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Post-traumatic stress disorder: pathogenesis, epidemiological characteristics, animal models, and potential therapeutic strategies

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Abstract

Post-traumatic stress disorder (PTSD) is a complex neurobehavioral disorder that disproportionately affects military service members. The clinical presentation of PTSD is heterogeneous and may overlap with other psychiatric conditions. According to the Fifth Edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), common symptoms include memory loss, mood and personality changes, impulsiveness, aggression, anxiety, and depression. The pathophysiological mechanisms underlying PTSD remain incompletely understood, although research implicates pathways involving the hypothalamic-pituitary-adrenal (HPA) axis, dysfunctional neural circuitry, neurochemical imbalances, neuroinflammatory processes, and genetic and epigenetic factors. Approximately 7% of the U.S. adult population has met the diagnostic criteria for PTSD in their lifetime, with a substantially higher prevalence of 12%–30% among military personnel. Multiple animal models, including single-stressor, intermediate complexity, social interaction, predator stress, and blast exposure paradigms, have been employed to investigate PTSD mechanisms. Current treatment strategies typically integrate pharmacotherapy and psychotherapy. Military service members are at increased risk for blast injuries, which frequently result in traumatic brain injury (TBI). Although some symptoms of TBI may resolve, approximately 20% of affected individuals develop new symptoms, including PTSD. Evidence suggests that exposure to blast shock waves (BSWs) serves as a critical trigger for the clinical manifestations of both TBI and PTSD. Recent studies have identified several mechanisms contributing to BSW-induced brain dysfunction, including intraneuronal accumulation of phosphorylated Tau (p-Tau), activation of the dynorphin/kappa opioid receptor, and activation of metabotropic glutamate receptor 2/3 signaling pathways. This review provides an overview of the clinical features, treatments, pathophysiology, and epidemiology of PTSD, as well as animal models and their limitations in replicating PTSD-like symptoms. It further examines the relationship between BSW exposure, brain injury, and PTSD, discusses animal models that simulate blast trauma and PTSD-like symptoms, and evaluates potential therapies to mitigate BSW-induced PTSD. Finally, the review addresses the limitations of current models and proposes future directions for elucidating the mechanisms linking brain trauma to PTSD.

Key words Post-traumatic stress disorder (PTSD), Traumatic brain injuries (TBIs), Axonal injury, Blast shock waves, Cognitive impairment, Hypothalamic-pituitary-adrenal axis, Mood dysfunction, Neuroinflammation

Background

Post-traumatic stress disorder (PTSD) is a complex neuropsychiatric disorder characterized by diverse clinical manifestations. It may develop following abuse, accidental injury, natural disasters, terrorism, medical trauma, occupational stress, or military combat [1]. The etiologies of PTSD are classified as type 1 or type 2 trauma [1]. Type 1 trauma generally involves a single, unexpected event, often occurring in childhood, whereas type 2 trauma results from repeated exposure to external stressors such as persistent abuse [1]. Military personnel are at greater risk for PTSD than civilians due to the frequency and severity of trauma exposures [2]. Diagnosis relies on the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria for trauma-related disorders [3,4]. The DSM-5 reclassified PTSD to distinguish it from anxiety and depressive disorders, thereby enhancing diagnostic precision. Diagnostic criteria require symptoms to persist for more than one month and include at least one intrusive symptom, one avoidance symptom, two indicators of altered arousal or reactivity, and two negative alterations in mood or cognition [3,4]. The heterogeneity of PTSD presentations complicates pharmacological management [4-6]. Frequently observed symptoms include

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memory impairment, mood and personality disturbances, impulsivity, aggression, anxiety, and depression [5,7].

The standard approach to PTSD treatment involves a combination of pharmacotherapy and psychotherapy [2,4]. First-line pharmacological agents include selective serotonin reuptake inhibitors (SSRIs) [2,8], while prazosin is frequently used to alleviate nightmares and sleep disturbances [9]. Pharmacological interventions generally demonstrate only moderate efficacy. Evidence-based psychotherapies, including cognitive-behavioral therapy, prolonged exposure therapy, and eye movement desensitization and reprocessing, are regarded as the gold standard for PTSD management. These therapeutic modalities facilitate the processing of traumatic memories and the reduction of avoidance behaviors.

Traumatic brain injury (TBI) is prevalent in both military and civilian populations and represents one of the most common injuries in deployed environments [10]. TBI may result from acceleration-deceleration forces, exposure to blast shock waves (BSWs), direct physical trauma to the head, or penetration of sharp objects through the skull into the brain. The diagnosis of mild TBI (mTBI) typically relies on a combination of clinical assessment and computed tomography (CT) scan findings. Symptoms such as loss of consciousness, episodes of confusion, and persistent impairments over several months assist in diagnosing moderate TBI. TBI is classified according to several criteria, including mechanism of injury, penetrating TBI, closed head TBI, and blast-induced TBI [10,11].

The incidence of blast-induced TBI (bTBI) is quite significant in the military population. It is estimated that 10%–20% of veterans who have served in the Afghanistan and Iraq wars suffer mTBI due to exposure to BSWs [7]. mTBI is associated with several mental health pathologies, such as anxiety, depression, insomnia, and impulsiveness [5,12]. While in many cases, symptoms tend to resolve days to months after exposure to BSWs, it is reported that approximately 20% of those who suffer from mTBI develop new symptoms such as PTSD [5,7]. While the specific mechanisms underlying the development of PTSD following exposure to BSWs have yet to be elucidated, some studies have suggested that concussive BSWs passing through some areas of the brain involved in functions such as memory formation, emotional behavior, and conditioned fear response predispose individuals to increased risk of developing PTSD [13,14]. BSWs traversing specific brain regions can induce axonal and vascular injuries in addition to neuroinflammation. These pathological changes may contribute to cognitive impairment, hyperreactivity, and insomnia, which are characteristic symptoms of PTSD [5,7,15,16].

This review presents an overview of the clinical features, current treatments, pathophysiology, epidemiological characteristics, and animal models of PTSD, as well as the mechanisms underlying PTSD-like symptoms in these models. Subsequently, the review discusses potential mechanisms underlying brain injury following exposure to BSWs.

Clinical features and current treatment of PTSD

Definition and diagnosis

PTSD is a psychiatric condition that can develop following exposure to a traumatic event such as actual or threatened death, serious injury, or sexual violence. According to the National Center for PTSD, approximately 6% of the U.S. population will experience PTSD at some point in their lives, with women being twice as likely as men to develop the disorder [17]. PTSD prevalence is exceptionally high in military populations due to increased exposure to combat-related trauma [18,19]. Clinically, PTSD is characterized by four symptom clusters that must last for over one month and result in significant functional impairment [3,20]. Accurate diagnosis requires careful assessment of both psychological and neurological factors. First-line pharmacological treatments for PTSD include selective serotonin reuptake inhibitors (SSRIs), particularly the U.S. Food and Drug Administration (FDA)-approved drugs such as sertraline and paroxetine [8]. Other medications, such as prazosin, have shown efficacy in reducing nightmares and sleep disturbances [9]. However, pharmacological interventions often yield only moderate improvements and are less effective for patients with comorbid mTBI. Evidence-based psychotherapies like cognitive-behavioral therapy, prolonged exposure therapy, and eye movement desensitization and reprocessing are considered gold standards for PTSD treatment [21]. These therapies aim to process and integrate traumatic memories and reduce avoidance behaviors.

