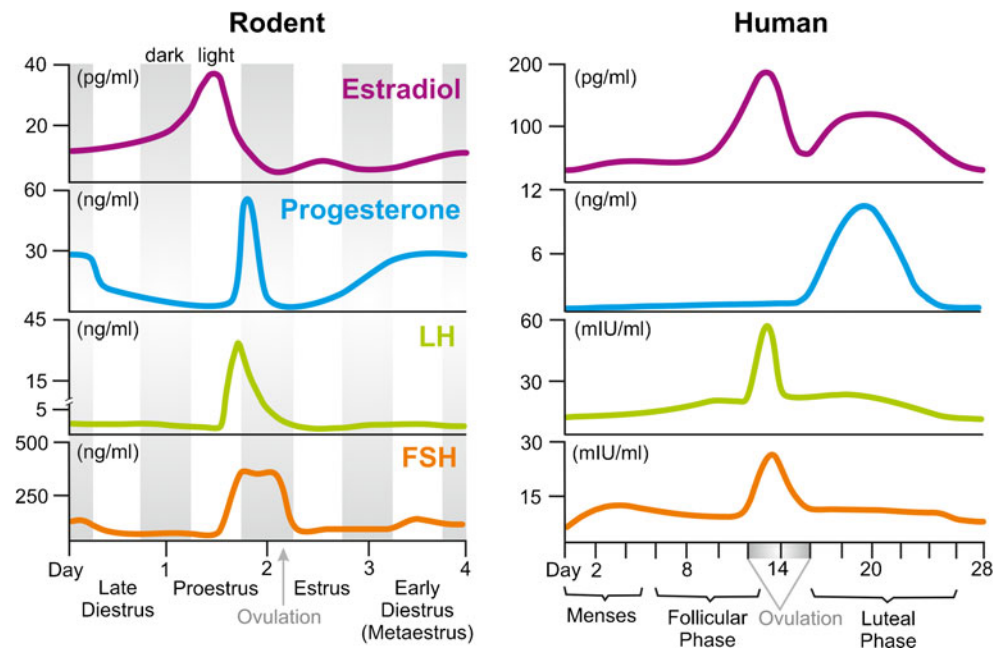
While research acknowledges existing gender differences in anxiety disorders, treatment remains largely indifferent towards those facts [37, 78]. Revealing biological substrates and mechanisms relevant to the etiology of anxiety disorders in females compared to males would relieve some of the economic and personal burden originating from ineffective treatment strategies.

Major questions and challenges for animal models

Key questions are whether sex differences in anxiety disorders originate mainly because of sex-chromosomal gene expression [89], sexually dimorphic developmental differentiation of brain regions and stress-response systems (organizational effects of sex steroids), female reproductive hormone fluctuations postpuberty, protective or vulnerability-inducing effects of reproductive hormones in adulthood (activational effects of sex steroids), or differences in stressor perception and emotional appraisal. Since the Y chromosome contains a very limited number of genes and the Barr body (second X chromosome in females) remains largely inactive in healthy cells of the female body [73, 74], the impact of chromosomal differences in the classic sense [19, 299] on anxiety-related behavior is probably small in comparison to developmental or adult neuroendocrine sex differences, but not negligible [35, 89, 241]. The role of the maternally inherited mitochondrial genome and its effects on energy balance should also not be ignored because a higher predisposition for anxiety and depressive disorders is detected in mothers and matrilineal relatives of children with maternally inherited mitochondrial diseases [48], and clinical *in vitro* fertilization studies among offspring of genetically related or unrelated mothers suggest that, in many cases, affective and anxiety-linked genetic traits may be inherited from the mother [38, 307, 308]. It also to be expected that anxiety-relevant biological sex differences exist with regard to stress vulnerability, meaning how the female brain perceives and processes stressful events, and that some of these differences should be detectable on a molecular level.

While neuroanatomy and physiology are very similar between female rodents and women, discrepancies in reproductive cycle duration (4 days in rodents vs. 28 days in humans), cycle pattern of estradiol and progesterone, and hormone amplitude differences [35, 120] exist. For a detailed comparison of the hormonal fluctuations across the rodent estrous cycle and the human menstrual cycle, please refer to Fig. 1.

Fig. 1 Schematic comparison of the 4-day rodent reproductive cycle and the 28-day human menstrual cycle. Depicted are average fluctuations of the circulating hormones 17-beta-estradiol, progesterone, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) in a female rat (left panel) vs. a female human (right panel). Gray bars in the left panel depict the dark phases. Data for individual hormones were adapted from [120, 339, 353]



Additional challenges are increased costs of studies comparing both sexes or analyzing all four stages of the rodent cycle (proestrus, estrus, early/late diestrus), instead of using ovariectomized or hormone-replaced females, and conceptual issues such as interpreting detected sex differences properly. Not every (neuro)biological sex difference indicates vulnerability, and many responses to acute or even chronic stressors may be adaptive not maladaptive [8]. For example, rodent research may find more acute stress-induced expression of the immediate early gene *c-fos* in several brain regions of male rats, but not proestrus or estrus female rats [45, 117], or increased memory loss in male rats compared to female rats [225] after chronic stress, but it remains to be determined whether such differences represent adaptive or maladaptive coping mechanisms. This leads to the importance of pairing neuroendocrine or neuroanatomical studies with appropriate behavioral tests. Since we cannot inquire about subjective states of anxiety in a rodent, we instead employ tests that have face validity (e.g., classic tests of conflict anxiety) and correlate those with biological measures (e.g., neuronal activation or gene expression). Useful behavioral tests thus either translate the human concept into a test situation that is evolutionarily comparable and relevant to the rodent without anthropomorphizing the animal's behavior or are based on known neurocircuits or neurotransmitter systems within the body.

While animal models cannot mimic societal injustice that still exists towards women in parts of the world or address how societal issues and gender-dependent reinforcement are processed by males vs. females, animal models can inform on underlying biological differences, sex-dependent symptomology, and coping mechanisms in

stress-related anxiety disorders and may lead to the identification of sex-specific targets for pharmaceutical treatment. In the following sections, we focus on sex differences in naturally occurring trait anxiety and sex differences in anxiety states induced by acute, repeated, or chronic stress exposure.

Sex differences in conflict anxiety and current animal models

Naturally occurring sex differences in classic anxiety tests

One behavioral symptom of GAD with face validity in rodents is conflict anxiety, meaning an inhibited approach when placed in an ambiguous situation that involves both potential reward and potential danger or punishment [140, 249, 250]. In other words, the rodent's inherent avoidance behavior (e.g., towards open/exposed/brightly lit areas, a novel object, or towards an aversive stimulus) competes with the natural explorative drive, for example, to seek a reward such as food or water. Similarly, human anxiety is maladaptive when it prevents the individual from participating in normal daily activities and interactions or from seeking reward due to an unrealistic, exaggerated fear of failure, social scrutiny, or punishment. Unconditioned behavioral paradigms such as the light–dark (white/black) box [256, 302], elevated plus maze (EPM) [170, 288], open field (OF) [298, 378], novelty-suppressed feeding [46, 161], or Vogel punished drinking [369] are classic approaches to test inherent conflict anxiety (for a schematic overview, see Fig. 2). The elevated T-maze (ETM) [397] evaluates both conflict anxiety, with longer latencies to enter the open arm of the maze as a measure of

