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SEX AND GENDER ISSUES IN BEHAVIORAL HEALTH (CN EPPERSON AND L HANTSOO, SECTION EDITORS)

What Does Sex Have to Do with It? The Role of Sex as a Biological Variable in the Development of Posttraumatic Stress Disorder

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Abstract

Purpose of Review This review highlights the neurobiological aspects of sex differences in posttraumatic stress disorder (PTSD), specifically focusing on the physiological responses to trauma and presents evidence supporting hormone and neurosteroid/peptide differences from both preclinical and clinical research.

Recent Findings While others have suggested that trauma type or acute emotional reaction are responsible for women's disproportionate risk to PTSD, neither of these explanations fully accounts for the sex differences in PTSD. Sex differences in brain neurocircuitry, anatomy, and neurobiological processes, such as those involved in learning and memory, are discussed as they have been implicated in risk and resilience for the development of PTSD. Gonadal and stress hormones have been found to modulate sex differences in the neurocircuitry and neurochemistry underlying fear learning and extinction.

Summary Preclinical research has not consistently controlled for hormonal and reproductive status of rodents nor have clinical studies consistently examined these factors as potential moderators of risk for PTSD. Sex as a biological variable (SABV) should be considered, in addition to the endocrine and reproductive status of participants, in all stress physiology and PTSD research.

Keywords Posttraumatic stress disorder (PTSD) · Sex as a biological variable (SABV) · Neurobiology · Stress physiology · Neurocircuitry · Gonadal hormones

Introduction

Initially codified by the American Psychiatric Association in the Diagnostic and Statistical Manual of Mental Disorders (DSM-III) in 1980 [1], posttraumatic stress disorder (PTSD) described the effects of combat-related trauma on male military Veterans. However, it has now been well established that PTSD disproportionately effects women and girls [2–5]. PTSD is codified most recently in the DSM-5 as a trauma- or stressor-related disorder [6] and requires the following functionally impairing symptoms to be present for a month at minimum for diagnosis: (a) direct or indirect exposure to a traumatic event which includes actual or threatened death, serious injury, or sexual violence; (b) persistent re-experiencing of the event; (c) persistent effortful avoidance of trauma-related stimuli after the event; (d) negative alterations in mood or affect that began or worsened after the event; and (e) alterations in arousal or reactivity. Women in the general population are less likely to experience traumatic events than men; however, epidemiologic studies suggest that women are approximately twice as likely as men to meet diagnostic criteria for PTSD [e.g., 3, 4] and are over four times as likely to experience chronic PTSD (lasting more than 6 months) [2]. This review aims to address the question of why females may be more vulnerable to the development of PTSD and/or trauma-related symptoms through consideration of sex as a biological variable (SABV) that influences risk and resilience to PTSD after trauma exposure.

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Before considering *sex* differences in the underlying biology that contributes to PTSD susceptibility, it is important to consider structural (types of traumas) and socialization (peritraumatic reactions/characteristics) theories as they address differential exposures and reactions to trauma that may differ between men and women because of their *gender more than their sex*. Though structural and socialization factors contribute to greater rates and prevalence of PTSD in women compared to men [7], it is unlikely that these factors act in isolation. Instead, individual reaction to and processing of a traumatic experience may depend as much on the type and duration of trauma and the environment or context in which the trauma is enacted as the underlying biology of the individual's stress reaction, genotype, or hormonal state.

The structural theory attempts to explain gender differences in PTSD vulnerability, severity, and chronicity as a result of the types of traumas to which men and women may be differentially exposed. A meta-analysis of research published over a 25-year span (1980–2005) found that men are more likely to experience accidents, non-sexual assaults, combat or war, disasters, illness, unspecified injuries, and witnessing the death or injury of others. Women, in comparison, are more likely to experience sexual assault and childhood sexual abuse (CSA). Despite these differences, however, the research is inconclusive in suggesting that trauma type predicts PTSD diagnosis; when researchers control for trauma type, gender differences in PTSD prevalence rates are still evident. Similarly, among both men and women with a history of childhood abuse and neglect, women were more likely to be diagnosed with PTSD and this gender difference remained even after controlling for subsequent rape and multiple stressor exposures [8]. Furthermore, that women exposed to more typically male-oriented traumas remain more likely to meet criteria for PTSD than men experiencing those same traumas lends validity to the hypothesis that the greater prevalence of interpersonal or sexual trauma among women is not the sole driver of sex or gender differences in PTSD prevalence and severity [5, 9].