Emerging therapies

Emerging therapies for PTSD include innovative drugs such as 3,4-methylenedioxymethamphetamine (MDMA) and ketamine, as well as neuromodulation techniques. MDMA, a psychedelic substance known for inducing euphoria, altering sensations, and boosting energy, works by enhancing the signaling of serotonin, dopamine, and noradrenaline in the brain [22,23]. Meta-analysis has shown that MDMA-assisted psychotherapy significantly lowers PTSD Scale scores compared with control groups [24]. However, despite these promising results in alleviating PTSD symptoms, concerns arise regarding the use of unregulated MDMA and the implications of administering it outside a rigorously controlled

setting, in addition to its potential side effects [23,24]. Ketamine, a N-methyl-D-aspartate (NMDA) antagonist and an anesthetic, has recently gained attention for its potential rapid antidepressant effects [22]. Meta-analysis of available data examining the broader impacts of ketamine indicated that ketamine treatment can reduce the frequency of PTSD symptoms [25]. However, due to differences in study designs and outcome measures, more research is needed to establish consistent protocols for its application in the treatment of PTSD [23,25]. Several neuromodulation therapies, including transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS), have been explored for their potential to influence neural circuits associated with PTSD [22,23]. TMS is a widely accepted, non-invasive method primarily used for treating major depressive disorder. It works by temporarily passing a magnetic field through targeted areas of the scalp and skull, thereby altering the activity of the underlying cortical and subcortical brain networks [22]. Given the diverse clinical manifestations of PTSD, some TMS protocols have shown promise in alleviating its symptoms [22,23]. tDCS is still relatively new in the context of PTSD treatment. This technique induces subtle shifts in the resting membrane potential by applying scalp electrodes over specific brain areas [22]. Research examining physiological arousal, fear conditioning, and memory extinction suggests that tDCS may hold potential for managing PTSD [22,26,27]. Despite the variety of treatment options discussed, a significant proportion of patients remain symptomatic. Furthermore, stigma, limited access to care, and variability in treatment response remain substantial barriers in both military and civilian populations.

Pathophysiology of PTSD

PTSD is associated with dysregulation of several neural circuits, particularly those involving the amygdala, hippocampus, and prefrontal cortex. Hyperactivity of the amygdala is thought to underlie the exaggerated fear response, while hypoactivity of the medial prefrontal cortex impairs emotional regulation. Reduced hippocampal volume has been correlated with impaired memory and context discrimination [15,28]. Additionally, chronic dysregulation of the HPA axis leads to abnormal cortisol levels, which may exacerbate stress sensitivity and emotional dysregulation [29,30]. Neuroinflammation and glial activation further contribute to persistent behavioral and cognitive symptoms [16]. The specific mechanisms underlying PTSD are still unknown, but several have been implicated, including dysregulation of the HPA axis, neuroinflammation, synaptic plasticity, and proteinopathies [16,31-37].

The HPA axis is a hormonal feedback loop that regulates cortisol levels. When an individual experiences stress, this axis is activated, leading to the release of corticotropin-releasing hormone (CRH). CRH binds to CRH type 1 receptors, which results in the release of adrenocorticotropic hormone (ACTH). In turn, ACTH binds to melanocortin 2 receptors in the adrenal cortex, prompting the release of cortisol. Cortisol has a systemic effect, supporting the stress response by regulating glucose availability and modulating the immune system. The HPA axis is also responsive to negative feedback from cortisol, meaning that when cortisol levels are elevated, the release of CRH and ACTH decreases [32]. The HPA axis is often dysregulated in individuals with PTSD, typically exhibiting reduced systemic cortisol levels while also showing a heightened dynamic range in its release [38]. This condition is associated with increased negative feedback, causing the brain to become less responsive to cortisol. As a result, the HPA axis may remain chronically activated while producing less cortisol over time. Such dysregulation of the HPA axis is believed to have a role in increased risk of illness in individuals with PTSD [38].

Neuroinflammation plays a crucial role in the pathogenesis of PTSD [16,34,36]. Hori and colleagues investigated both the factors driving increased proinflammatory activity and the effects of neuroinflammation, identifying several biological pathways through which trauma exposure and chronic stress can lead to ongoing neuroinflammation in individuals with PTSD [34]. A key factor is dysregulation of the HPA axis. Such HPA dysregulation weakens the anti-inflammatory feedback mechanism, causing immune cells to remain in a proinflammatory state and to release increased amounts of interleukin (IL)-1β, IL-6, tumor necrosis factor-α (TNF-α), and C-reactive protein (CRP) [32,34]. Additionally, the study completed by Hori and colleagues noted that an imbalance in the autonomic nervous system plays a significant role, characterized by increased sympathetic activation and decreased parasympathetic tone. This imbalance leads to a heightened release of stress mediators, such as norepinephrine, which can further activate inflammatory pathways through adrenergic receptors on immune cells [34,36]. Another study completed by Michopoulos and colleagues [39] indicated that elevated levels of proinflammatory cytokines can affect the amygdala, hippocampus, and prefrontal cortex, the critical brain regions involved in fear processing, memory consolidation, and emotional regulation. Neuroinflammation may also hinder neurogenesis in the hippocampus as well as disrupt synaptic plasticity, which can lead to memory deficits and difficulties in contextual fear discrimination, the hallmarks of PTSD [40]. Moreover, chronic neuroinflammation has

been connected to altered neurotransmission of monoamines (serotonin, dopamine, and glutamate), potentially contributing to symptoms like emotional numbing and cognitive disturbances [40]. These pathological alterations underscore that neuroinflammation is not just a byproduct of PTSD-related stress but also plays a role in perpetuating the disorder by reinforcing neural circuits associated with fear and stress sensitivity.

Synaptic plasticity is the ability of synapses to strengthen or weaken over time, influenced by experience or activity. This mechanism plays a crucial role in learning, memory, and emotional regulation [31]. Abnormal synaptic plasticity can contribute to the development, persistence, and symptoms of PTSD [31,34]. A study explored the effects of (2R,6R)-hydroxynorketamine, a metabolite of ketamine, after exposure to a single prolonged stress and foot shock protocol, a model for PTSD. By administering various concentrations of (2R,6R)-hydroxynorketamine, the study reported that this compound can promote exploration, reduce avoidance and freezing behaviors, and reduce immobility, which is often associated with depressive symptoms [41]. Analysis of brain tissues showed that treatment with (2R,6R)-hydroxynorketamine increased proteins such as glutamate ionotropic receptor AMPA type subunit 1 (GluA1), brain-derived neurotrophic factor (BDNF), and postsynaptic density protein-95 (PSD-95) in the prefrontal cortex, while also restoring synaptic ultrastructure. Although this mechanism is not the only factor contributing to PTSD, the presence of maladaptive synaptic plasticity remains a significant characteristic of the disorder.