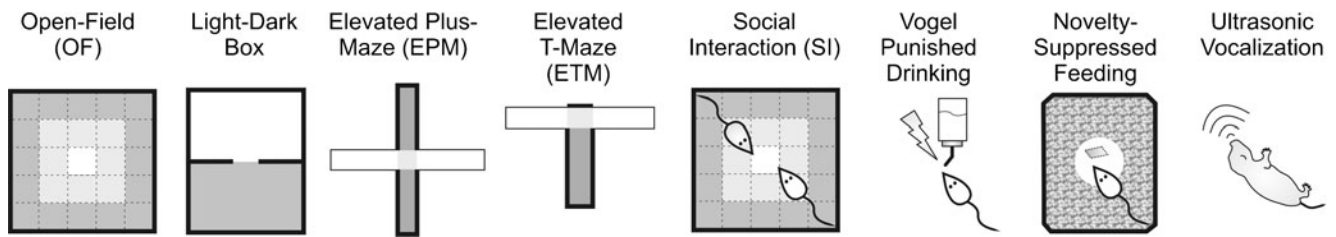


Fig. 2 Schematic overview of commonly used tests of unconditioned conflict anxiety in adult rodents and of neonatal ultrasonic vocalization. *Shades of gray* represent darker (or, in case of the *OF* and *SI* test, more protected) zones of the respective test paradigm. *Thick black lines* designate walls of the test apparatus or cage (in the case of novelty-suppressed feeding/neophagia). In the *OF*, light–dark (white/black) box, *EPM*, and *ETM*, an increased latency to enter into and less time spent in the brighter (or more exposed) zones designates anxiety-like behavior. Similarly,

inhibitory avoidance, and panic-like escape responses, with shorter latencies to escape from the open arm of the maze as an index of increased panic-like behavior. The social interaction (*SI*) test [118], using a novel adult conspecific of the same age, weight, and sex, and the juvenile social exploration test [75], using a novel adolescent conspecific of the same sex, evaluate anxiety in the context of rodent-specific, nonaggressive social identification, contact, and play behaviors initiated by the experimental rat.

Interestingly, most murine rodent models report lower anxiety-like behavior in females, compared to males. Table 1 lists examples of adult sex differences, as well as age-dependent and estrous stage-dependent female behavior in classic conflict anxiety paradigms. We also list sex differences in ultrasonic vocalization of isolated neonates (40–50 kHz) because it has proven to be positively correlated with adult trait anxiety [68, 389, 392] and is used to screen for anxiolytic drugs [168, 255], such as 5-hydroxytryptamine receptor type 1A (5-HT_{1A}) agonists or benzodiazepines [121], targeting GABA_A receptors. A major advantage of assessing the duration or frequency of ultrasonic vocalization is that it is an objective behavioral endpoint, easily quantifiable, automated, locomotion-independent, and requires no conditioning procedure. Early studies using adult rodents [182, 195] often entirely failed to distinguish between anxiety-like behavior and locomotion or general activity, which is commonly higher in females [115], but even in more careful evaluations, it is impossible to evaluate anxiety-like variables distinctly from locomotor activity because locomotion is the driving force underlying the variables of interest [102]. In contrast, the *SI* and Vogel punished drinking tests tend to detect a sex bias towards increased anxiety-like behavior in females [182, 343]. However, male–male vs. female–female *SI* may have inherently different components, and more avoidance in the Vogel punished drinking paradigm might be compromised by enhanced female pain sensitivity [119]. Sex differences in anxiety-like behavior also depend on the species (with monogamous, alloparenting species such as Mongolian gerbils

decreased *SI* behavior with an age-matched, weight-matched, and sex-matched conspecific, decreased numbers of shock-punished licks (1 shock every 20 licks) at the drinking bottle after 16–24 h of water deprivation in the Vogel punished drinking test, and suppressed consumption of food in a brightly lit, novel cage or arena also indicate an anxiety-like behavioral state. Frequency and duration of neonatal ultrasonic vocalizations at 40–50 kHz are used to screen for anxiolytic drugs and are strongly correlated with adult trait anxiety

[66] and prairie voles [26] potentially proving to be better rodent models for sex differences in anxiety than mice and rats), strain [13, 309, 358], age [110, 175], and whether female data were pooled for all estrous stages or not. In fact, estrous stage appears to be a major determinant of conflict anxiety, with diestrus females acting more anxious than males or estrus, metaestrus, and proestrus females [125, 133, 234, 261]. Also, circadian testing time, light or dark phase, light intensity, and other methodological differences, such as pretesting conditions or test order, can profoundly alter outcome variables [72, 172, 302]. Conclusively, it seems necessary to evaluate existing paradigms more carefully, e.g., using principal component analyses [13, 115] or *z*-scoring computation [146], to develop novel behavioral tests that are not driven by anxiety-irrelevant behaviors or physiology and to identify reliable, easily measurable correlates of conflict anxiety in order to properly address and quantify sex differences in rodent emotionality models.

Adult anxiety states induced by adverse early life experience

A large body of literature exists on the development of adult anxiety states following adverse early life experience [315], an effect that is likely dependent on epigenetic modifications that result in long-lasting alterations of brain physiology and stress-coping strategies [171], and many of these models report sex differences in anxiety-like behaviors. To discuss this literature in detail is beyond the scope of this review, but it is worth mentioning several anxiety-relevant sex differences discovered in a variety of rodent models using manipulations of maternal diet, other gestational stressors, neonatal lipopolysaccharide (LPS) exposure, maternal separation (MS) or low maternal care, and adolescent stressors to investigate resilience-inducing or vulnerability-inducing effects of early life adversity. For a review of comparable developmental ages in rodents [14] vs. humans, refer to Eiland and Romeo [108], and for a species-comparative table listing the developmental windows relevant for the formation of anxiety-relevant mesolimbocortical brain regions, see Weinstock et al. 2001 [380].

Table 1 Examples of naturally occurring sex differences and estrous stage-dependent female behavior in unconditioned, classic rodent tests of adult conflict anxiety and neonatal ultrasonic vocalization

Test paradigm	Species and strain	Sex difference or major finding	Reference
Light–dark box	Mouse, FVB/NHsd	↓ anxiety in females vs. males	[370]
	Rat, Lewis	↓ anxiety in females vs. males	[303]
	Mongolian gerbils	↑ anxiety (dark-side entries, but not dark-side time) in females throughout all estrous stages vs. males	[66]
Elevated plus maze	Mouse, DAB/2	↓ anxiety in females vs. males	[309]
	Rat, Wistar	↓ anxiety in 90-day-old females vs. males	[175]
	Rat, Long Evans	↓ anxiety in proestrus females vs. males and other estrous stage females	[125]
	Rat, Wistar	↑ anxiety in diestrus vs. proestrus females	[234]
	Mouse, 129S2/SvHsd× C57BL/6J	↓ anxiety in females vs. males	[370]
	Rat, Lewis	↓ anxiety in females vs. males	[303]
	Rat, Wistar	↑ anxiety in early diestrus females vs. males and other estrous stage females	[97]
	Mongolian gerbils	↑ anxiety in females, throughout all estrous stages vs. males	[66]
	Prairie voles	↑ anxiety in females (two times more time in closed relative to open arms) vs. males	[26]
	Rat, Wistar	↓ anxiety in 60-day-old females vs. males	[110]
	Rat, Long Evans	↑ anxiety in senescent vs. reproductively competent females	[372]
	Mouse, C57BL/6J	↑ anxiety in females vs. males	[13]
Elevated T-maze	Rat, Sprague Dawley	↓ avoidance in females vs. males	[5]
	Rat, Lewis	↓ avoidance in females vs. males	[303]
	Rat, Wistar	↑ avoidance and decreased escape in diestrus females vs. males	[133]
Novelty-suppressed feeding	Rat, Sprague Dawley	↑ anxiety in diestrus females vs. females in other estrous stages	[261]
Open field	Rat, Long Evans	↓ anxiety in proestrus females vs. males	[125]
	Mouse, C57BL/6J	↑ anxiety in females vs. males	[13]
Social interaction	Rat, Lister hooded	↓ social interaction in females vs. males	[182]
	Rat, Long Evans	↑ social interaction in proestrus females vs. males and females in other estrous stages	[125]
	Mongolian gerbils	↓ (aggressive) social interaction in females, throughout all estrous stages vs. males	[66]
	Rat, Sprague Dawley	↓ social interaction in proestrus and diestrus females vs. males	[343]
	Mouse, C57BL/6J	↑ social interaction in females vs. males	[13]
	Ultrasound vocalization	Rat, Wistar	↑ vocalization in male pups when female pups in litter vs. male-only litters
	Mouse, various strains	↑ vocalization in male pups on postnatal days 2–6 vs. females	[149]
Vogel punished drinking	Rat, Lister hooded	↓ punished licks in females vs. males	[182]
	Rat, Long Evans	↓ punished licks in senescent vs. reproductively competent females	[372]