According to the socialization theory of PTSD development, men and women have been shown to display different peritraumatic cognitive, emotional, and behavioral responses [10–13]. To what degree cognitive appraisal of traumatic events is due to biological differences between sexes or socio-cultural norms that lead to gender differences in response to trauma is not clear. After puberty, women in general are at greater risk than men for depression and anxiety disorders, which may increase their risk for PTSD development after trauma exposure [14, 15]. While greater exposure to more types of toxic trauma and a higher prevalence of pre-existing psychiatric disorders [16] have been purported to contribute to gender or sex differences, respectively, in prevalence of PTSD, studies controlling for trait anxiety [17] and pre-existing mood or anxiety disorder were not able to fully explain the elevated PTSD rates among women [18, 19].

Women and men's immediate post-trauma reactions are markedly different and may be a contributing factor to the later development of PTSD. For example, women's reliance on emotion-focused coping styles has been associated with increased PTSD severity [10, 11]. These types of reactions include the following: a greater likelihood to report self-blame and a greater belief in their own incompetence, damaged state, or that the world is a dangerous place [12, 13]; wishful thinking, mental disengagement, and suppression or avoidance of trauma memories, all cognitive strategies which have been shown to enhance PTSD symptoms [20]; and trauma-related dissociation which is a predictor for the development of PTSD [21–25]. These female reactions contrast with a more typically male problem-focused coping style, which has been shown to be protective against PTSD [10, 11, 26]. Again, these factors may be better characterized as gender differences as they are routed in the socio-cultural context in large. As they explain a relatively small portion of the observed differences in prevalence, natural history, and treatment of PTSD, it is critical to consider sex as a biological variable (SABV) with respect to risk and resilience for PTSD among men and women.

Sex Differences in the Physiologic Response to Trauma

The female-specific risk factors related to trauma and its aftermath suggest that the physiologic response to trauma differs in women compared to men, perhaps due to the changing hormonal environment necessary for female reproductive function. Recent evidence in clinical and preclinical studies have also pointed to sex differences in hypothalamic pituitary adrenal (HPA) axis and autonomic response to threat, contributing to risk for PTSD and post-traumatic stress symptoms in females compared to males [27•, 28••, 29••, 30].

Sex Differences in Corticotropin Releasing Factor

There are well-described differences between males and females with respect to their HPA axis response to stress [29••]. Corticotropin-releasing factor (CRF) is implicated in the pathophysiology of disorders that are more common in women; specifically, hypersecretion of this peptide is associated with both major depressive disorder (MDD) and PTSD [31, 32]. Given this association, it was hypothesized that sex differences in CRF reactivity could contribute to disease expression and the increased prevalence in women [33•]. For example, neuronal differences in response to CRF likely contribute to these differences as noradrenergic neurons in the locus coeruleus (LC) arousal system showed a higher sensitivity to CRF in female compared to male rodents. This phenomenon was linked to sex differences in CRF receptor coupling and signaling [34]. Similarly, in female rats, CRF receptor binding

in the amygdala and certain regions of the cortex are higher than in male rats. And lastly, sex differences have been found in CRF receptor co-localization with GABAergic neurons in the dorsal raphe and delta opioid receptor-containing neurons in the hippocampus [35•, 36, 37]. Combined with earlier research showing that central administration of CRF can induce stress-related behaviors in male rats (e.g., head-shaking, burying, self-grooming) [38], and anatomical research which showed differences in CRF-induced activity in cortical, limbic, and hindbrains regions in males, the findings that CRF receptors differ by sex even at the cellular/neuronal level suggest that CRF may regulate brain circuits and behavior differently across the sexes.