Proteinopathies are disorders characterized by the abnormal accumulation, misfolding, or aggregation of specific proteins in the brain [33,35,37]. Research suggests that protein homeostasis is disrupted in PTSD through several pathways. These include chronic stress and dysregulation of glucocorticoids, as well as neuroinflammation, oxidative stress, and compromised protein clearance mechanisms [37]. First, ongoing stress can elevate glucocorticoid levels, which, in turn, can disrupt cellular processes and promote protein misfolding [33,35,37]. Second, elevated proinflammatory cytokines in PTSD can hinder the function of molecular chaperones, which are crucial for protein folding and clearance, particularly affecting autophagy and the ubiquitin-proteasome system [33,35,37]. Furthermore, increased oxidative stress in PTSD can damage proteins, leading to their aggregation and the generation of harmful oligomers [33,35,37]. Overall, PTSD is a complex disorder associated with several pathological alterations implicated in its development and persistence.

Epidemiological characteristics of PTSD

PTSD can arise from various traumatic experiences, demonstrating the complexity of individual stress responses [42,43]. Although often linked to combat, PTSD can also stem from natural disasters, accidents, interpersonal violence, chronic abuse, and neglect [43,44]. Additionally, witnessing trauma or working in high-stress jobs can also play a role in PTSD development [45]. Such variability of causes emphasizes that PTSD is a broader psychological response to overwhelming stress. Epidemiological studies have helped determine its prevalence, affected groups, and influencing factors, which are discussed briefly in the following section and listed in Table 1 [44,46-56].

PTSD linked to military combat or assault

Military combat is a major contributor to PTSD [57]. One

Table 1 Epidemiological studies of post-traumatic stress disorder (PTSD)

Causes and exposure definition	Study population	PTSD measurement performed	Major findings linked to PTSD	Reference
Military combat	195 military personnel (130-PTSD, 65-healthy)	Sleep metrics, and PTSD Checklist for DSM-5 (PCL-5)	Individuals with PTSD had multiple sleep issues and greater night-to-night variability in sleep onset latency and wake after sleep onset. Sleep fragmentation index correlated with PTSD severity	[46]
Military combat	806 military personnel	PCL-5	Engagement in hand-to-hand combat is associated with PTSD development. Responsibility for the death of a non-combatant and exposure to human remains were associated with probable PTSD	[46]
Assault or bullying	86 adult female sexual adult survivors; 41.9% identified as LGBTQ$^+$	Tonic Immobility Questionnaire to assess peritraumatic tonic immobility (TI); Dissociative Experiences Scale II; PCL-5; Post-traumatic Cognitions Inventory	The LGBTQ$^+$ population displayed higher rates and severity of TI, and greater PTSD symptoms. LGBTQ$^+$ status and TI experience were significant predictors of greater PTSD symptoms	[47]

(**Continued**)

Causes and exposure definition	Study population	PTSD measurement performed	Major findings linked to PTSD	Reference
Abuse	1050 trauma patients; 176 are victims of violent injury	12-item short form survey; Trauma quality of life; PTSD screen; Chronic pain	47.1% screened positive for PTSD. A violent mechanism was significantly associated with PTSD	[48]
Abuse	1292 [502 healthy controls, 610 with alcohol use disorder (AUD), and 180 comorbid AUD and PTSD]	Structured Clinical Interview for DSM-4/5; Childhood Trauma Questionnaire; Psychological phenotypes of negative emotionality; Perceived Stress Scale, State-Trait Anxiety Inventory	The comorbid AUD and PTSD group displayed: 1) the highest severity of both alcohol use and childhood trauma history; 2) dysregulated psychological negative emotionality markers	[49]
Abuse	426 adult women (288 with a history of childhood abuse and 138 controls)	Childhood Trauma Questionnaire; International Trauma Questionnaire to assess PTSD and complex PTSD; Sensory Responsiveness Questionnaire	Individuals with a history of childhood abuse exhibited higher sensory responsiveness and a greater proportion of sensory over-responsiveness, associated with PTSD or complex PTSD	[50]
Accidents	Meta-analysis of 26 empirical studies (24,276 individuals)	Impact of Event Scale or Versions; Symptom Check List-90R; Structured clinical interviews; PTSD Self-Rating Scale	The prevalence of PTSD after major accidents is 18.57%. Longitudinal studies showed persistence of PTSD for many years. Greater intensity/extent of exposure, physical injury, economic loss, lack of social support, and female sex were risk factors for PTSD	[44]
Human-caused disaster (terrorist attack)	475 police personnel	Direct vs. indirect exposure vs. non-exposed; PCL-5; Patient Health Questionnaire-9; Suicide risk	Higher prevalence among those directly exposed to the terrorist attack. Partial PTSD was 12.6%. Complete PTSD was 6.6%. Event centrality was significantly associated with PTSD	[51]
Natural disaster (Earthquake)	198 adolescents and their mothers	Children's Post-traumatic Stress Scale-Self Report (adolescents); PCL-5 (mothers); Post-traumatic Growth Inventory	6.1% of adolescents displayed PTSD; the relationship between PTSD and post-traumatic growth was curvilinear for both adolescents and their mothers	[52]
Medical trauma	200 with spinal cord injury due to earthquake; 161 with other traumatic etiology	PCL-5; Quality of life assessment	The prevalence of PTSD in the injured group was 64.1% as opposed to 10% with other etiology	[53]
Unexpected death	157 parents of children who died in a Pediatric Intensive Care Unit	Impact of Event Scale-Revised; Short PTSD Rating Interview; Inventory of Complicated Grief; Patient Health Questionnaire-8	At 6 months post bereavement, 21.6% displayed PTSD symptoms. Parents whose children died suddenly had higher rates of PTSD symptoms	[54]
Work-related stress	550 healthcare personnel	Impact of Event Scale-Revised; Dissociative Experiences Scale II	Certain subgroups (women, younger age, longer time spent in direct patient care) displayed a greater risk for developing PTSD. Overall, 22% showed symptoms of PTSD	[55]
Work-related stress	653 healthcare personnel	PCL-5; Mental Health Continuum Short Form	39.8% received a provisional PTSD diagnosis. Women, younger age, nurses, and frontline workers were more likely to be associated with the risk of PTSD	[56]

DSM-4/5. Forth/Fifth Edition of the Diagnostic and Statistical Manual of Mental Disorders

study explored the connection between the severity of PTSD and sleep disturbances among 130 service members diagnosed with combat-related PTSD, comparing them to 65 healthy military controls. By employing a polysomnographic "headband" to monitor sleep patterns over five nights, the study found that those in the PTSD group experienced longer sleep onset latency, more wakefulness after initially falling asleep, diminished sleep efficiency, and reduced deep and REM sleep compared with the control group. Furthermore, they exhibited greater variability in their sleep patterns from night to night. Notably, disruptions in non-REM sleep were significantly correlated with the overall severity of PTSD symptoms, particularly in relation to intrusive thoughts and avoidance behaviors [46]. Another study focusing on Israeli reserve soldiers following the October 7 war [58] investigated the relationship between combat experiences and PTSD symptoms. This study involved 806 soldiers and utilized a self-report assessment tool. The findings revealed a significant

connection between hand-to-hand combat and the likelihood of developing PTSD, particularly linked to negative cognitive and arousal symptoms. Interestingly, while being responsible for an enemy's death was not strongly correlated with PTSD, being responsible for a noncombatant's death was significantly associated with probable PTSD across various symptom clusters. Thus, the prevalence and manifestation of PTSD can differ because of the specific nature of traumatic events.

