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Sex Differences in Trauma-Related Psychopathology: a Critical Review of Neuroimaging Literature (2014–2017)

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Abstract
Purpose of Review Sex differences in the epidemiology and clinical presentation of trauma-related psychopathology have long been documented. Multiple underlying mechanisms have been examined, both psychosocial and biological. Among the most promising biological mechanisms are neural substrates of trauma-related psychopathology that have been uncovered in recent years.
Recent Findings Neuroimaging studies of sex-related heterogeneity published over the past 3 years (2014–2017) demonstrate an interaction between sex and type, timing, and load of trauma exposure. These studies suggest that, for males, early trauma exposure may involve a loss of gray matter in the limbic system, including the prefrontal cortex (PFC), amygdala, and hippocampus, and an over-activity and increased connectivity of salience hubs, and particularly dorsal anterior cingulate cortex (dACC). For females, however, early trauma exposure may involve overactive and possibly an enlarged amygdala, as well as decreased connectivity of salience hubs such as the dACC. Underlying mechanisms may include interaction with several endocrine systems and result in differential neural response to naturally occurring and added endocrine ligands, as well as sex-specific genetic and epigenetic risk and resilience factors. This complex interaction between multiple biological systems may be associated with sex-specific behavioral patterns, in turn associated with trauma-related psychopathology.
Summary While substantial number of published studies present preliminary evidence for neural mechanisms of sex-specific posttraumatic responses, there is a paucity of research directly designed to examine sex as a biological factor in trauma-related psychopathology. Specific foci for future studies aiming to bridge current gaps in the literature are discussed.

Keywords Sex as a biological variable · Gender medicine · Women's mental health · Neurobiology · Traumatic stress

Introduction

The adverse mental health effects of exposure to traumatic events have been long documented and studied [1]. Exposure to a traumatic event is defined as exposure to death, threatened death, actual or threatened serious injury, or actual or threatened sexual violence [2]. Such experience is almost ubiquitous, affecting 70–90% of the population [1]. Most of those exposed to trauma evince resilience [3]. Yet, a significant minority (20–30%) will likely develop psychopathology, most markedly, depression, anxiety, and posttraumatic stress disorder (PTSD) [4–6], as well as substance use [7, 8] and eating disorders [9].

Women comprise a disproportionate group among those developing psychopathology, being twice as likely to develop trauma-related psychopathology as men [10], and symptom patterns following traumatic exposure appear gendered, with women developing more affective disorders and men presenting with more substance abuse [11]. Empirical examination of the mechanisms underlying this disproportion has included type and load of the traumatic exposure, cognitive factors,

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coping strategies, and biological factors related to sex [12–15]. Among the most promising biological substrates of these epidemiological differences is neural processing [16].

Studies examining the neural mechanisms of development and maintenance of trauma-related psychopathology have focused mainly on circuits implicated in fear processing [17–19], emotional regulation [20, 21], and stress response [22, 23], including cortical, limbic, and salience regions. Most commonly, these regions have included the amygdala, limbic and salience hub linked to emotional processing and response [24, 25], hippocampus, associated with learning and memory [26], insula, a major salience hub implicated in self-referential processing [20], and prefrontal cortex (PFC). The PFC is involved in executive functions [27] and includes subregions such as the orbitofrontal (OFC; implicated in emotional processing [28]) and anterior cingulate (ACC; associated with monitoring [29]) cortices. More recently, the involvement of reward- and motivation-related striatal regions [30], most commonly implicated in depression [31] and substance use [32], has also been explored [33•, 34]. These various neural circuits have been examined in relation to either adult or childhood exposure.