Maternal high-fat diet

Obesity rates are alarmingly high in Western societies. A recent survey concluded that, by 2008, 68 % of all adult Americans were overweight [122], and the percentage is likely to have increased since then. While genetic predisposition is estimated to contribute < 2 % to the body mass index variation between individuals [219], sedentary lifestyle and high-fat dietary choices are likely to explain many obesity cases. In addition to the numerous physiological and mental comorbidities [210], including increased risk for anxiety and depression [310], that are associated with obesity, animal studies recently revealed that poor nutritional choices by the mother may also imprint the offspring to

suffer from a disadvantageous energy balance [57, 367], increased susceptibility to metabolic disorders [184], increased brain inflammation [41], and anxiety-like behavior [41, 287, 350]. Specifically, Bilbo et al. [41] fed rat dams a high-fat diet (HFD; both a saturated-fat diet and a trans-fat diet had similar consequences) for 4 weeks prior to mating and throughout pregnancy and lactation. Upon weaning, rat pups were raised on standard rat chow. After reaching adulthood, male, but not female, HFD offspring displayed increased anxiety on the EPM. In contrast, female, but not male, juveniles born to Japanese macaques that were fed an HFD for up to 4 years, including pregnancy and lactation, displayed increased anxiety when presented with a novel object task in a study by Sullivan et al. [350], while the

mRNA expression of both *tph2*, encoding tryptophan hydroxylase 2 (Tph2, the rate-limiting enzyme for serotonin synthesis), and *htr1a*, encoding the inhibitory 5-HT_{1A} autoreceptor, were increased about twofold within the serotonergic dorsal raphe nucleus (DR) in fetuses (third trimester) of both sexes. This indicates maternal diet-induced alterations of brain serotonergic systems, which may become further dysregulated during puberty when reproductive hormones become active. Sullivan's nonhuman primate HFD model is consistent with the human sex bias in anxiety disorders and may, to date, be one of the best animal models for anxiety and depression, as *TPH2* mRNA and TPH protein expression have repeatedly been shown to be increased in depressed suicide victims [21, 22, 47, 359] and because the association between obesity and affective as well as anxiety disorders is 1.5-fold to 2-fold stronger in women than men [92].

Other gestational stressors

A variety of other gestational disturbances, including malnutrition, maternal exposure to psychological (e.g., repeated restraint) or social stressors (e.g., defeat by a lactating, highly aggressive dam), or increased maternal inflammatory milieu due to bacterial or viral infections, have been shown to alter brain development and increase adult-life anxiety in the offspring, as reviewed by Markham and Koenig [236]. Some of these behavioral alterations may reflect adaptive emotional coping strategies from an evolutionary standpoint [315]. If you are born into a stressful world, increased vigilance and avoidance may save your life while you are vulnerable and developing, and only become maladaptive when applied to safe or potentially rewarding situations later on. Interestingly, prenatal stress appears to partially reverse extremes of genetically inbred trait anxiety, with prenatal stress reducing anxiety in the offspring of high-anxiety-behavior rats and increasing it in the offspring of low-anxiety-behavior rats [50]. With regard to sex differences due to gestational stressors, outcomes depend on the choice of stressor and anxiety test. Gestational malnutrition (6 % vs. normal 25 % protein content) increases open-arm exploration of female offspring tested on the EPM (an anxiolytic effect), but significantly decreases social exploration in both sexes in the SI test due to increased rearing behavior, possibly indicative of increased explorative escape behavior, vigilance, and impulsivity at the expense of social behaviors [6, 7, 209]. A similar hypervigilance, together with faster escape behavior, was detected in female offspring of a prenatal stress model by Louvart et al. [220]. Schulz et al. [326] exposed pregnant rats to daily unpredictable stressors during the last gestational week, resulting in paradigm-dependent elevated anxiety-related behaviors in male (decreased SI time) and female offspring (less time in the open compartments of the elevated zero maze, an

open/closed-arm paradigm that lacks the ambiguous center square of the EPM). In contrast, prenatal restraint stress was found to selectively increase OF anxiety-like behavior of female offspring [55].

Maternal separation

MS appears to be a reliable way to induce a chronic anxiety state in male, but not female, offspring. MS protocols, consisting of several hours of litter isolation from the dam, typically between postnatal days 2 to 14 (while maintaining adequate temperature conditions), often produce a bidirectional sexually dimorphic effect on later-life anxiety, with exaggerated anxiety-like behavior in male offspring, but less intense [390] or even anxiolytic outcomes in females tested in conflict anxiety paradigms such as the OF, EPM, and ETM [245, 263, 305, 311, 338, 390]. MS also increases startle and adult (20–28 kHz) ultrasonic vocalization responses to acoustic stimulation in males, but not females [188]. Sexually dimorphic sensitivity to reduced sensory stimulation (tactile, olfactory, and auditory) during MS may also exist because neonatal tactile stimulation can reverse MS-induced increases in contextual fear-conditioned freezing to that of non-isolated controls in females, but not in males [174]. Similarly to MS, early weaning from maternal care also exerts sex-dependent anxiogenic effects in both mice [200, 201] and rats [208], with a strong bias towards pronounced and longer-lasting male vulnerability.

A recent animal study found that same-strain cross-fostered male Fischer 344 (but not Sprague Dawley) rats scored higher on adult anxiety-related behaviors in the SI and novelty-suppressed feeding tasks than controls [358]. Female offspring were also cross-fostered in this study, but excluded from behavioral assessment. This suggests that, in addition to classic MS models, adoption may also increase the risk to develop anxiety states later in life [148].

Neonatal lipopolysaccharide

Several research groups have demonstrated that an immune challenge early in life, for example, with the endotoxin LPS (a pyrogenic cell wall component of gram-negative bacteria), can result in a long-lasting anxiety-like state throughout adulthood and even senescence [58, 374], in particular in “double-hit” models, including a second immune response activation [351] or psychological stress exposure [376] during adulthood. Indicating a similar male-biased trend of early life disturbances as observed in MS models, Tenk et al. describe that neonatally LPS-challenged male rats are more anxious in the OF test 2 h after a second homotypic immune challenge in adulthood [351] than females, and that neonatal LPS (without a second challenge during adulthood) actually decreases anxiety in female rats tested in the light–dark box [352]. Walker et al. [376] used a “hide box/OF” setup, offering rats a protected

box within the OF to retreat into, to reveal that neonatal LPS together with adult restraint stress causes increased risk assessment and overall vigilance in both sexes, but that neonatally LPS-challenged males are more susceptible to anxiety-like behavior in the OF and EPM after restraint during adulthood than females. Interestingly, the anxiety state induced by neonatal LPS persists into the F2 offspring generation when male or female LPS-group rats are mated with control rats, potentially due to epigenetic changes in the paternal line [373]. In the maternal line, however, this anxiety inheritance depends on maternal lactation patterns and maternal care and is reversible by cross-fostering F2 pups with saline mothers [373].

Adolescent stressors

Adolescence is the somewhat ill-defined phase between nutritional independence and adulthood, defined by the endocrine, neural, and behavioral events of sexual maturation [336], and is accompanied by both increased social stressors and a need for social buffering as attention naturally shifts from parent to peer interactions [202]. During this period, social behaviors, such as aggression, risk taking, social play, dominance establishment, and mating, as well as stress-responsive limbic [312] and cortical brain regions [185, 237] take on adult patterns. In fact, a certain amount of stress exposure or socio-environmental stimulation is probably necessary for normal development and exerts long-term stress-protective, anxiolytic, and antidepressant effects later in life [240, 277, 355, 356], especially if the adolescent stressor remains controllable [211]. Following the murine postweaning phase (postnatal days 21–30), rat/mouse adolescent days 31 to 60 include puberty and are roughly commensurate with human ages of 10 to 18 years [108]. However, rodent offspring are weaned from maternal care before adolescence, while humans remain under parental care for much longer. Research now attempts to parse out stress-related and anxiety-related sex differences and to match prepubertal and postpubertal endocrine profiles between the species throughout different developmental stages within adolescence [67].