Assault, encompassing both physical and sexual violence, is a prevalent cause of PTSD [43]. One study explored the differences between female sexual assault survivors who identify as LGBTQ$^+$ and their straight cisgender counterparts concerning peritraumatic tonic immobility (TI) during the assault and its subsequent link to PTSD [47]. The study, involving 86 adult female survivors, evaluated PTSD symptoms through self-report questionnaires, and TI, an involuntary state of paralysis experienced during the assault, was also examined. The study revealed that LGBTQ$^+$ survivors reported significantly higher levels of PTSD symptoms compared with straight survivors, with more intense experiences of TI strongly correlating with increased symptom severity. Notably, both LGBTQ$^+$ identity and TI were found to independently predict the severity of PTSD, highlighting distinct risk factors that contribute to poorer psychological outcomes. Overall, the study indicates that LGBTQ$^+$ survivors who experience TI are particularly vulnerable to severe PTSD symptoms.

PTSD emerging from abuse or accidents

Abuse is a significant traumatic event associated with PTSD, including childhood and domestic abuse, which can be physical, emotional, or sexual [59]. A study comprising 1292 individuals belonging to healthy controls, those with alcohol use disorder (AUD), or comorbid AUD and PTSD found that the comorbid group had the highest levels of childhood trauma and negative emotionality [49]. Notably, the severity of childhood trauma was associated with greater psychological negative emotionality. In another study involving 426 adult women, 288 reported childhood abuse. The researchers assessed trauma severity, PTSD symptoms, and sensory modulation using the Sensory Responsiveness Questionnaire Intensity Scale [50]. They found that women with a history of childhood abuse had higher sensory responsiveness and over-responsiveness, which were significantly associated with PTSD and self-organization disturbances. Notably, the gap between PTSD and complex PTSD diagnoses doubled in the presence of sensory over-responsiveness. Similarly, another study evaluating 1050 adult trauma patients across three Level 1 trauma centers identified 176 victims of violent injury [48]. Among all participants, 47.1% screened positive for PTSD, and 52.3% reported chronic pain. Analysis revealed that violent injury was significantly linked to PTSD but not to chronic pain outcomes.

Accidents, particularly major ones, can have significant spatial and temporal consequences that lead to lasting psychological effects [60]. A meta-analysis identified 26 studies involving 24,276 participants, including survivors and rescue workers, related to 15 major accidents [44]. The time frame for measuring psychological impact ranged from 2 months to 36 years post-accident. Key risk factors for PTSD included exposure intensity, physical injury, economic losses, and lack of social support. Standard assessment tools included the Impact of Event Scale (9 studies) and others. The pooled prevalence of PTSD was 18.6%, much higher than the general population estimate of 2.1%–2.3%. Longitudinal studies indicated that PTSD symptoms can persist for years. Consistent risk factors identified were exposure intensity, physical injury, economic loss, lack of support, and female sex [61-63]. However, the meta-analysis noted limitations due to diverse methodologies and the lack of standardized diagnostic instruments [44].

PTSD linked to natural disasters, terrorist attacks, medical trauma, unexpected death, and work-related stress

Natural disasters and human-made events, like terrorist attacks, can lead to significant trauma within affected populations over a relatively short period [51,64]. For instance, a study involving police personnel following the 2018 Strasbourg terrorist attack revealed a 12.6% rate of partial PTSD and 6.6% for full PTSD among those who were directly exposed to the event [51]. The findings indicated that direct exposure to the attack was closely associated with a heightened risk of developing PTSD. In contrast, sleep deprivation following the incident did not show a similar correlation. Moreover, higher scores on event centrality were linked to increased levels of PTSD and depression, underlining the dual impact of the disaster and work-related exposure. Another study examined the aftermath of the 2023 Kahramanmaras earthquake in Turkey, focusing on adolescents and their mothers 17–18 months after the event [52]. This research explored the connection between PTSD symptoms and post-traumatic growth. It found that only 6.1% of adolescents (12 out of 198) met the criteria for PTSD. Notably, the study found that moderate PTSD symptoms were associated with greater growth. In comparison, very high or very low symptoms tended to correlate with lower growth. Additionally, the post-traumatic growth experienced by adolescents was a positive predictor of maternal growth scores, although the reverse was not observed [52].

Medical trauma, including critical illness and traumatic

childbirth, can lead to PTSD symptoms [65]. For example, a study evaluating PTSD in 200 spinal cord injury patients after an earthquake found a prevalence of 64.1% compared with 10.0% in those with other trauma types [53]. Unexpected deaths can also lead to PTSD in some [66]. A study surveying the parents of children who died in a Pediatric Intensive Care Unit assessed complicated grief, depression, and PTSD symptoms [54]. The study reported that at 6 months post-bereavement, 21.6% displayed PTSD symptoms. Work-related stress, particularly in high-stress environments like emergency response, has also been linked to PTSD development [45]. A longitudinal study surveying 550 hospital workers during the COVID-19 pandemic, assessing general psychological discomfort, PTSD symptoms, and anxiety, revealed that 22.0% developed PTSD [55]. The study concluded that direct exposure to COVID-19 patient care was associated with a greater risk of PTSD, particularly among those with prolonged or intense exposure. Another study found that 39.8% of healthcare workers met criteria for provisional PTSD diagnosis, with increased risk among women, nurses, and frontline workers, highlighting the impact of exposure type and duration on PTSD development [56].

Additionally, ongoing trauma can persist across generations, leading to complex PTSD. A study examining the intergenerational effects of trauma by analyzing mothers' trauma histories and PTSD symptoms alongside their children's exposure to violence and startle responses has suggested that maternal trauma and PTSD may impact children's fear modulation capabilities, indicating an intergenerational transmission of altered fear/safety learning [67]. Overall, the complexities surrounding the causes of PTSD further complicate its diagnosis and management.