More recently, this literature was tied together with a study comparing the effect of central administration of CRF in both male *and* female rats, in order to see how these cellular and anatomical differences in CRF reactivity impacted anxiety-like behaviors. Consistent with the current hypotheses that CRF mediates the anxiety response differently in males and females, this study showed that higher doses of CRF resulted in increased anxious behaviors for female rats compared to male rats [29••]. Interestingly, there seems to be an interaction with female gonadal hormones as the female rats in their proestrous phase (higher ovarian hormones) showed even more anxious behaviors than females in the diestrous phase. Furthermore, brain regions associated with the anxiety-like behaviors were identified; the infralimbic region, responsible for regulating anxiety, showed a positive association between CRF-induced neuronal activation and anxious behaviors in proestrous females. However, this association was negative for diestrous females and males. Similarly, hormonal status altered the association between CRF-induced neuronal activation and brain region activation, especially in the prefrontal cortex, and other forebrain regions. These findings highlight the role of CRF in the expression of anxiety, not only from a cellular and anatomical perspective, but also with respect to how ovarian hormones alter brain response to CRF infusion. While this observation in rodents underscores the potential for ovarian hormones to sensitize the female to stress, this relationship is complicated in humans with studies suggesting modification by reproductive stage [39, 40].

Sex Differences in Learning and Memory Processes

Sex differences in neurobiological processes, such as those involved in learning and memory, have also been implicated in the sex differences in PTSD prevalence following a traumatic experience. Specifically, deficits in fear extinction are implicated in PTSD as patients experience exaggerated fear/startle response to events reminiscent of the original traumatic event. Sub-optimal fear extinction is central to the development of PTSD as it contributes to the hyperarousal and hypervigilance that are considered hallmark symptoms of the disorder. While the sexual dimorphisms found in the brain structures (i.e., medial prefrontal cortex, amygdala, and hippocampus) that respond to stress and fear conditioning are thought to contribute to the sex differences seen in poor or adequate fear learning and extinction, results of preclinical and clinical studies have been mixed [27•]. Some, but not all [41], studies show male rats have superior fear conditioning and/or fear extinction, [e.g., 42, 43, 44, 45, 46] compared to female rats [47].

Importantly, anxiety-like response in fear conditioning and extinction experiments may be skewed towards more male-typical behaviors (i.e., freezing) given early studies focused solely on male rodents. Female rodents may show a different set of anxiety behaviors (i.e., darting, rearing, or scanning), which, when overlooked, contributed to the seemingly lower fear acquisition and increased extinction in females in earlier studies [48, 49, 50••, 51]. In an elegant experiment meant to examine this potential sex difference in anxiety-like behaviors, no sex differences were evident over the course of fear conditioning, fear extinction, and extinction retrieval (i.e., long-term memory of the extinction). Rats of both sexes displayed variable responses to an aversive tone (conditioned stimulus). In female rats, however, the behavioral distinction between resilience and susceptibility to anxiety-like behaviors in response to the tone emerged earlier, during fear conditioning, compared to male rats who only showed differentiating responses at fear extinction. Among both male and female rats who showed the susceptible response (high freezing to the tone), extinction retrieval did not differ. This suggests that despite showing the same behavioral response, the underlying neural mechanism may differ as a result of the different point of susceptible/resilience distinction [50••].

Inconsistencies regarding potential sex bias in fear conditioning and extinction are not limited to preclinical models. Men performed better than women in the conditioned fear response during fear acquisition in one study [52], but women showed greater fear conditioning in another [53]. Neuroimaging studies in humans support preclinical findings suggesting sex differences in fear conditioning and extinction. Functional and structural irregularities in the ventromedial prefrontal cortex (vmPFC) and hippocampus result in reduced activation in these areas in individuals with PTSD compared to healthy controls during fear conditioning and extinction paradigms [54]. Others have shown that women and men display distinct patterns of neural activation when under acute stress [55] and during fear learning tasks [56, 57]. Specifically, in healthy individuals, right rostral anterior cingulate (rACC) activity was found to be greater in women than men during extinction recall [58], while among PTSD patients, there is a significantly greater acquisition of conditioned fear (higher skin conductance response (SCR)) in women compared to men [59]. In an fMRI study that compared women and men with and without PTSD after exposure to a traumatic event, men with PTSD were found to show increased activity in the left

rostral dACC during extinction recall compared to women with PTSD [28••]. While this work corroborated other studies' findings that dACC activation is implicated in PTSD, it failed to provide an explanation of the mechanism responsible for the greater prevalence of PTSD in women. Notably, menstrual cycle phase was not considered in the above studies. Given the prominent effects of gonadal steroids on brain neurochemistry, structure and function [60•, 61, 62, 63•, 64, 65] across various stages of development and preclinical models indicating estrous cycle effects on stress neurocircuitry, we would argue for controlling for hormonal and reproductive status in all stress- and PTSD-focused research.