In healthy adults, a vast body of literature has demonstrated sex differences in the structure and function of these same circuits. Amygdala activation was found to be more pronounced in females in response to negative stimuli and more pronounced in males in response to positive stimuli [35], suggesting differential valence-bound limbic activation. Functional and structural connectivity of fronto-limbic circuits also appears to follow sex-specific patterns, with increased connectivity among females when compared to males (e.g., [36], see for review [37]), although some contradictory results have also been found suggesting that other factors may moderate this difference [38]. These circuits have been also implicated in sex-specific patterns in cognitive processes relevant to trauma and related psychopathology, including memory, reward processing, and emotional regulation. Semantic memory associates with increased PFC and dorsal ACC (dACC) activations among females as compared to males, suggesting more emotional encoding [39]. Reward-based risk taking involves higher striatal activation in females vs. males [40], and emotional regulation has been found to associate with stronger negative amygdala-PFC connectivity and positive amygdala-insula connectivity among females and with weaker connectivity in these pathways among males [41]. Sex differences have even been found in the neural underpinnings of automatic, universal processes such as autonomic arousal, with a positive association between arousal and amygdala activation among females, and a negative one among males [42]. Additionally, underlying neural circuitry of drug dependence and depression has demonstrated sex-specific cortico-striatal and limbic patterns. Among cocaine-dependent females and males, cortico-striatal-limbic hyperactivity has been associated with stress cues in females but drug cues in males [43] and gray matter deficits in depressed vs. healthy adults were localized in limbic regions of females but striatal regions of males [44]. It appears that females evince stronger amygdala and PFC activation than males do when faced with affect-laden, mostly negative, cues. Furthermore, females seem to require little prefrontal, but more salience, involvement in emotional regulation of the amygdala. Overall, among females versus males, more limbic and less striatal involvement may be evident during emotional processing and decision making. However, the question remains whether these patterns hold following trauma and whether they are involved in the sex differences in subsequent psychopathology. Specifically, divergent pathways may explain some of the clinical and epidemiological findings of sex differences in trauma-related psychopathology. Indeed, many recent works have pointed to sex differences as an important future direction for additional research in trauma-related psychopathology [19, 37, 45, 46]. However, only a few recent studies have followed this suggestion. The goal of the current review is to search the recent research on sex differences or sex-specific patterns in neuroimaging of trauma-related psychopathology. We will review these studies in the following sections, considering as well indirect evidence of possible mechanisms that may explain sex differences in neuroimaging research, such as endocrine, behavioral, and genetic mechanisms.

Method

Selection Criteria

The search conducted included manuscripts based on original data, published in peer-reviewed journals between 2014 and 2017. Manuscripts were included if they: (1) used neuroimaging methodology, such as magnetic resonance imaging (MRI), positron emission tomography (PET), or single-photon emission computed tomography (SPECT); (2) examined trauma-related psychopathology; and (3) directly examined sex or gender as a variable (e.g., not simply statistically or methodologically control for it). Manuscripts discussing neural function or structure among those with mechanical damage to the brain (e.g., traumatic brain injury) were excluded.

Search Strategy

The search included three steps: entering search terms, reviewing abstracts and excluding manuscripts that did not meet criteria, and reviewing full text and excluding manuscripts that did not meet criteria. Search terms used included the following keywords: (1) Trauma; (2) PTSD, depression, anxiety, substance, *or* psychopathology; (3) Neuroimaging, MRI, fMRI, PET, *or* SPECT; (4) Sex *or* gender.

Search Results

The original search yielded 54 results. Of these 54, only 13 studies directly examining sex differences in neuroimaging following exposure to traumatic events were eligible for inclusion. All manuscripts employed MRI imaging methods but one, which employed PET. Of these, five [47•, 48, 49, 50•, 51] used structural imaging only, four of which included only gray matter volumetrics and one also employed diffusion tensor imaging (DTI) for structural connectivity. Of the eight remaining studies, which used functional imaging, one [52•] employed resting state functional connectivity (rs-FC) analyses as well as DTI, and six studies [53•, 54•, 55•, 56•, 57•, 58•] employed task-bound functional MRI (fMRI). Of these, two [56•, 57•] employed fear-learning paradigms, one employed an emotional face encoding and working memory task [59], one employed a behavioral inhibition task [55•], and two were taken from the same research group employing an emotional face-matching task [53•, 54•] (for a full review of methods, see Table 1). The remaining study [33•] employed PET to detect dopamine receptor availability during a reward-based task. These will thus be presented by imaging and experimental modality in the following section.

Direct Evidence of Sex Differences in Trauma-Related Psychopathology Using Neuroimaging

Structural MRI

The evidence for the involvement of specific neural structures in trauma-related psychopathology comes primarily from the study of PTSD, with most evidence suggesting a diminished hippocampus [25, 60, 61], smaller prefrontal structures [62–64], and possibly an enlarged amygdala [65, 66]. However, recent findings suggest sex-related heterogeneity in all these structures.