Compared to other early life stressors discussed previously, postweaning and/or adolescent stress models are a reliable way to produce long-lasting alterations in female emotional behavior. Male rats are especially prone to develop a chronic, long-lasting anxiety state when the stressor, such as social isolation, is initiated in preadolescence [283, 386, 393], while male social isolation initiated during adolescence may be anxiolytic [17, 18, 354, 382] or have no effect [59, 217]. With the exception of Weiss et al., who found anxiogenic effects of social isolation in male, but not female [386] rats, social and nonsocial stressors during both preadolescent and periadolescent time windows seem to result in elevated anxiety states of female rats during adulthood [18, 217, 242, 297, 382]. Bourke and Neigh [52] chose a mixed-modality

adolescent stress paradigm (restraint, isolation, and social defeat) in Long Evans rats of both sexes (using retired breeder males or ovariectomized females for social defeat) that also increased adult anhedonic behavior in the sucrose preference test and reactive stress coping (increased immobility) in the forced swim test (FST) in females, but not males. Also, only female adolescence-stressed rats of this study displayed increased adult locomotor activity, rears, and overall vigilance on the EPM (without altering open-arm time) and three times as many escape-seeking dives during the FST than unstressed controls, indicating a complex alteration of context-dependent risk assessment and coping strategies (active or reactive) that may closely resemble the behavioral symptoms of panic disorder or PTSD. Postweaning isolation protocols in female rats result in increased adult anxiety, as measured by deficits in SI behavior, OF exploration, and novelty-suppressed feeding [161], and increased vigilance and arousal upon injection of an anxiogenic pharmacological compound [229]. These chronic anxiety states have been associated with altered central serotonergic [227, 229], GABAergic [226], and glutamatergic functions [161].

Adult anxiety states induced by acute or chronic stress

While only a few acute stressors have been shown to produce long-lasting anxiety-like states in adult rodents, a variety of chronic stress conditions, some employing an array of unpredictable heterotypic stressors [145, 146, 257, 319] and others using repeated exposure to a homotypic stressor such as restraint [54, 172, 203], result in chronically increased anxiety-like behavior and commonly also depressive-like behavior. To avoid an exhaustive description of such models, we here solely discuss learned helplessness and psychosocial stress models in light of the female-specific physiology and behavioral outcomes. Glucocorticoid (GC)-mediated or CRF/urocortin-mediated adult anxiety states are integrated into the “**Potential mechanisms for sex differences in stress-related anxiety states**” section.

Inescapable stress and learned helplessness

Responding to and coping with acute or temporary stressors belongs to the normal repertoire of mammals. However, severe, traumatic, or uncontrollable stressors are capable of inducing a depression-like and anxiety-like state for up to 48 h, also termed “learned helplessness,” in which the individual then also perceives controllable situations as uncontrollable. Very few studies use female rodents as subjects, but in male rats, 1 session of 100 inescapable tail shocks (about 1 h 40 min total duration) is sufficient to induce a 48-h-long anxiety-like and depressive-like behavioral phenotype [231]. Learned helplessness is thought to be due to a prolonged release of serotonin within the DR and its

target regions during and after stress exposure, resulting in functional desensitization of 5-HT_{1A} autoreceptors [313] and subsequent exaggerated serotonin release within fore-brain structures controlling anxiety-like behaviors [10].

Acutely, inescapable shock activates stress-induced serotonin release from local axon collaterals [238] and induces the expression of the immediate early gene *c-fos* [137] in a mid-brain serotonergic region that is also activated by urocortin 2 [152, 344], a CRF-like peptide that preferably binds to CRF type II receptors (CRFR₂), certain anxiogenic pharmacologic compounds [1], and anxiogenic environmental stimuli [126, 341]. This subdivision has been identified as the dorsal and caudal DR (DRD/DRC; see Fig. 3). In contrast, escapable tail shock, in other words experiencing control by being able to terminate each shock, while receiving exactly the same physical

stressor as a yoked rat receiving inescapable tail shock, prevents the behavioral and neurobiological phenotype of learned helplessness and even renders the individual resilient towards subsequent inescapable stress [11]. Projections from the medial PFC to the DRD/DRC region mediate some of the behavioral manifestations of controllability [31]. Both the PFC and the DRD/DRC are sensitive targets for fluctuating concentrations of reproductive hormones, especially estrogens [116, 364].

Whether inescapable shock-induced learned helplessness also manifests itself in females remains to be determined, although recent evidence suggests that female rats maintain their escape-seeking behavior, interpretable as a sign of resilience [87, 332]. In humans, on the other hand, overly active escape-seeking or hypervigilance may be symptomatic of panic or agoraphobia. Bland et al. [45] was one of the first to use females in the learned helplessness model and found that, immediately following inescapable tail shock, male rats display a greater increase of both *c-fos* and *bdnf* expression (encoding the presumably neuroprotective brain-derived neurotrophic factor [BDNF]) in the PFC than females, compared to home cage controls. In contrast, expression levels of both genes were either similar in both sexes or increased in females, compared to males, 60 min after inescapable shock. These findings suggest differential temporal response patterns in males vs. females, while the behavioral consequences and neuronal effects within downstream target sites of the female PFC remain to be determined.

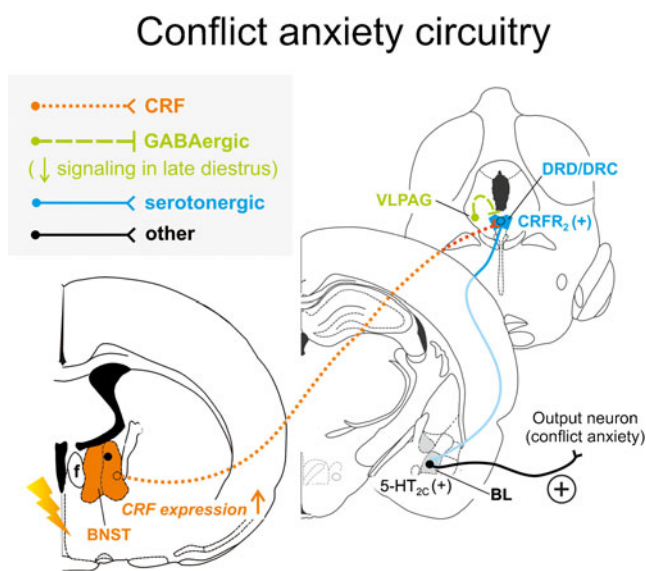


Fig. 3 Hypothetical model of how stress-induced increases in corticotropin-releasing factor (CRF) expression and signaling from the bed nucleus of the stria terminalis (BNST) may interact with decreased GABAergic inhibition from the ventrolateral periaqueductal gray (VLPAG) during late diestrus to enhance serotonergic output in the conflict anxiety-related dorsal and caudal DR (DRD/DRC). During late diestrus in rodents, declining circulating concentrations of progesterone and its neuroactive metabolite allopregnanolone cause increased expression of $\alpha 4$, $\beta 1$, and δ subunits of the γ -aminobutyric acid (GABA) receptor type A within the PAG [143, 144], including the VLPAG, ultimately resulting in attenuated ongoing GABAergic inhibitory signaling [221]. Attenuated activity of GABAergic neurons from the VLPAG render serotonergic neurons in the DRD/DRC more active [183], and stress induces CRF expression in the conflict anxiety-related BNST [232, 331, 375]. Enhanced CRF release from BNST projections further activates serotonergic neurons through CRF receptor type 2 (CRFR₂) [204] within the DRD/DRC [335]. Together with stress-induced desensitization of autoinhibitory 5-HT_{1A} receptors on DRD/DRC serotonin neurons [313], late diestrus-enhanced hyperactivity of the DRD/DRC causes increased serotonergic output to distal target sites controlling conflict anxiety-like behavior, in particular through actions on excitatory 5-HT_{2C} receptors [76] in the BL [12, 150]. Neuronal projections are drawn unilaterally solely for simplicity and do not imply functional laterality

Psychosocial stress models

Since female rodents do not display the same aggressive, territorial, and hierarchy-establishing behaviors as males, only few relevant and effective psychosocial stress models exist. Among those, the resident–intruder test, exposing the experimental female to an aggressive lactating dam after temporary removal of her pups [266], and novel chronic psychosocial stress mouse models based on disruption of the animal's social stability, such as social isolation (single housing) or rotation of cage mates [279, 322], are most promising. Schmidt et al. [322], for example, rotated the group composition of four female mice per cage twice a week for a total of 7 weeks from adolescence throughout young adulthood, resulting in increased anxiety in the novelty-suppressed feeding task. There is a clear need for more psychosocial stress models in females because results from both human TSST studies [193] and rodent models [177] indicate that females perceive socially stressful situations as much more fear-inducing and distressing than males despite similar or comparably low GC responses. Because social stressors are most pervasive to humans and are key contributors to the etiology of anxiety and mood disorders, stress models that are derived from socially important and evolutionary meaningful contexts from the rodent's perspective currently offer the best face,

construct, and predictive validity [153, 154, 162] and an alternative to socially irrelevant or painful stress procedures.