Contribution of Gonadal Hormones and Neurosteroids-

The emergence of sex differences in anxiety at puberty [66, 67] and the increased risk of anxiety disorder development or symptom exacerbation that occurs during the luteal phase of the menstrual cycle and under conditions of suppressed endogenous hormone production such as that occurring with steroid contraceptive use [68] highlight the importance of considering neuroactive steroid levels and reproductive status of the individual when evaluating the response to stress and trauma [69••, 70•]. Reproductive hormones and neurosteroids such as the progesterone metabolite and $GABA_A$ receptor agonist allopregnanolone (ALLO) not only impact stress neurocircuitry [54, 70•], they act through receptor and ion channel pathways to regulate numerous neurotransmitter systems involved in the regulation of affect and learning and memory [60•, 71]. Lowered progesterone and estradiol levels characteristic of hormonal contraceptive use are associated with decreased ALLO in women [72], a possible risk factor for contraceptive-induced depression and menstrual cycle-related negative affective states such as premenstrual dysphoric disorder [73, 74].

However, high progesterone levels characteristic of the mid-luteal phase of the menstrual cycle may contribute to the development of more salient and intrusive memories following an aversive event [69••, 75–78]. Elevated exogenous progesterone levels have been implicated in increased amygdala activity and increased functional coupling of the amygdala and the dorsal anterior cingulate cortex, both of which are associated with the acquisition of learned fear [79]. That ALLO is a metabolite of progesterone suggests that the so-called progesterone effects may actually be a result of associated elevations of this neurosteroid [80]. Manipulations of the ALLO activity within the bed nucleus of the stria terminalis (BNST) have been shown to modulate the expression of conditional contextual fear in rats [81]. This extended previous research on contextual fear behaviors [e.g., 82, 83] which together suggests that the reduced levels of context-dependent fear in female rodents with elevated levels of progesterone may actually be more closely related to ALLO's actions within the BNST. However, this preclinical data is inconsistent with human data. Females, compared to males, have higher levels of ALLO naturally, but are *more* susceptible to development of PTSD [84, 85] perhaps due to its fluctuation across the cycle or secondary to organizational differences between males and females at birth that are unmasked by such fluctuations after puberty [86]. Studies of ALLO effects in rodent models have largely been conducted with contextual fear paradigms, not fear extinction paradigms, and it is the deficits in fear extinction that are widely believed to be responsible for PTSD development and maintenance [87, 88]. Pregnant women with PTSD had greater fear-potentiated startle to a safety signal than non-pregnant women with PTSD, which correlated with PTSD hyperarousal symptoms [89]. This suggests that discrimination between the danger signal (the reinforced conditioned stimulus) and safety signal (non-reinforced conditioned) was impaired among the pregnant women. Although ovarian hormones such as progesterone were not assessed, they may play a role in this impaired inhibition of conditioned fear. At this point, it is unknown how progesterone and its metabolites contribute to fear extinction [81]. Work by Milad and colleagues suggests that in fear extinction paradigms, estrogen may be more strongly associated with deficits in extinction recall than progesterone [90]. Women with higher levels of estradiol during an extinction learning task had enhanced extinction recall, however, estradiol had no impact on fear acquisition or extinction learning. In a fear-potentiated startle study, fear acquisition was similar among women with PTSD and trauma-exposed controls, regardless of gonadal hormone levels [56]. However, fear extinction differed by diagnosis and estradiol level; women with PTSD and low estradiol exhibit heightened fear-potentiated startle during extinction training compared with trauma-exposed controls, which was not exhibited by women with higher estradiol. This suggests that estrogen influences ability to inhibit learned fear.