Much of the recent evidence of structural differences between males and females in trauma-related psychopathology comes from studies examining impact of childhood adversity. These support specific gray matter deficits among exposed males but not females. One such study found that maltreated males (but not females), with and without PTSD, showed less gray matter in the left superior PFC compared to maltreated females, with and without PTSD, and a trend for maltreated males with PTSD to show less left superior PFC gray matter than male controls [47•]. This suggests a male-specific prefrontal gray matter deficit associated with early maltreatment, which is exacerbated in those who develop PTSD. Another study examined the relationship between brain volumes and current and childhood negative interpersonal events, and current and childhood socioeconomic status (SES). In males, but not females, childhood SES was marginally related to left hippocampal volumes and higher adversity associated with higher right amygdala volume in females and with lower right amygdala volume in males [50•]. However, this study also found gray matter surplus among females, with higher adversity associated with higher right amygdala volume in females and with lower right amygdala volume in males. Higher right amygdala volume in females, but not males, was associated with current SES, and lower amygdala volume was found to associate with current interpersonal events among males, but not females [50•]. This suggests specific effects on the amygdala and hippocampus dependent on sex and timing of stressor. This, perhaps, may explain previous discrepancies in findings in these regions. However, no sex-specific patterns were found in the structure of the PFC and hippocampus among PTSD and non-PTSD youth [48], possibly suggesting the changes found among adults with early trauma, may better represent a long-term, or delayed, outcome.

No evidence exists, to our knowledge, for sex-specific patterns of neural structure following traumatic stress in adulthood, suggesting similar structural deficits for males and females in hippocampal [49] and amygdalar [51] volume, as well as amygdala-PFC connectivity [67].

Taken together, the above findings suggest long-term, male-specific gray matter deficits in prefrontal and limbic regions of individuals suffering childhood adversity. While no such deficit appears to be in females, a female-specific increase in amygdala volume may characterize adults suffering specific early stressors. Sex nonspecific deficits in limbic structure volume and connectivity appear to characterize those exposed to trauma in adulthood. Thus, a complex interaction of sex, region, and timing of trauma emerges may exist and should be further studied. Additional insight into underlying processes may derive from functional neuroimaging studies, which examine neural activation.

Functional Neuroimaging

Several different means of understanding neural function have been employed in the study of trauma. These include functional MRI (fMRI), exploring the neural activation of regions during specific tasks, as well as connectivity between regions of interest (ROI), either dependent (psychophysiological interaction; PPI) or independent (resting state functional connectivity; rs-FC) of a task. Additional techniques, such as using PET to track molecular processes, have also been used.

Task-Related fMRI

Six of the studies reviewed examined sex-related patterns in task-related functional neuroimaging. These have used tasks gauging fear processing and response inhibition, two constructs implicated in trauma-related psychopathology. One

Table 1 Summary of reviewed studies

Author	Population	*N* (by sex)	Neuroimaging technique	Neuroimaging modality	Imaging analysis	Pharmacology	Type of trauma	Main trauma/ clinical measure used in analysis	ROIs	type of psycho-pathology
De Bellis et al. [47•]	Youths with and without PTSD	38 chronic PTSD (21 F), 35 TEHC (17 F), 59 HC (33 F)	MRI	Structural and DTI	Volumetric, DTI tractogra-phy	NA	Physical or sexual abuse, neglect, emotional abuse, witness or victim of other personal violence, corporal punishment	Kiddie schedule for affective disorders and schizophre-nia (K-SADS; DSM adherent clinical interview)	Cerebral and cerebellar volumes, cortical regional measures, and corpus callosum DTI values	PTSD
Elton et al. [55•]	Adults	40 (21 F)	fMRI	Task-based fMRI (stop-signal task)	ICA, graph theory, SEM	NA	Nonspecific	Childhood trauma question-naire (CTQ)	Inhibitory control network	Nonspecific
Frijling et al. [59]	Adults	41 (32 F)	fMRI	Task-based fMRI (emotional-face--matching task)	GLM	Oxytocin	Traffic accident, accident at work, interpersonal trauma	Clinician administered PTSD schedule (CAPS; DSM adherent clinical interview)	Amygdala	Nonspecific
Gupta et al. [52•]	Adults	124 (63 F)	fMRI	rs-fMRI, DTI	Graph theory	NA	Nonspecific	Early trauma inventory (ETI-SR)	Amygdala, aMCC, subgenual ACC, pregenual ACC	Nonspecific
Keding et al. [48]	Youth	27 PTSD (18 F), 27 HC (13 F)	MRI	Structural	VBM	NA	Sexual abuse, witnessing violence, traumatic death of loved one, accident	CAPS	Medial PFC, amygdala, hippocampus	PTSD
Koch et al. [53•]	Adults	37 PTSD (16 F), 40 without PTSD (20 F)	fMRI	Task-based fMRI (emotional-face--matching task)	GLM, correla-tion	Oxytocin	Police officers, trauma type not included in the paper	CAPS	Amygdala	PTSD
Lawson et al. [50•]	Adults	46 HC (23r	MRI	Structural	Volumetric	NA	Nonspecific	Childhood socioeco-nomic status (SES),	Amygdala, hippocampus	Nonspecific