Sex differences in animal models of panic disorder

To our knowledge, no physiologically and behaviorally validated female rodent models for panic disorder exist to date. However, there are well-characterized models in male rodents that could easily be replicated in females while monitoring estrous cycle stage through hormonal profiling or vaginal smears [35] and would contribute important information on sex differences in panic-like behaviors and panic-like physiological responses. Also, many behavioral and physiological characteristics of chronic anxiety states in rodent models, as described previously, may pertain to panic-specific biological symptomatology.

Clinically relevant sex differences may exist in response to stimulation with panicogenic agents. Genest et al., for example, report more hypercapnia-induced tachypnea (increased respiratory rate), as measured in a plethysmography chamber, only in maternally separated female rats, whereas neonatally separated males hyperventilated less than controls [129]. Estrous stage-dependent variations in reproductive hormones may be a critical factor for altering the sensitivity of cardiovascular and respiratory control centers to a panic-inducing stimulus because intravenous administration of the synthetic, panicogenic peptide pentagastrin has been shown to cause increased tachycardia and tachypnea during diestrus compared to proestrus in anesthetized female rats [56]. Concordant with Klein's "false suffocation alarm" hypothesis of panic disorder [206], hypercapnia is a useful tool to compare human (see the "Panic disorder" section) to rodent responses [34, 178]. Similar to increased CO₂ sensitivity and predisposition to panic disorder in humans from unstable parental environments [33], recent studies have shown that female and male rodents exposed to neonatal MS in infancy or to an unstable cross-fostering environment show an increased hypercapnic ventilation response to the panicogenic agent CO₂ as adults [86, 104]. An equally relevant method to detect panic-related physiology and behavior in both humans and rodents is intravenous infusion of sodium lactate. Sodium lactate infusions, through central actions of sodium rather than changes in osmolarity or lactate [259], are sufficient to induce panic attacks in panic disorder patients, but not in healthy controls [84, 131, 290], and likewise cause panic-like responses in animal models of panic disorder [301, 316]. Sodium lactate infusion into male control rats activates serotonergic neurons in the "lateral wings" of the DR, the so-called ventrolateral DR/ventrolateral periaqueductal gray (DRVL/VLPAG), while male rats that have been rendered panic-prone (through disinhibition of the medial hypothalamus with the GABA synthesis inhibitor L-allylglycine) fail to

activate these neurons [179]. Five days of subthreshold priming of CRFR₁ with the CRF-like peptide urocortin 1 locally within the basolateral amygdala (BL) also affects the DRVL/VLPAG region, causing an increase in *tph2* mRNA and reduced SI in male rats [99]. Rats of the same intra-BL priming model react with panic-like physiological and behavioral responses to sodium lactate infusion, while controls do not [301]. Serotonergic DRVL/VLPAG projections are likely to travel through the periventricular tract to innervate the dorsal periaqueductal gray (DPAG) [36, 349]. This region controls a spectrum of defensive behaviors ranging from freezing to escape, depending on the perception of how close or imminent a threat is [44, 296], and controls autonomic responses to stress in mammals [134, 173, 191, 249]. Serotonergic signaling is capable of inhibiting those responses, for example, through actions on postsynaptic 5-HT_{1A} [296] and 5-HT_{2A} receptors [295]. The serotonergic DRVL/VLPAG is thus ideally positioned to control escape behaviors and panic-like responses. Failure to activate the DRVL/VLPAG, in contrast, may result in increased vulnerability to stress and facilitate escape-like and panic-like responses. The questions that remain are whether these panic models can be reproduced in females and if they would reveal (as we expect) sex-dependent or estrous stage-dependent (re) activity of the DRVL/VLPAG.

Another new rodent model of panic disorder uses a noninvasive ultrasound stimulus to induce panic-like responses in adult rats, but also has yet to be tested in females. Namely, Lister hooded rats respond with tachycardia and hyperthermia to a noninvasive 22-kHz (typical frequency for an adult rat) ultrasound stressor without altering HPA axis function, and this is associated with increased *c-fos* activation of the DPAG/dorsolateral periaqueductal gray (DLPAG) [207]. This is of interest because one core characteristic of a classic panic attack in humans is the activation of autonomic, but not neuroendocrine, stress-response systems [135]. Concordantly, excitatory stimulation of the DPAG/DLPAG in primates [191] and (electrically) in awake non-panic disorder human patients [173] causes panic-like emotional and autonomic responses (e.g., tachycardia and hyperventilation) and, when increased in intensity, a shift from reactive freezing behavior to active escape in rodents [321].

Sex differences in animal models of PTSD

Rodent models of PTSD are hard to validate, and only little substantiated evidence for sex differences exist. PTSD rodent models generally strive to avoid chronic or repeated exposure to homotypic stressors in order to prevent habituation, but instead try to mimic the isolated, traumatic, and life-threatening nature of the inducing stressor(s), ideally in a species-relevant context, such as exposure to a predator or

to predator smell [4]. Such protocols appear to be most successful in modeling increased vulnerability in females. While 10 min of protected exposure to an actual cat produces a long-lasting anxiety state in both sexes of C57BL/6J mice, only females are just as susceptible to the feline odor by itself [3]. As a hint towards serotonergic involvement in this sex difference, male serotonin transporter knockout mice (*SERT*^{-/-}) take on the same vulnerability as females by also developing a long-lasting anxiety state upon exposure to cat odor alone [2]. An observation of potential relevance for wild-type mice as well is that 5-HT_{1A} receptor functionality appears to be particularly impaired in *SERT*^{-/-} females [51, 112], probably as a result of estrogenic downregulation of 5-HT_{1A} autoinhibitory functionality that can be reversed by ovariectomy [51, 239, 276]. A rise in 17-beta-estradiol during the late diestrus and early proestrus could thus impair autoinhibition of serotonergic neurons, rendering them more active. Classic inescapable and uncontrollable stress paradigms (see the “Inescapable stress and learned helplessness” section) are also often interpreted as PTSD models [80, 394] and are certainly useful to elucidate the inescapability aspect of a trauma-inducing event, but often fail to induce behavioral expression of learned helplessness in females [80, 96].

Potential mechanisms for sex differences in stress-related anxiety states

Many sexually dimorphic characteristics, including neurotransmitter systems [15, 103, 164, 362], neuroactive peptides [85, 244, 337], actions of reproductive steroid hormones within the mesolimbocortical system [98, 383, 384, 398], functionality of the GC receptor and HPA axis negative feedback [27, 42, 53, 70, 342, 366], neonatal microRNA spectrum [262], BDNF polymorphisms and PFC expression of *bdnf* [32, 45, 109], and immunological/inflammatory responses [159, 253, 278], have emerged as candidates for mechanisms underlying sex differences in anxiety states. To discuss all of them is beyond the scope of this review. However, in an attempt to integrate interactions of reproductive hormones, GCs, CRF-related signaling, and brain serotonergic systems, we here describe models for neural circuits controlling conflict anxiety (Fig. 3) and panic-like anxiety (Fig. 4) that, based on recent evidence, may be more vulnerable to stress-induced disturbances in females than in males.