PTSD linked to exposure to BSWs

Injury resulting from exposure to BSWs is a significant concern among military service members, particularly those deployed in combat zones. The interaction between physical trauma, particularly mTBI, and psychological stressors has placed exposure to BSWs at the center of discussions of long-term mental health outcomes, especially PTSD [68,69]. An expanding body of literature demonstrates both independent and synergistic effects of BSWs exposure on the development and persistence of PTSD. Multiple studies have investigated the contribution of BSWs exposure to PTSD and related neurobehavioral outcomes [14,70-73]. For example, Ord *et al*. [73] classified post-9/11 United States combat veterans with ongoing PTSD and those who had recovered, finding that greater severity of BSWs exposure was significantly associated with persistent PTSD. Veterans with ongoing PTSD reported exposure to higher average and maximum blast pressure scores than those who had recovered. Recovery was linked to lower levels of depression, pain interference, and sleep disturbance, as well as higher self-reported quality of life and satisfaction with cognitive abilities [73]. Similarly, Lange *et al*. [70] evaluated the additive and interactive effects of PTSD, sleep quality, resilience, and BSWs exposure, identifying PTSD as the strongest independent predictor of poor neurobehavioral functioning, with odds ratios ranging from 4.3 to 72.4 depending on the outcome measure. Nelson *et al*. [14] reported that both BSW-induced concussion and PTSD independently predicted poorer neuropsychological performance, with compounded effects when both were present. Martindale and colleagues found that veterans exposed to BSWs reported higher levels of psychiatric symptoms, including increased severity of PTSD, depression, and anxiety, compared with non-exposed counterparts [72]. Another study examined the relationship between self-reported BSW exposure, history of mTBI, and current PTSD symptoms among active-duty service members [71]. Participants with three or more mTBIs reported higher total PTSD Checklist-Civilian version (PCL-C) scores than those with fewer or no mTBIs, with differences also observed across PCL-C subscales (avoidance, re-experiencing, and hyperarousal).

A primary limitation of most of these studies is the inability to infer causality between BSWs exposure and PTSD. Additional confounding factors, such as pre-existing mental health conditions and concurrent traumatic experiences, may also influence outcomes. Nevertheless, these studies collectively emphasize the substantial impact of BSWs exposure on cognitive and psychological functioning among veterans.

PTSD animal models

No single animal model replicates all features of PTSD. Researchers have employed various rodent models, each representing distinct aspects of PTSD, including fear memory, exposure to life-threatening situations, anxiety-like behaviors, and long-term memory deficits. Although these models are essential for translational research, a comprehensive model encompassing most PTSD characteristics has not yet been developed. Animal models of PTSD are broadly classified as single-stressor, intermediate complexity, social interaction, and predator stress models [74]. Key features and limitations of each model are summarized below.

Single-stressor model

The single-stressor model uses one acute traumatic exposure

to induce lasting PTSD-like phenotypes. Common paradigms include electric foot-shock, immobilization, underwater trauma, and sudden acoustic stress [74,75]. In the foot-shock paradigm, animals receive unpredictable electric shocks in a chamber, usually paired with contextual cues to produce persistent fear memories, anxiety-like behaviors, and impaired extinction. This model enables high experimental control and reproducibility and reliably induces conditioned fear, heightened anxiety, and hyperarousal that can be addressed through pharmacological interventions [74,76]. However, it mainly addresses associative fear learning and conditioned anxiety, not the full scope of PTSD symptoms. It also fails to capture individual differences and does not fully represent the complexity of human trauma [74,76].

Immobilization models restrain rodents for set periods, leading to sustained anxiety-like behaviors [74,77,78]. These models show strong construct validity by addressing molecular and cellular features of PTSD [74]. Their strengths include robust data on HPA axis changes and the ability to investigate structural and functional changes in the prefrontal-hippocampal-amygdala network [74,75,78]. Nonetheless, outcomes depend on restraint duration and apparatus, and these models do not mimic trauma-specific experiences or life-threatening stressors [74]. The underwater trauma model forces rodents to swim and briefly places them underwater (25–40 s), simulating an acute life-threatening stressor [74]. This test is more ethologically relevant than shocks and can produce long-term memory impairments and PTSD-like traits, though it raises ethical issues and risk of injury. The acoustic stress model exposes rodents to intense, unexpected noises, inducing hyperarousal and strong startle responses [74,77]. It targets hyperarousal and sensory hypersensitivity in PTSD and, as a non-contact stressor, does not cause direct harm. However, it often causes weaker or more transient behavioral changes and may not model impaired extinction or context conditioning unless additional procedures are used [74,77].

Intermediate complexity model

The intermediate complexity model seeks to more accurately mimic the cumulative and dynamic nature of trauma exposure. It does this by integrating multiple temporal sequences of stressors and the sensitization that develops over time. This moves beyond a focus solely on a single acute event [74]. The most extensively studied paradigm within this model is single prolonged stress. This involves a sequence of stressors, including prolonged restraint, forced swim, and brief exposure to an anesthetic, followed by a defined, undisturbed incubation period of about 7 d. During this time, PTSD-like alterations emerge [74,75]. This model demonstrates reasonable core features of PTSD [74,75]. Its strengths include reproducibility, moderate ethological relevance, and a distinct neurobiological signature. These features are suitable for mechanistic investigations of fear, stress hormone feedback, and neural plasticity. Limitations include variability in behavioral outcomes across laboratories and reliance on the incubation period for consistent phenotypes. It also has only moderate translational validity, as the specific combination of stressors does not precisely replicate natural traumatic experiences in humans [74,75]. Another relevant model is the time-dependent sensitization paradigm. In this approach, an initial stressor sensitizes the subject to subsequent stress exposure, often resulting in sustained HPA-axis alterations and heightened anxiety-like responses. The primary advantage of this model is its capacity to simulate a trigger-response cycle. This parallels clinical observations where trauma reminders provoke symptom recurrence [78]. However, repeated stress exposure may also activate generalized stress or depression pathways. This can potentially confound PTSD-specific mechanisms with broader chronic stress effects [78]. A third approach, unpredictable variable stress, can be adapted for PTSD research. In this model, animals experience a series of different stressors in a random order over several days or weeks [74]. By removing predictability, this paradigm induces persistent anxiety-like behaviors and HPA-axis dysregulation that resemble aspects of chronic PTSD. Its advantages include greater ecological validity for ongoing, unpredictable life stress. This is pertinent to understanding resilience and vulnerability [74]. However, because this model reflects the effects of chronic rather than acute traumatic stress, it may be less specific to classical PTSD and more indicative of generalized anxiety or depressive phenotypes [74].