Table 1 (continued)

Author	Population	*N* (by sex)	Neuroimaging technique	Neuroimaging modality	Imaging analysis	Pharmacology	Type of trauma	Main trauma/ clinical measure used in analysis	ROIs	type of psycho-pathology
								Adverse Childhood Experiences (ACE)		
Luo et al. [49]	Adults	57 PTSD (37 F), 11 TEHC (5 F), 39 HC (20 F)	MRI	Structural	Volumetric	NA	Lost only child	Time since trauma, CAPS	Amygdala, hippocampus	PTSD
Oswald et al. [33•]	Adults	28 HC (9 F)	PET	PET	D2 receptor availability (binding potential of injected ligand)	Intravenous saline, amphet-amine	Nonspecific	Perceived Stress Scale (PSS), Early Trauma Inventory Short Form (ETI-SR-SF)	Putamen, caudate nucleus, and cerebellum, motor (posterior putamen), associative striatum (anterior putamen and anterior and posterior caudate nucleus) and limbic ventral striatum subdivisions	Nonspecific
Pohlack et al. [56•]	Adults	112 HC (39 F), 73 HC (24 F)	fMRI	Task-based fMRI (contextual fear conditioning)	GLM, genetic	NA	Nonspecific	NA	Amygdala, hippocampus	PTSD (PAC1-R risk--allele for PTSD)
Shvil et al. [57•]	Adults	31 PTSD (18 F), 25 TEHC (13 F)	fMRI	Task-based fMRI (fear conditioning and extinction)	GLM	NA	Accident, sexual assault, physical assault, combat exposure, terrorism, natural disaster, witnessed a trauma	NA	Amygdala, hippocampus, dorsal ACC and ventromedial PFC	PTSD
Sublette et al. [51]	Adults	40 MDD, 21 bipolar depression, 60 HC	MRI	Structural	Volumetric, linear regres-sion model	NA	Nonspecific	St. Paul-Ramse-y Scale	Amygdala	Nonspecific
Vukojevic et al. [58•]	Adults	152 Trauma-expo-sed (69 F, 83 M; 93 PTSD, 59 TEHC), 72	fMRI	Task-based fMRI (encoding of and recognition of affective and neutral stimuli)	Genetic	NA	Survivors of Rwandan genocide (1994), healthy Swiss subjects	Posttraumatic diagnostic scale (PDS; DSM adherent	Inferior FG, superior FG, STG, cuneus	PTSD, TEHC, HC

Table 1 (continued)

Author	Population	*N* (by sex)	Neuroimaging technique	Neuroimaging modality	Imaging analysis	Pharmacology	Type of trauma	Main trauma/ clinical measure used in analysis	ROIs	type of psycho-pathology
		HC (47 F; 25 M)						self-report question-naire)		

PTS posttraumatic stress disorder, *HC* healthy controls, *TEHC* trauma-exposed healthy controls, *DTI* diffusor tensor imaging, *GLM* general linear model, *VBM* Voxel-based morphometry, *aMCC* anterior mid cingulate cortex, *ACC* anterior cingulate cortex, *PFC* prefrontal cortex, *F* frontal gyrus, *STG* = superior temporal gyrus

such study examined the association between childhood trauma and PFC activation, as well as performance on a response inhibition task (stop signal), testing executive function, an important construct in multiple types of potential posttraumatic psychopathologies [68]. Sex-related interactions were found among high-trauma-exposed, but not low-exposed, males and females. Among this high-exposed subsample, the relationship between connectivity of the dorsal anterior cingulate (dACC; involved in appraisal) to left inferior frontal cortex (IFC; a PFC subregion involved in inhibitory processes), with response inhibition, was sex-specific. In males, decreased response inhibition was related to more (negative) dACC-IFC connectivity and in females, increased response inhibition was related with more (negative) dACC-IFC connectivity. These results were interpreted as less inhibition of the right IFC by the dACC in males with higher overall cumulative childhood trauma experiences improving inhibitory control ability among males but decreasing it among females, and only under conditions of high childhood adversity [55•]. Therefore, it appears that neural substrates of inhibitory control are altered among high-early trauma youths in a sex-specific manner, and, in fact, with a reversed pattern of PFC-ACC connectivity.