Sex differences within a neural circuit controlling conflict anxiety

A conflict anxiety-related serotonergic region that may be particularly vulnerable in females is the midbrain DRD/DRC. In a rat model of violence in intimate relationships (females cohabiting with aggressive males, inducing a long-lasting

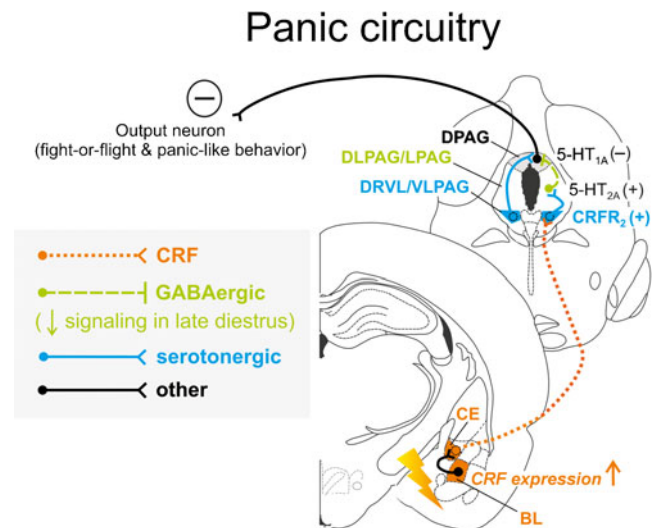


Fig. 4 Hypothetical model of how stress-induced increases in corticotropin-releasing factor (CRF) expression and signaling from the basolateral (BL) and central (CE) amygdaloid complex likely function to activate serotonergic output from the “lateral wings” of the dorsal raphe nucleus (DR) and may interact with decreased GABAergic inhibition from the periaqueductal gray (PAG) during late diestrus to increase panic-like responses. During late diestrus in rodents, declining circulating concentrations of progesterone and its neuroactive metabolite allopregnanolone cause increased expression of $\alpha 4$, $\beta 1$, and δ subunits of the γ -aminobutyric acid (GABA) receptor type A within the PAG [143, 144], ultimately resulting in attenuated ongoing GABAergic inhibitory signaling [221] within the panic-related dorsal PAG (DPAG). Stress-induced elevation of CRF within the BL leads to increased CRF release from CE projections that target the “lateral wings” of the DR, namely, the ventrolateral portions of the DR and PAG (DRVL/VLPAG), either acting on CRF receptor type 2 (CRFR₂) directly on serotonergic neurons [204] or indirectly via CRFR₂-mediated inhibition of nonserotonergic neurons [289]. This normally leads to increased activation of the DRVL/VLPAG, increased serotonergic output to distal target sites, and postsynaptic 5-HT_{1A}-mediated and/or 5-HT_{2A}-mediated inhibition of panic-like responses. During late diestrus, however, decreased GABAergic signaling disinhibits the DPAG, facilitating fight-or-flight and panic/escape-like responses [134]. Neuronal projections are drawn unilaterally solely for simplicity and do not imply functional laterality

anxiety state in the females), Cordero et al. [83] recently found selective hyperactivation of the DRD/DRC, a serotonergic system that appears to control conflict anxiety-like behavior (see Fig. 3), upon subsequent exposure to an unfamiliar male. Interestingly, this effect persisted into the F1 generation even when rearing conditions were controlled for. DRD/DRC hyperactivation is likely dependent on CRF overexpression in a specific region of the extended amygdala complex. Mechanistic studies in male rodents suggest that projections from the BNST specifically target the DRD/DRC region because overexpression of CRF within the lateral BNST [335] has recently been reported to enhance the expression of contextual fear (similar to conflict anxiety) after conditioning and to alter CRFR₂ receptor density selectively within the DRD. The DRD/DRC responds with increased *c-fos* expression in response to various anxiogenic stimuli, such as threatening

situations, anxiogenic drugs, or urocortin 2 [1, 126, 152, 285, 344, 345]. Additional support for an important role for the BNST in controlling DRD/DRC serotonergic neurons comes from the observations that learned helplessness [231] depends on BNST functionality [155], that inescapable, relative to escapable, tail shock specifically activates serotonergic neurons in the DRD/DRC region [9], and that the delivery of only two foot shocks 24 h following inescapable tail shock produces a markedly increased release of serotonin within limbic target areas of the DRD/DRC, for example, the BL [10]. Desensitization of 5-HT_{1A} autoreceptors within the DRD/DRC appears to facilitate this effect [313]. Importantly, antagonism of 5-HT_{2C} serotonergic receptors in the BL is sufficient to block the DRD/DRC-mediated learned helplessness effects of inescapable tail shock 24 h later, as measured in the juvenile SI test [76]. Other prominent anxiety-related or fear-related distal target sites of DRD/DRC projections are the BNST itself [292] and a conflict anxiety network that includes the BL [150, 151] and the ventral hippocampus [284] and is activated by exposure to an OF, a comparably mild conflict anxiety-inducing stressor [151]. The ventral hippocampus is an important region for fear conditioning and memory consolidation of fearful events [79, 114], but also serves to assess risk in typical conflict anxiety situations [249].

It is unclear what mechanisms may cause this conflict anxiety circuit to be overly responsive or active following stress, but the DRD/DRC system has been demonstrated to be more sensitive to estrogens than other DR regions. Local wax pellet implants of 17-beta-estradiol flanking the DR of ovariectomized female rats increase *tph2* expression in the DRD/DRC [98] and in the DRC when 17-beta-estradiol is given systemically [166]. In contrast to the topographic match of altered *tph2* expression, the anxiety-related behavioral effects of estrogen treatment in the aforementioned studies, however, were inconclusive. Five days of local delivery of 17-beta-estradiol or of an estrogen receptor beta (ER β)-specific compound within the immediate surround of the DR did not alter anxiety-like behaviors [98] of ovariectomized female rats, whereas systemic administration of 17-beta-estradiol to ovariectomized female rats can have anxiolytic or anxiogenic effects, with the latter being correlated with decreased expression of the gene encoding the autoinhibitory 5-HT_{1B} receptor in the ventromedial DR [98, 165, 167]. These seemingly contradictory effects may partially be due to the expression pattern of the two ER systems within the brain. While only very few serotonergic neurons express the androgen receptor in either sex [329], ER α is found primarily in nonserotonergic neurons (e.g., in GABA neurons in the inhibitory surround of the DR) and ER β appears to be predominately localized within serotonergic cell nuclei [272, 329]. ER α is generally accepted to exert anxiogenic actions, while ER β has repeatedly been

shown to display anxiolytic function [357, 371, 383], but where exactly within the brain those dichotomous ER receptor systems are exerting these effects and whether they contribute to the development of female-specific anxiety states remains subject to further investigation [383–385]. Luine reported in 1993 that the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) increases by 580 % in the DR within a 5-h period of the proestrus afternoon, while no such increase happens during diestrus [224]. Another group found that female rats, independent of estrous stage, display a much higher ratio of 5-HIAA to serotonin (a measure of serotonergic metabolism, which is often correlated with serotonergic activity) than male rats [97], but only in the DR, not in the median raphe nucleus (MnR). Interestingly, a single exposure to the EPM conflict anxiety paradigm in the same study, lastingly and sex-specifically decreased the 5-HIAA/serotonin ratio in the DR of females (but not males) and in the MnR of males (but not females) for almost 2 weeks.

We have determined that chronic administration of corticosterone via the drinking water [100] creates a conflict anxiety-like behavioral phenotype and elevated *tph2* expression in anxiety-related serotonergic systems of male rats, but have yet to determine if similar effects are evident in females or how *tph2* expression and enzyme activity respond to estrous stage. Animal models of chronic stress [243] or chronic GC exposure during adulthood [82, 88, 100] are likely to be mediated through GC-induced elevation of CRF expression within the BNST [232, 330] and reliably result in increased conflict anxiety-like behavior as a major behavioral outcome, associated with increased *tph2* expression (see supplemental material to [100]) and in vivo tryptophan hydroxylase activity [101] specifically in the DRD/DRC region.