Social interaction stress model

Social interaction-based stress models incorporate environmental and developmental factors such as chronic social isolation, housing instability, juvenile social exploration or manipulation, early-life stress, and social defeat. These models are designed to simulate trauma exposure in which social context, peer relationships, and social support systems are critical determinants of stress vulnerability and resilience [74]. Social isolation protocols typically involve prolonged individual housing after weaning or during adolescence. In socially isolated mice, reductions in corticolimbic allopregnanolone are associated with increased contextual fear, impaired extinction, and the emergence of social withdrawal phenotypes, alongside neurobiological alterations in

GABAergic systems [79]. The primary strengths of this model are its high reproducibility and relevance to social withdrawal, although it is limited by low ethological specificity. Housing instability stress, in which animals are repeatedly shuffled between cage mates or environments during sensitive periods, mimics unpredictable social environments. This model induces chronic psychosocial stress that affects social behavior and HPA axis function [74,80]. Its advantages include the ability to replicate real-world environmental instability and the cumulative impact of social stressors, but outcomes can be heterogeneous and are influenced by procedural details [74]. Juvenile social exploration manipulations disrupt critical social developmental processes, resulting in persistent deficits in social competence, altered fear-related behaviors, and increased vulnerability to stress in later life. Although there is some overlap with social isolation, the emphasis on developmental timing provides insight into how disrupted social interactions during childhood or adolescence influence later PTSD-relevant outcomes [81]. This approach is valuable for modeling developmental sensitivity to social trauma, but it may conflate general social skill deficits with trauma-specific pathophysiology [74]. Social defeat stress paradigms expose rodents to repeated aggressive encounters with dominant conspecifics, leading to persistent social avoidance, submissive behaviors, and heightened stress responses [82]. These models are recognized for their proficiency in simulating threat from conspecific aggression and measurable social avoidance. However, limitations include strain-dependent variability in aggressor behavior and the potential activation of depression-like neural circuits, which may complicate interpretation as PTSD-specific symptoms [79].

Predator stress model

Predator stress models expose animals to naturalistic threats, including direct encounters with predators or predator-related cues such as odors, to induce intense innate defensive responses and persistent behavioral and neurobiological changes that parallel core features of human PTSD [74,78]. A frequently used variant is predator odor exposure, in which rodents are placed in environments containing predator urine, fur, or bedding. This method provokes hyperarousal, pronounced avoidance, freezing, and sustained defensive behaviors after a single exposure [83]. Other protocols utilize predator-exposure stress by placing a live predator behind a barrier, thereby combining olfactory, visual, and auditory threat cues to intensify stress. The primary advantages of this model are its high ecological and etiological validity, as it replicates natural threats that rodents have evolved to recognize, eliciting innate defensive reactions consistent with PTSD symptoms [74]. Additionally, these models often reveal individual differences in vulnerability and resilience. However, limitations include challenges in standardizing protocols due to variability in predator stimuli and the inability to fully capture the complex cognitive and episodic memory alterations characteristic of human PTSD [83].

Blast exposure model

Three types of animal models have been used to study BSWs: rodent, large-animal, and zebrafish models. Rodent models use blast shock tubes to generate controlled BSWs and offer low cost, ease of handling, extensive genetic tools, and well-established behavioral assays [84]. However, they differ substantially from humans in brain structure and face technical challenges in scaling BSWs' exposure [84,85]. In contrast, large-animal models such as swine offer greater translational fidelity, with brain structures resembling human neuroanatomy [86,87]. They enable invasive monitoring, advanced neuroimaging, and comprehensive neurocognitive assessments, all of which are crucial for translational studies [88]. However, they face logistical complexities, ethical concerns, and lower genetic tractability [84,86,89,90]. As an alternative model, zebrafish offers genetic tractability and high-throughput screening capabilities, enabling simulation of blast injuries via hydrodynamic pressure waves [91]. Their optical transparency enables real-time imaging of neuroinflammatory responses, making them valuable for screening therapeutics and studying injury mechanisms at the cellular level. However, translational relevance is limited by differences in cellular composition and reproducibility compared with humans, with variability in BSWs generation and assessment methods complicating outcomes [84]. Thus, animal models of BSWs differ in scale, complexity, and translational relevance, each offering unique insights into BSWs-induced pathophysiology.

Moreover, exposure to BSWs produces diverse pathophysiology distinct from traditional TBI, including focal and diffuse injuries without external trauma, involving unique mechanisms such as cavitation, blood-brain barrier disruption, and vascular damage [84]. The results from a few studies are briefly discussed below. Researchers exposed anesthetized rats to 74.5 kPa/d BSWs for 3 d, reflecting common multiple exposures among veterans [5,7,12,92-96]. BSWs-exposed animals showed immediate and persistent anxiety phenotypes at 36–40 weeks post-exposure, delayed anxiety at 36 weeks, decreased memory, and exaggerated fear responses at 36–42 weeks despite normal fear learning at 5 weeks [5,94]. This delayed PTSD phenotype, appearing around 8 weeks and

persisting 3–4 months post-exposure, provided insights into delayed symptom presentation relevant to military veteran care and suggested that repeated exposure to BSWs has lasting consequences [5,94]. Similarly, Dickstein *et al*. [7] found that rats exposed to repetitive BSWs (74.5 kPa/d for 3 d) developed chronic anxiety and increased phosphorylated Tau (p-Tau) in the anterior cortex and hippocampus starting at 6 weeks post-exposure. Additionally, veterans with the highest cortical diffusivity scores showed elevated plasma neurofilament levels, suggesting neurodegenerative changes, implicating frontal brain structures in PTSD pathogenesis [7]. Furthermore, Schindler *et al*. [97] found that only repetitive exposure to BSWs leads to chronic aversive reactions to neutral environmental cues, while both single and repetitive exposure caused acute stress responses. In contrast, Zuckerman *et al*. [98] found that a single low-pressure BSW can produce long-lasting psychoneurobehavioral sequelae in unanesthetized rats, with 16% presenting severe PTSD-like behavioral patterns within 15 d of exposure. Notably, animals with PTSD-like phenotypes showed fewer hippocampal neuronal changes but increased proliferation of neural cells in the amygdala, highlighting that the amygdala is a key area for study and demonstrating that PTSD-like consequences can emerge early post-exposure [98].

Sex-specific effects and microbiome changes

Most PTSD studies focus on male animals despite PTSD being twice as prevalent in women (10%–20%) versus men (5%–10%) [92,99]. With females comprising 15% of active-duty military, understanding PTSD pathogenesis in women is critical [92]. Studies demonstrate that PTSD presentation is more complex in females due to biological, psychological, and social factors, including heightened HPA axis reactivity and hormonal influences on fear extinction and memory [92,100,101]. Females with PTSD show increased amygdala activation and altered prefrontal cortex functioning [102]. Women experience more interpersonal violence and sexual assault, often earlier in life, and demonstrate higher peritraumatic dissociation, contributing to chronic PTSD risk [99,103,104]. Women adopt "tend-and-befriend" responses and emotional coping, while men exhibit "fight-or-flight" and problem-focused strategies [104]. Furthermore, females exhibit greater rumination, stress internalization, and comorbid mood disorders, predicting more severe PTSD [105]. Hormonal fluctuations across the menstrual cycle affect PTSD. For example, higher estradiol levels improve fear extinction in laboratory studies but correlate with greater re-experiencing symptoms clinically during the luteal phase [102,106,107]. Also, Baskin *et al*. [92] found sex-specific PTSD-like symptoms after BSWs exposure, with females showing longer loss of righting reflex but no anxiety phenotypes, while males exhibited anxiety and prolonged scent aversion.