Additional evidence demonstrates sex differences in neural processing during a task requiring retention (i.e., recall) of extinguished, previously conditioned, fear [69] among individuals with PTSD. This process has repeatedly been implicated in PTSD and has been suggested as an important potential underlying process in the pathophysiology of this disorder [45, 70]. In this study, males with PTSD exhibited increased activation in the left rostral dACC during extinction recall when compared with females with PTSD. This increases associated with decreased extinction recall, as measured behaviorally using skin conductance response [57•]. These results suggest decreased ability to retain extinguished fear among males (but not females) with PTSD.

One recent study employed rs-FC to gauge the interconnectedness of nodes (regions) in the neural system based on graph theory following early adverse events. This study found an association between type of event and interconnectedness that is moderated by sex. Increased centrality in the anterior mid cingulate (a region overlapping with dACC) was specifically associated with higher physical and emotional adversities among males only. Increased segregation of the insula was associated with increased general adversity in males only. Centrality of the amygdala was associated with physical symptoms for all, and segregation of the insula was correlated with higher somatization among males only, with a non-significant but negative relationship among females. Decreased centrality of the insula and pregenual ACC (pgACC; involved in regulatory functions) associated with increased general early adversities in females [71]. Thus, the association between centrality of salience hubs and childhood

adversities appeared to be reversed in adult males and females, as was the relationship between segregation of insula and physical symptoms. This again demonstrates the potentially different pathways linking similar experiences and symptoms among males and females (e.g., increased connectivity of salience hubs as risk factor for females and decreased connectivity as a risk factor for males).

Taken together, the above functional studies suggest that neural processing in the salience network, and particularly the dACC, is associated with both early exposure to trauma and with clinical presentation of PTSD among adults in a sex- and trauma-specific manner, wherein overactivation and connectivity of dACC are associated with traumatic exposure, and dysregulated inhibitory processes, among males specifically, whereas this pattern is reversed in females. This heterogeneity supports a relationship between neural and cognitive processing, so that different processes may be associated with similar symptoms among males and females.

In order to better understand possible factors underlying this equifinality of different neurocognitive processes, both endocrine and genetic factors should be taken into consideration. Indeed, five of the studies reviewed examined interactions between neuroimaging data and genetic or endocrine factors.

Endocrine-Neural Interactions

Several endocrine systems have been implicated in the development of stress and trauma-related pathologies [66, 72], most notably the hypothalamic pituitary adrenal (HPA) system [73–75] but also the noradrenergic [76] system, as well as systems governing neurotransmitters such as the serotonergic [77] system. More recent studies have included novel possible endocrine targets: dopamine (DA) and oxytocin (OT). DA is involved in the experience of pleasure and has been implicated in multiple trauma-related pathologies such as depression [31] and substance use [32]. OT is known for its role in social bonding [78] but has been further implicated in depression [79], anxiety [80], and more recently in stress and related disorders [81, 82], marking its relevance for trauma-related psychopathology. Further studies have uncovered sex-related heterogeneity in the relationship of both OT and DA to trauma-related psychopathology.

Examination of DA release and receptor availability in striatal regions using PET, and their relationship to childhood adversity and the pleasant effects of drugs, attempted to disentangle the relationship between childhood adversity and drug abuse [33•, 83]. Associations between childhood trauma and DA release did not differ in males and females, but relationships between childhood trauma, DA receptor availability, and pleasant drug effects were significantly modified by sex. Childhood trauma was positively associated with DA receptor availability in males, whereas a trend for a negative relationship was observed in females. Although not significant, similar sex differences in directionality were observed in relationships between ACEs and pleasant drug effects. Perceived stress was also positively associated with pleasant drug effects in males; whereas, no relationship was observed in females. No associations were found between perceived stress and DA receptor availability [33•]. Childhood trauma, therefore, may alter DA-related pathways in striatal regions in a way that is experienced differently in males and females and may thus explain increased risk of drug abuse among males relative to females.

A series of studies examining neural processing of neutral and emotional faces among trauma-exposed males and females and its relationship with OT administration has uncovered some sex-specific heterogeneity. Significantly, greater left amygdala reactivity to neutral faces after OT administration in trauma-exposed females as compared to males was found, without sex-related effects for happy or fearful faces [54•] suggesting oxytocin modulation of amygdala response to emotionally ambiguous cues among females only within trauma-exposed population. When OT administration in regard to this task and differing between individuals with and without PTSD was examined, no sex differences were found: PTSD patients showed lack of differentiation between affect-laden and neutral stimuli (i.e., did not show greater amygdala activity toward fearful-angry faces compared with happy-neutral faces) and OT administration dampened amygdala reactivity toward all emotional faces in male and female PTSD patients, but enhanced amygdala reactivity in healthy male and female trauma-exposed controls, independent of sex and stimulus valence. Authors suggest lack of sex-related effects may be due to inclusion of women of all menstrual phases and those taking oral contraceptives [53•], as oxytocin effects have been shown to interact with estrogen [84]. However, this may also reflect specific effects of OT in PTSD, particularly as naturally circulating OT levels appear to differentiate male PTSD patients from trauma-exposed healthy controls, but to be similar among trauma-exposed females with and without PTSD [59].