Recent results from female nonhuman primate studies suggest that elevation of reproductive steroids, namely 17-beta-estradiol, may sensitize CRF receptor systems, in a female-specific manner. In support of estrogen-induced alteration of female-specific stress responsiveness within the DRD/DRC, 28 days of 17-beta-estradiol replacement in ovariectomized female macaques markedly increased *crfr2* expression within laser-captured serotonin neurons of the DR in comparison to ovariectomized controls without hormone replacement or combined estradiol/progesterone administration [317]. In addition, both estradiol and combined estradiol/progesterone treatment in ovariectomized female macaques altered the composition of cell adhesion molecules within serotonergic neurons and thus their synapse assembly [40]. How may this specifically affect the DRD/DRC system? CRF is likely to act directly in the DRD/DRC, via actions on CRFR₂ receptors, to increase serotonergic neuronal firing rates. The DRD/DRC densely expresses *crfr2*/CRFR₂ [91, 335], CRFR₂ is expressed directly on serotonergic neurons of the DRD/DRC [230], and CRF elicits CRFR₂-mediated currents in ex vivo electrophysiological studies of DR serotonergic neurons

[204]. Thus, female vulnerability of the DRD/DRC circuitry may be increased, depending on fluctuating concentrations of estradiol.

Sex differences within a neural circuit controlling panic and escape

An anxiety-related neurocircuit that includes the BL, CE, and serotonergic DRVL/VLPAG [99] probably exerts inhibitory control over panic-like and escape-like autonomic and behavioral responses originating in the DPAG and may also display reproductive steroid-dependent sex differences, especially with respect to developmental manipulations. In an early life adversity model, Lukkes et al. [229] recently discovered that adult female, but not male (unpublished data), rats that underwent social isolation during adolescence display increased vigilance behavior and decreased basal *tph2* expression in the panic-related “lateral wing” region of the DR (DRVL/VLPAG; see Fig. 4). Expression of panic-like anxiety is thought to depend on CRFR₁ signaling within the BL [319]. Five days of sub-threshold intra-BL priming of CRFR₁ with urocortin 1, a CRF-like peptide, for example, decreases SI time and renders male rats prone to sodium lactate-induced tachycardia, hypertension, and hyperventilation [301]. Conversely, the anxiogenic effects of intra-BL priming with urocortin 1 are reversible when a CRFR₁ antagonist is locally infused into the BL prior to assessment of behavior in the SI test [128]. In a recent collaboration with the Shekhar laboratory [99], we also found that the same intra-BL urocortin 1 priming model selectively alters *tph2* expression in the DRVL/VLPAG. Serotonin neurons within the DRVL/VLPAG may be required to suppress panic attacks [136]. When activated, serotonergic projections to the DPAG are thought to inhibit panic-like autonomic and behavioral responses [36, 296, 349]. Only control, but not panic-prone, rats respond with increases in *c-fos* expression in DRVL/VLPAG serotonergic neurons following sodium lactate infusion [179]. Failure to activate DRVL/VLPAG neurons may not only decrease inhibitory serotonergic signaling from the DRVL/VLPAG to the DPAG [296], but also to the rostral ventrolateral medulla (RVLM), a brainstem region exerting sympathoexcitatory control over physiological responses including heart rate, blood pressure, and respiration [23, 24, 223], and to the perifornical region of the hypothalamus, from where orexin/hypocretin neurons control arousal and vigilance behaviors [180, 181]. Both CRFR₁ and CRFR₂ are expressed within the DR and in the immediate inhibitory surround of the DR [91]. During stress, CRF from CE-derived afferents likely binds to CRFR₁ on GABAergic interneurons within the DRVL/VLPAG to facilitate and maintain appropriate inhibitory control of DR serotonergic neurons [204]. Meanwhile, intra-DR activation of CRFR₂-expressing serotonergic neurons, possibly within the DRVL/VLPAG, appears to facilitate anti-panic/anti-escape behaviors such as freezing [123]. Likewise,

local blockade of CRFR₂ prevents serotonin release in distal target regions [124, 228]. Interestingly, *crfr1* expression within (laser-captured) DR serotonin neurons is highest in ovariectomized female macaques without hormone replacement compared to female 17-beta-estradiol-treated or estradiol/progesterone-treated ovariectomized animals [39, 317], and combined estradiol/progesterone treatment (28 days of estradiol/progesterone during the last 14 days) reduces both *crfr1* and *crfr2* expression [317]. Estrous cycle stages of low estradiol and progesterone may thus exaggerate CRFR₁-mediated inhibition of DRVL/VLPAG serotonergic neurons. Developmentally, our data [229] and findings from other groups [283, 386, 393] support the idea that females are particularly vulnerable to the anxiety-inducing effects of social isolation during adolescence and that this may be a good model for panic disorder because it results in decreased basal *tph2* mRNA expression in the DRVL/VLPAG [229]. Decreased inhibitory serotonergic signaling from serotonin neurons in this region to distal autonomic target sites would consequently be expected to disinhibit escape behaviors and arousal systems [136, 296].

Sex differences in CRF signaling and receptor expression within anxiety and arousal systems

Aside from reproductive hormone-dependent *crfr1* and *crfr2* expression within DR serotonergic neurons, other sex differences in CRF systems may also pertain to sexually dimorphic stress perception, response, and adaptation and thus contribute to the sex-specific prevalence of chronic conflict-like or panic-like anxiety states. Rat research, for example, has shown that females typically express more CRF than males in certain brain regions, including the paraventricular hypothalamic nucleus, but also the CE and BNST [105, 176, 347, 365]. Receptor binding studies furthermore revealed that, throughout puberty, more CRFR₂ becomes expressed within the CE, BL, and medial amygdala of male, but not female, rats, whereas adult females display more CRFR₁ in the posteroventral medial amygdala and in the BL [214, 379]. Adult males of two monogamous and two promiscuous prairie vole species are also reported to have elevated CRFR₂ expression in the BNST compared to their female counterparts [218]. The fact that these sex differences do not occur until puberty together with findings of response elements to reproductive steroids in the promoter region of CRF receptor genes suggest a key role for gonadal hormone regulation. Abnormal stress hormone exposure during certain developmental windows, in contrast, may lead to a “feminized” expression pattern of CRF receptors in the brain. Consistent with the idea that, in some forebrain regions, the anxiogenic effects of CRF are mediated via CRFR₁, while CRFR₂ counteracts these effects, a prenatal stress model [69] that only causes anxiety in adult male, but not female, offspring demonstrated that increased anxiety in

male offspring was correlated with a higher *crfr1/crfr2* expression ratio in the amygdala. Also, only prenatally stressed males had more *crfr1* mRNA in the BL and CE, but lower *crfr2* expression in the BL. It remains to be determined how different ratios of CRFR₁/CRFR₂ [25] within other mesolimbocortical brain regions of relevance, such as the DR, may contribute sex differences in anxiety-like behaviors.

Immunoprecipitation studies of Bangasser, Valentino, and colleagues recently revealed sex differences in the intersection of stress and the noradrenergic arousal center of the locus coeruleus (LC), especially with regard to sexually dimorphic intracellular signaling and trafficking of the CRFR₁ receptor [27, 30, 361]. In unstressed control rats, the CRFR₁ receptor associated more strongly with its GTP-binding protein G_s (signaling through the cyclic adenosine monophosphate/protein kinase A pathway) in females than it did in males [28], and only male rats displayed CRFR₁ coupling with β -arrestin after stress exposure, an integral step of receptor internalization. The latter finding is consistent with electrophysiological evidence of stress-induced desensitization to CRF in males, but excessive or non-desensitizing CRF-mediated activation of LC neurons in females [85]. Consistently, a genetic mouse model of (global) CRF overexpression found equally increased CRF fiber innervation of the LC in both males and females, but a much higher discharge rate of female LC slices in vitro, in concert with a preponderance of membrane-localized (not internalized) CRFR₁ immunostaining in females compared to more cytoplasmic CRFR₁ in males [29]. These findings offer an entirely new perspective on sex-dependent stress adaptation of CRFR₁-mediated signaling, not only in the LC, but possibly also in other brain regions.