Stress also disrupts the gut microbiome, affecting neural circuits linked to fear and emotional regulation [108]. PTSD is associated with altered gut microbial diversity and metabolites that modulate the HPA axis and stress pathways [109]. Baskin *et al*. [92] found sex-specific differences in nine bacterial orders after BSWs exposure. However, longitudinal studies are needed, given limitations in current animal models and confounding factors [108,109]. Thus, sex-specific differences in PTSD development and persistence are prevalent, emphasizing the need to study gender-specific mechanisms [92,99,104,110].

Mechanisms underlying PTSD-like symptoms

Influence of dysfunctional neural circuitry

Dysfunction in core neural circuits involving the amygdala, prefrontal cortex (PFC), and hippocampus is fundamental to the mechanisms underlying PTSD pathophysiology. Evidence from both animal models and human studies demonstrates characteristic patterns of neural activity, including exaggerated fear responses, impaired extinction, hypervigilance, and deficits in contextual processing [111-113]. The amygdala, a limbic structure essential for fear acquisition and emotions, exhibits hyperactivity following traumatic stress in animal studies. This hyperactivity manifests as enhanced defensive behaviors, heightened conditioned fear, and exaggerated responses to threat cues, often resulting from dysregulated inhibitory control by cortical and hippocampal inputs [102]. For instance, socially isolated rodent models with impaired cortico-hippocampal projections to the basolateral amygdala exhibit reduced inhibitory neurosteroid regulation, increased fear responses, and poor extinction. These findings support the hypothesis that amygdala overactivity underlies maladaptive emotional responses after trauma [79].

In contrast, the prefrontal cortex, particularly the ventromedial and infralimbic regions in rodents (homologous to the human ventromedial PFC), is critical for top-down regulation of emotional responses [114]. In animal models of PTSD, hypoactivity or impaired function of the PFC is associated with deficits in fear extinction and inadequate suppression of amygdala-driven responses. Interventions that enhance PFC activity, such as repetitive transcranial magnetic stimulation (rTMS) applied to the ventromedial PFC in a rodent foot-shock model, can reverse behavioral impairments and engage distributed networks involving the amygdala and hippocampus. This illustrates the contribution of PFC

dysfunction to the persistence of fear memory and anxiety-like behavior [114]. The hippocampus is also implicated in contextual encoding and discrimination [112,113]. A study indicates that hippocampal dysfunction, often characterized by reduced activity or plasticity, coincides with impaired contextual processing and generalized fear responses [111]. Dysfunctional hippocampal circuits result in poor encoding of trauma-specific contextual details and overgeneralization of fear to safe environments [112,113]. Collectively, these findings support circuit-level models of PTSD in which amygdala hyperactivity, PFC hypoactivity, and hippocampal contextual processing deficits interact to contribute to PTSD-like symptoms.

Role of the dysregulated HPA axis

Dysregulation of the HPA axis is widely implicated in PTSD pathology. It reflects altered stress hormone regulation that contributes to both the development and maintenance of symptoms. Many clinical and preclinical studies report enhanced glucocorticoid negative feedback sensitivity and blunted cortisol or ACTH responses to challenge tests [115-117]. This pattern, also seen in rodent models such as single prolonged stress, indicates altered receptor function and HPA axis sensitivity at multiple levels [75]. Dysregulation can present as hypocortisolemia at rest despite ongoing stress pathology. This reflects a hypersensitive feedback system that suppresses cortisol output more than expected [118]. These alterations are linked to changes in glucocorticoid receptor expression and signaling, as well as to genetic and epigenetic variation in stress-related regulatory genes. There is also disrupted interplay between CRH, ACTH, and cortisol across the axis [32]. Although findings vary across studies, animal models support the idea that chronic or traumatic stress alters HPA axis set points, receptor sensitivities, and hormone dynamics. This can predispose to PTSD-like phenotypes and sustain dysregulated stress responses. Dysregulation affects endocrine balance and also impacts neural circuits underlying fear learning, memory, and emotional regulation [119].

Effects of neurochemical imbalance

Imbalances in key neurotransmitters, including norepinephrine, gamma-aminobutyric acid (GABA), serotonin, and glutamate, are supported by evidence from animal models of traumatic stress [120]. One of the most consistent findings is hyperactivity of the noradrenergic system, leading to elevated norepinephrine release in limbic and cortical regions such as the amygdala and PFC [121,122]. In rodent PTSD models, increased norepinephrine signaling is linked to hyperarousal, exaggerated startle, enhanced fear conditioning, and impaired extinction [122]. In parallel, PTSD is characterized by deficits in GABAergic inhibitory tone, which normally constrains excitatory and stress-responsive circuits [79,111]. Consistent with this, animal models of PTSD display reduced GABA synthesis, altered GABA-A receptor subunit composition, and decreased concentrations of neurosteroids such as allopregnanolone following traumatic stress, notably in social isolation and fear-conditioning prototypes [79]. Reduced GABAergic function, therefore interacts with elevated norepinephrine and glutamate signaling to amplify emotional reactivity. Alterations in serotonergic signaling also play a modulatory role. Stress-exposed rodents exhibit changes in serotonin release and receptor expression within the hippocampus, amygdala, and PFC, contributing to anxiety-like behavior, mood dysregulation, and impaired stress coping [123,124]. Furthermore, growing evidence implicates glutamatergic dysregulation in PTSD, particularly excessive glutamate release and altered NMDA and AMPA receptor function within fear-related circuits [125,126]. In rodent models, traumatic stress enhances glutamatergic transmission in the amygdala while disrupting prefrontal and hippocampal glutamate signaling, leading to impaired synaptic plasticity, fear overgeneralization, and extinction deficits [125,126]. Taken together, animal studies support a concept in which PTSD arises from a neurochemical imbalance favoring excitatory and stress-promoting signaling (norepinephrine, glutamate) over inhibitory and modulatory control (GABA, serotonin), resulting in persistent fear, hyperarousal, and impaired emotional regulation.

Role of neuroinflammatory microenvironment

Chronic low-grade neuroinflammation or neuroinflammaging is increasingly recognized as a key biological mechanism underlying PTSD pathophysiology. Exposure to traumatic stress results in sustained activation of the innate immune system, marked by elevated concentrations of proinflammatory cytokines, IL-1β, IL-6, TNF-α, and interferon-γ (IFN-γ), in both peripheral tissues and the brain [36,127]. In rodent models of PTSD, these cytokine increases are associated with microglial activation in brain regions critical for fear and stress regulation [128]. Neuroimmune activation disrupts synaptic plasticity, impairs fear extinction, and increases anxiety-like behaviors, thereby linking inflammatory signaling to behavioral phenotypes relevant to PTSD [39,129]. Inhibition of inflammatory pathways or pharmacological suppression of microglial activation in rodents has been shown to reduce stress-induced behavioral abnormalities.