In summary, trauma exposure may change neural connectivity and neural response to neurotransmitters and neuromodulators in a sex-, developmental timing-, and trauma-type-dependent manner. This dovetails with findings suggesting sex-specific reorganization of neural circuitry depending on developmental variables such as age [85] and pubertal status [86, 87]. Mechanistically, such individual differences in neural plasticity may involve not only the effects of specific ligands such as OT and DA in ROIs, but also genetic organization of receptors in relevant regions.

Genetic and Epigenetic Substrates of Neural Function

Neural plasticity is organized by the interplay between receptor expression and ligand availability. An important system

implicated in neural organization of response to stressful experiences is the hypothalamic pituitary adrenal (HPA) system, including glucocorticoids (GC), pituitary adenylate cyclase (PAC1), and other signaling pathways with roles in initiation and regulation of the stress response. Both GC and PAC1 have been implicated in trauma-related psychopathologies such as PTSD [56•, 88–92] and depression [93–97], and have evinced sex differences [56•, 88, 98–101]. Recent evidence delineates sex-specific genetic risk factors entailing both GC and PAC1.

In a study of males and females surviving the Rwandan genocide, DNA methylation at the NGFI-A (nerve growth factor-induced protein A) binding site of the NR3C1 (glucocorticoid receptor gene) promoter was associated with less intrusive memory of the traumatic event and reduced PTSD risk in males, but not females. This same methylation was found to associate with PFC activation during successful memory performance on a retrieval task among males only. This was interpreted as an epigenetic modification of the glucocorticoid receptor gene promoter linked to inter-individual and sex-specific differences in memory functions and PTSD risk [58•]. More broadly, this may indicate a male-specific resilience factor whereas plasticity in the stress response may reduce PTSD risk by downregulating neurocognitive mechanisms behind intrusions.

In a study examining the relationship between PTSD symptoms and allelic variation in the PAC1-R (pituitary adenylate cyclase receptor, found in the PFC, the ligand of which is involved in regulation of stress hormones) gene among trauma-exposed males and females, a specific allele was found to be associated with impaired contextual conditioning and PTSD symptoms among females only, and directionality of relationship between hippocampal activation during contextual conditioning and risk gene appeared to be reversed: Female carriers of the PAC1-R risk-allele for PTSD showed a significantly reduced activation in the left hippocampus and male carriers of the PAC1-R risk-allele showed significantly increased activations in the right hippocampus [56•]. Therefore, a female-specific risk factor may include genetically induced impairment of prefrontal regulation of stress, which may particularly hinder utilization of contextual cues, as evident in underutilization of the hippocampus, an important aspect of overgeneralization of fear that is prevalent in trauma-related psychopathologies such as PTSD and generalized anxiety disorder [102, 103].

These results suggest that genetic risk factors may affect neural plasticity related to stress response and related threat processing in a sex-dependent manner, which informs sex-specific pathways to trauma-related psychopathology (e.g., impaired inhibition for males vs. overgeneralization for females). These sex differences appear not only to involve HPA response but also interaction with hypothalamic-pituitary-gonadal (HPG) axis activations, whereas estrogen, a gonadal steroid hormone, appears to modulate effects of both GC [104] and PAC1 [105]. No studies in recent years have directly examined the interactions between these systems in association with trauma and subsequent psychopathology; however, many studies provide indirect evidence of these mechanisms.

Indirect Evidence for Relevant Mechanisms

The literature reviewed earlier supports the notion of significant sex-related heterogeneity in the neural underpinnings of trauma-related psychopathology, as well as their temporal unfolding. The findings also raise major questions, mostly regarding the interplay between different biological systems and the way trauma-related responses relate to known sex differences in neural, cognitive, and emotional processing.