Estrous stage-dependent variations in GABAergic neurotransmission

The elegant work of Lovick and colleagues [221] has demonstrated that GABAergic neurotransmission in the PAG is highly sensitive to estrous stage-related hormonal fluctuations. Due to its value as a pharmacological target for anxiolytic drugs, such as benzodiazepines [255, 391], or as a site of action for anxiogenic compounds, such as FG-7142 [111, 291], the GABA_A receptor has been a major focus of anxiety research. During late diestrus (late luteal phase in humans), concentrations of progesterone and its anxiolytic metabolite allopregnanolone [400, 401] rapidly drop, and this decrease in allopregnanolone alters the subunit composition of the GABA_A receptor, meaning a shift towards decreased expression of the $\alpha 1$ subunit and increased expression of the $\alpha 4$, $\beta 1$, and δ subunits [143]. This reduces the ongoing inhibitory output of the GABA neurons within the PAG [222] and is correlated with increased anxiety-like

behaviors in diestrus rats, but not proestrus, metaestrus, or estrus rats [93, 94]. Decreased inhibitory output from GABAergic PAG neurons during diestrus is likely to disinhibit the DPAG and thus reduce the suppression of panic-like responses. Indeed, stimulation of the PAG during late diestrus, either via a local electrode within the PAG [320] or through systemic administration of the panicogenic agent pentagastrin [56], lowers the threshold for escape behaviors and enhances autonomic responsiveness. Interestingly, both allopregnanolone and BDNF are found to be decreased in corticolimbic brain regions of PTSD and depressed patients, but in socially isolated mice, a rodent model of PTSD-like behavioral deficits, antidepressant treatment with fluoxetine reduces anxiety-like behavior and restores corticolimbic levels of allopregnanolone and BDNF at lower doses than those required for serotonin reuptake inhibition [271, 294].

Integrative model of sex differences in conflict anxiety vs. panic

Taken together, estrous stage, estradiol, progesterone/allopregnanolone, different expression patterns of CRF receptor systems, and inherent differences in female vs. male CRF receptor signaling and CRF receptor-dependent stress adaptation may all contribute to sexually dimorphic serotonergic activity within anxiety-related circuitries.

In the conflict anxiety circuitry (Fig. 3), evidence from male rats suggests that stress-induced increases in CRF signaling from the BNST [375] act on CRFR₂ either directly on serotonergic neurons [335] or indirectly via inhibition of local GABAergic interneurons [289] to activate serotonin neurons in the DRD/DRC. During late diestrus in females, however, stress-induced increases in CRF expression and signaling from the BNST may interact with decreased GABAergic inhibition from the VLPAG to enhance serotonergic output from the conflict anxiety-related DRD/DRC [183]. Declining circulating concentrations of progesterone and its neuroactive metabolite allopregnanolone during late diestrus cause increased expression of $\alpha 4$, $\beta 1$, and δ subunits of the GABA receptor type A within the PAG [143, 144], including the VLPAG, ultimately resulting in attenuated ongoing GABAergic inhibitory activity towards serotonergic target neurons [221]. Attenuated activity of GABAergic neurons from the VLPAG would subsequently render serotonergic neurons in the DRD/DRC more active [183]. During a conflict anxiety-relevant stress exposure, CRF expression in the BNST [232, 331] and CRF release from BNST projections would become enhanced and further activate serotonergic neurons through CRFR₂ [204] within the DRD/DRC [335]. In fact, CRF overexpression in the lateral BNST has been shown to alter CRFR₂ receptor density specifically in the DRD [335]. Together with possible stress-induced desensitization of autoinhibitory 5-HT_{1A} receptors on DRD/DRC serotonin

neurons [313], this hyperactivity of the DRD/DRC is likely to cause increased serotonergic output to distal target sites controlling conflict anxiety-relevant behavioral parameters, mainly through actions of serotonin on postsynaptic 5-HT_{2C} receptors in the BL [12, 76, 150]. Other relevant target sites of the DRD/DRC are the anxiety-related BNST [187, 292, 306, 375], the fear-related CE [81, 377], and the ventral hippocampus, an area that is involved in risk assessment during conflict anxiety [151] and facilitates memory consolidation of stressful situations [79, 114].

In the panic circuitry (Fig. 4), several sexually dimorphic, CRF-mediated mechanisms may occur. Based on our working hypothesis, stress-induced increases in CRF signaling from the CE, a region with volume reductions in panic disorder patients [160], may act directly on CRFR₂-expressing serotonin neurons of the DRVL/VLPAG to increase their inhibitory actions within the DPAG in both females and males. Pharmacological and electrophysiological studies suggest that DRVL/VLPAG serotonergic neurons exert their panic-suppressive actions directly via postsynaptic, inhibitory 5-HT_{1A} receptors on local “pro-panic” glutamatergic and DPAG output neurons or indirectly via excitatory actions on 5-HT_{2A} receptors located on GABAergic interneurons within the PAG [295, 296, 304]. Conversely, blockade of 5-HT_{1A} or 5-HT_{2A} receptors within the PAG promotes panic-like escape behaviors [295]. During late diestrus, however, GABAergic inhibitory tone from PAG interneurons towards the DPAG decreases [221] in females, thus rendering the system more vulnerable to stress and panicogenic situations. Lastly, it is also possible that females display a steroid hormone-dependent increase in *crfr1* expression on GABAergic DRVL/VLPAG interneurons during late diestrus (similar to the high *crfr1* expression in serotonergic neurons of ovariectomized macaques [39, 40, 317]) or (comparable to the sexually dimorphic CRF receptor signaling and trafficking principles discovered in the LC [27]) a prolonged CRFR₁-mediated activation of GABAergic DRVL/VLPAG interneurons compared to males. These mechanisms would lead to an overly pronounced inhibition of DRVL/VLPAG serotonergic neurons and, consequently, to hyperactive or hyperresponsive panicogenic output neurons within the DPAG. Overall, a failure to properly activate these DRVL/VLPAG serotonergic neurons would facilitate escape-like fight-or-flight responses [134] via the DPAG, sympathoexcitation and hypertension [23, 24, 223] via the RVLM, and hyperarousal and hypervigilance due to hyperactive orexin/hypocretin neurons in the perifornical region of the hypothalamus [181].

Conclusions

Considering the hormonal fluctuations in premenopausal women, not even considering pregnancies, one may deem

female physiology as quite stress-resilient and the 2:1 gender ratio of emotional disorders as surprisingly small. At the same time, this is exactly the biological interface where research can discover which mechanisms maintain resilience or how dysregulation of specific systems creates increased vulnerability. Future studies should address questions like: what keeps some individuals from experiencing PMDD or increased anxiety during certain estrous cycle stages or what protects most maternal brains from developing postpartum blues? To assess which sex differences are worth in-depth research, two separate considerations may aid the decision: first, does the sex difference have clinical relevance or does it pertain to translational studies? If yes, then we have an ethical obligation to pursue the matter and use the opportunity to develop sex-specific preventive, diagnostic, and therapeutic tools. Second, how can a sex difference help us better understand a certain biological system? Longitudinal human studies can now identify elevated trait anxiety, and genetic, behavioral, or physiological parameters, such as anxiety sensitivity [268] or baseline proinflammatory state [169] as early markers of inherent vulnerability (allowing for a chance for prevention or early intervention), jointly with the characterization of acquired state anxiety later on, for example, due to stressful or traumatic life events. Also, to date, no comprehensive literature exists on the interaction of biological sex and gender identity regarding anxiety disorders in transgender men and women [71, 399] before and after hormone therapy, an area of research that may contribute valuable insight on the relative impact of sex chromosomes, reproductive hormones, as well as neuronal and psychosocial aspects. Anxiety-relevant research on sex differences within central autonomic control of sympathetic and parasympathetic pathways, too, are chronically under-researched and deserve more attention [30, 362], and much work still lies ahead to increase the validity and translational value of behavioral endpoints in rodent models that differentiate not only between the expression of male vs. female anxiety states, but also between conflict-relevant, panic-relevant, or PTST-relevant anxiety-like behaviors.

In summary, the sex bias in anxiety and affective disorders provides reason enough to acknowledge, instead of ignore, the complexity introduced by the female menstrual cycle and to intensify research on sexually dimorphic developmental programming of the brain and on sex-dependent stress coping mechanisms in adulthood.

Conflicts of interest None of the authors report conflicts of interest related to the submitted manuscript.

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