That higher levels of estradiol are associated with increased activation of brain structures responsible for learning and memory (different sub-regions of the insular and cingulate cortices, amygdala, hippocampus, and hypothalamus) during fear conditioning suggests that the sex differences in the activity of these structures may be partially attributed to female gonadal hormones [91•]. Relevant to the development of PTSD, elevated activation of the circuitry responsible for arousal (hypothalamus, amygdala, and cingulate cortex) is also associated with elevated estradiol in response to emotional stimuli [55]. Notably, women using oral contraceptives, who have prolonged, non-cycling levels of lower endogenous estradiol, but higher levels of synthetic estrogen show reduced extinction memory as compared to women in a high estradiol menstrual phase such as peri-ovulation [92, 93]. Women using oral contraceptives also have enhanced acquisition of a conditioned eyeblink response compared with naturally cycling women, particularly mid-cycle [94]. These

findings were consistent with those of rodents under similar hormonal conditions [92].

Given that the experience of intrusive memories and physiological arousal are common symptoms of PTSD, the relationship between sex hormones, emotional memory formation, and fear association seems to be implicated in women's vulnerability to the disorder.

Sex Differences in Stress Neurocircuitry

Another area of research into the discrepancy in PTSD prevalence between men and women is potential differences in brain anatomy and function responsible for fear conditioning. For example, the amygdala plays a key role in conditioned fear and has been shown to activate differently in healthy women and men when exposed to threatening conditions [37, 95]. Other brain structures are at play in these differences, too; women displayed greater activation than men in the dorsal anterior cingulate cortex (ACC), hippocampus, periaqueductal gray region of the brainstem, and cerebellum in response to viewing fearful faces [37]. These patterns of enhanced activity compared to men were sustained in healthy women when individuals were expecting a mild shock [96]. These findings were also confirmed in a meta-analysis of 65 studies showing that women experienced greater activation in the subcallosal ACC, thalamus, midbrain, and brainstem when exposed to affective stimuli [97]. Interestingly, the studies included in the meta-analysis did not consider female hormonal state, indicating that gonadal hormones are not solely responsible for sex differences. Rather, we must consider the organization of the male versus female brain in utero as being responsible for some of the differences noted here.

Among women exposed to trauma and those with PTSD, there is comparatively more activity in the dorsal brainstem (including the superior colliculi, reticular activating system, and midbrain periaqueductal gray region) compared to men with any level of trauma exposure or PTSD, suggesting that brainstem activity is enhanced in women following trauma exposure but may not be as relevant in the pathophysiology of PTSD among males. These are the same regions which are activated more readily in women than men in healthy samples being exposed to aversive stimuli suggesting baseline sex differences regardless of trauma exposure or PTSD status [37, 96, 97]. Greater brainstem arousal in women is also associated with autonomic arousal, orienting to threat, and an automatic alarm mechanism. Prospective studies have found that heightened autonomic arousal (i.e., tachycardia, hyperventilation) in the immediate aftermath of trauma is associated with later development of PTSD [23]. While in these studies, women with PTSD showed increased activity in regions that may be responsible for PTSD acquisition, men showed an increase in amygdala inhibition via unexpected heightened hippocampal activity. Because the hippocampus works with the ventral medial prefrontal cortex to inhibit amygdala activity, this greater hippocampal activity seen in men may suggest the greater contextual processing and activation of inhibitory networks over fear and arousal networks, contributing to the lower prevalence of PTSD in men [98].

Conclusions

Sex differences in PTSD prevalence are numerous and often attributed to one particular area of research investigation. This review attempts to shed light on the multiple types of differences that exist between the sexes, in order to explain women's vulnerability to the development of this disorder after traumatic exposures. While overall, men may be the more visible recipients of care for PTSD due to the high-profile nature of war and combat trauma and their higher lifetime prevalence of trauma exposure, women are more vulnerable to the aftermath of traumatic events. This review highlights the unique contribution of neurobiology, hormonal shifts, and anatomy that may lead to risk or resilience for PTSD among females. Future research should take into consideration the endocrine conditions, specifically menstrual phase and oral contraceptive use, under which women experience traumatic events as reproductive hormones have pronounced impact on neurochemistry and stress neurocircuitry underlying the development of PTSD.

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Compliance with Ethical Standards

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