While recent studies have not directly examined the role of HPA, HPG, and their interaction in sex-related heterogeneity of trauma-related psychopathology using neuroimaging, evidence from the study of healthy subjects exists. Examining the relationship between HPA response and limbic function revealed a sex-dependent association between functional connectivity of the amygdala and cortisol. Females showed stronger rs-FC than males between the left amygdala and prefrontal regions, as well as hippocampus, and an interaction of sex and cortisol appeared: In females, cortisol was negatively associated with connectivity of the amygdala with areas including striatal regions (involved in motivation and reward experience) and prefrontal regions. Contrarily in males, positive associations of cortisol with rs-FC of the left amygdala and these structures were observed [106]. Thus, fronto-limbic emotional regulation may have a reversed relationship with cortisol among males and females.

Multiple examinations of the relationship between emotional processing and estrogens have solidified understanding of the role of this gonadal hormone in emotional response [107, 108], as well as stress response [109–111]. Recent studies have focused on fear processing in relation to sex, estrogen levels, and neural function. These studies present evidence for significantly higher activations in different sub-regions of the insular and cingulate cortices, amygdala, hippocampus, and hypothalamus, among high-estrogen females compared to males, but not low-estrogen females, during conditioning, extinction, and recall. However, during the unconditioned response, a different pattern was observed, with males showing significantly higher brain activations [112].This suggests that long-term impact of threat exposure in females may be mediated by estrogens and is in line with findings of PTSD-specific menstrual phase differences in threat processing among females as compared to trauma-exposed counterparts [113]. Therefore, future studies may build on this evidence and directly test relationships between HPA, HPG, and multiple

behavioral processes and neural networks in the context of trauma-related psychopathology.

Discussion

Despite repeated indication for need of direct examination of sex as a biological variable in posttraumatic psychopathology, our review found that only few studies have indeed examined sex- and gender-related variability directly. The existing, most current, literature provides preliminary information regarding sex-specific patterns of neural networks involving insula, ACC, PFC, hippocampus, and amygdala, associated with processing of emotional response, fear learning, and emotional regulation (see Table 1).

For males, early trauma exposure may involve a loss of gray matter in the limbic system, including the PFC, amygdala, and hippocampus. Such a loss in limbic structures may explain the over-activity and increased connectivity of salience hubs, and particularly dACC, as a possible compensatory mechanism. This over-activation and connectivity have been linked to extinction recall and impaired inhibition, thus mechanistically tying dACC dysregulation to symptoms of PTSD. Additionally, availability of DA receptors in striatal regions following trauma exposure may potentiate a reward sensitivity which makes males further vulnerable to posttraumatic substance use. Still, most men exposed to traumatic events will not develop subsequent psychopathology and genetic resilience in the form of methylation in specific binding sites for glucocorticoid receptors may allow for adaptive HPA functioning despite adversity.

For females, overactive and possibly enlarged amygdala may follow early trauma exposure, with downregulation and decreased connectivity of salience hubs following. The effects of traumatic experience on the amygdala may be modulated by OT, which may, in turn, be modulated by estrogens. Additionally, female-specific risk of trauma-related psychopathology may include genetic risk alleles of the PAC1 receptor gene, which may induce plasticity in a generalization-potentiating manner. Together, overgeneralization and amygdalar dominance may lead to a female-specific, durable sensitivity to negative stimuli.

In summary, the findings above suggest that female-specific fronto-limbic/salience patterns associated with emotional processing and specifically in response to stressful events and negative stimuli may constitute a risk factor for development of PTSD and other trauma-related pathologies of an affective nature. The literature demonstrating a male-specific risk factor related to fronto-striatal function and structure may further explain clinical and epidemiological findings regarding heightened risk for posttraumatic substance use among males. However, the impact of trauma on the fronto-limbic-striatal circuits appears not only sex-dependent, but type-, timing-, and dose-dependent, with the severity, chronicity, type, and developmental timing of exposure interacting with sex in determining neurobehavioral outcome. Furthermore, some findings, such as dampening of amygdala activation by oxytocin being male-specific among trauma-exposed, healthy individuals, and apparent in males and females with PTSD, may suggest that

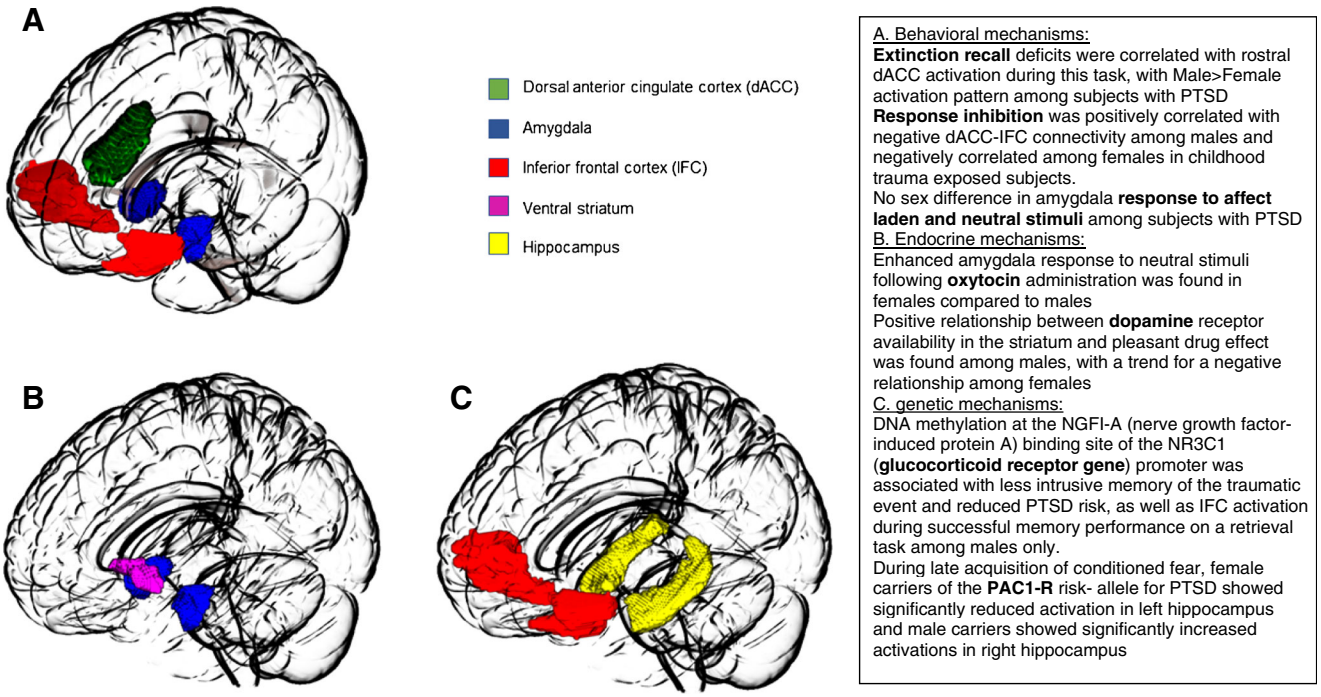

Fig. 1 Key findings of sex-dependent activations by mechanisms

trauma-related psychopathology may involve different processes following trauma (multipotentiality) but result in similar presentation (equifinality). Therefore, similar symptom presentations, including physiological responses, may result from widely different biobehavioral trajectories following the exposure. Thus, both immediate biobehavioral responses and those which unfold over time and in relationship to symptom presentation must be examined. Direct and indirect evidence suggests underlying mechanisms involving genetic and endocrine factors related to neural plasticity and maturation, and particularly HPA- and HPG-axis-related factors, which may further affect subsequent neural response to naturally occurring and added endocrine ligands (for a summary of direct evidence of neural correlates of behavioral, endocrine, and genetic mechanisms, see Fig. 1).

The studies reviewed here have examined several different neural systems (e.g., executive, salience, reward, limbic), endocrine systems (HPA, HPG, OT, DA), and behavioral constructs (e.g., inhibition, fear processing, emotional response to social cues) using variable neuroimaging methods, mostly MRI-based (e.g., rs-FC, fMRI and structural MRI). This wide variability, alongside lack of studies including multiple systems and measures, preclude direct comparison of processes and therefore the cohesive understanding of interplay between them and, therefore, any strong conclusions. Additionally, many studies do not directly examine psychopathology or, when they do, focus on PTSD (for comparison of studies, see Table 1). Therefore, it is advised that future studies would focus on within-sex patterns of impact of trauma, using a multi-method approach, inclusive of neural, behavioral, genetic, and endocrine measures, and their interactions. Studies should also focus on the role of developmental timing, type, and load of trauma as between-subject variables interacting with sex. Finally, psychopathology should be defined broadly (e.g., depression, anxiety, substance use) rather than focusing on PTSD as a single outcome. Studies following such guidelines may better address the current gaps in literature and lead to a thorough understanding of sex as a biological variable in trauma-related psychopathology. Such an understanding may inform the tailoring of treatments to target specific, individually relevant targets, both processes and deficits, underlying trauma-related psychopathology in patients, and in so, bringing precision medicine into mental health.

Compliance with Ethical Standards

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