Increased concentrations of proinflammatory cytokines can adversely influence neurotransmitter metabolism, HPA axis regulation, and neural circuit function, thereby providing a mechanistic link between immune dysregulation and the neurochemical and neuroendocrine disturbances observed in PTSD [36]. For instance, IL-1β and TNF-α modulate glutamatergic and GABAergic neurotransmission, while chronic neuroinflammation can impair glucocorticoid signaling, further exacerbating dysregulation of the stress response [36]. Animal studies indicate that stress-induced neuroinflammation may become self-perpetuating through feedback interactions among microglia, cytokines, and stress hormones, which contribute to the persistence of PTSD symptoms long after the initial trauma [130]. Overall, these findings support a concept in which PTSD is typified by chronic, low-grade neuroinflammation that interacts with neural circuits, neurochemical pathways, and endocrine systems to sustain maladaptive fear and stress responses.

Impact of genetic and epigenetic factors

Genetic and epigenetic factors can contribute to individual vulnerability and resilience to PTSD by interacting with environmental trauma to influence long-term outcomes [131,132]. FK506 binding protein 5 (FKBP5), a co-chaperone protein that regulates glucocorticoid receptor sensitivity and HPA axis feedback, is among the most extensively studied genetic contributors. Polymorphisms in FKBP5 are associated with increased PTSD risk, particularly in individuals exposed to early or severe trauma, as these variants enhance glucocorticoid receptor resistance and disrupt stress hormone regulation [133,134]. Animal studies corroborate these human findings by showing that stress exposure alters FKBP5 expression in limbic and hypothalamic regions, resulting in persistent changes in corticosterone feedback and stress reactivity [134]. Brain-derived neurotrophic factor (BDNF), a key regulator of synaptic plasticity, learning, and memory, is also implicated in PTSD through both genetic variation and stress-induced dysregulation [135-137]. The common BDNF Val66Met polymorphism is linked to impaired fear extinction, reduced hippocampal plasticity, and increased anxiety. These effects are replicated in rodent models, where altered BDNF signaling in the hippocampus and prefrontal cortex contributes to deficits in contextual memory and extinction learning following trauma [138]. Furthermore, epigenetic modifications also contribute to mechanisms by which traumatic experiences induce long-lasting changes in gene expression without altering the genetic code [139,140]. Particularly, PTSD is associated with altered DNA methylation patterns in stress-related genes such as FKBP5, nuclear receptor subfamily 3 group C member 1 (NR3C1), and BDNF. Evidence indicates that trauma exposure can demethylate regulatory regions of FKBP5, resulting in its overexpression and persistent HPA axis dysregulation [135,141]. Animal models further demonstrate that stress-induced epigenetic changes in these genes occur in brain regions central to fear and emotion regulation and can persist long after the traumatic event, influencing behavior throughout the lifespan [139,140]. Collectively, these findings support a framework in which genetic predispositions establish PTSD risk, while epigenetic mechanisms mediate the translation of environmental trauma into enduring molecular and behavioral changes.

Other mechanisms underlying PTSD

Changes in p-Tau (Thr-181) levels and their link to cognitive dysfunction and PTSD

Several studies have observed pathological changes in specific brain regions after repetitive blast exposure [7,142,143]. Like other neurodegenerative diseases, such as Alzheimer's disease (AD), accumulations of abnormally p-Tau have been seen in models receiving repetitive blast exposures. The Tau protein is a microtubule-associated protein that plays a vital role in the axonal cytoskeleton. Elevated Tau concentrations indicate axonal injury, which is also observed in TBI patients [111,144]. Several animal models have exhibited chronic tauopathy and a distinctive type of astroglial scarring at the junction between gray and white matter. This type of scarring appears to be unique to blast exposure and injury [7]. The blast exposure also resulted in abnormal perivascular p-Tau accumulation within astrocytes in the cerebral cortex and hippocampus of rats. In a parallel investigation, Dickstein and colleagues also observed that half of the veterans with a history of repetitive blasts had an increased amount of cortical retention of ^{18}F-Flortaucipir (^{18}F AV1451) (a Tau ligand), supporting the occurrence of tauopathy [7]. In a clinical study by Olivera *et al*. [142], United States military personnel at the Madigan Army Medical Center who had been deployed within the preceding 18 months were assessed. Volunteers were classified with a history of TBI using the Warrior Administered Retrospective Casualty Assessment Tool, and various neurobehavioral symptoms were measured. They observed that PTSD symptoms were correlated with total Tau concentrations (r=0.21; P=0.04). Thus, repetitive head injuries, such as blast exposures, are correlated with the progression of tauopathies and axonal injuries, thereby elevating the likelihood of developing PTSD and other neurodegenerative disorders.

Perez Garcia *et al*. [94] investigated the association between

p-Tau accumulation in specific brain regions and behavioral changes. Following repetitive blast or sham exposures, behavioral assessments and p-Tau accumulation measurements were performed. Elevated p-Tau levels were observed in the anterior cortex and right hippocampus after exposure. Although fear learning and novel object recognition did not correlate with total Tau levels, a positive correlation was identified between p-Tau levels in the anterior cortex and the magnitude of freezing, as well as between hippocampal p-Tau and distance moved in the elevated zero maze. Despite the modest sample size, these findings indicate the need for further research, as Tau accumulation in specific brain regions may represent a potential therapeutic target. For instance, epothilone D, a microtubule-stabilizing agent that reduces Tau aggregation and phosphorylation, has been proposed as a therapeutic drug [145,146]. Stathmin 1, a protein that regulates microtubule dynamics, may also serve as a therapeutic candidate [13].

Changes in Stathmin and corticosterone and their link to cognitive dysfunction and PTSD

A study investigated differences in behavioral responses and underlying molecular markers, specifically Stathmin and corticosterone, at 3 weeks and 6 months after exposure to BSWs [147]. In this study, male rats were exposed to repeated BSWs (three consecutive exposures at peak pressure of 74.5 kPa), following which behavioral tests were completed to assess anxiety-like behaviors associated with PTSD. The study categorized animals as "affected" or "unaffected" based on whether they displayed anxiety-like behavior using a modified profiling method [148]. The "affected" rats displayed elevated plasma corticosterone levels and increased Stathmin concentration in the amygdala compared with the "unaffected" rats. At 6 months post-exposure, the amygdala Stathmin levels of the "affected" animals remained elevated. Of note, the elevated corticosterone-anxiety correlation seen at 3 weeks was not observed at 6 months, suggesting possible changes in regulatory feedback over time. The persistent elevation of amygdala Stathmin suggests it may be a potential biomarker for long-term anxiety, following exposure to BSWs, which might have significance in PTSD [147]. Typically, Stathmin proteins (Stathmin 1 and 2) act as microtubule-destabilizing proteins. However, after injury, their expression and function are likely altered to promote axonal regeneration [149], which may lead to aberrant or maladaptive circuitry and contribute to PTSD development.

Role of dynorphin/kappa opioid receptor pathway

In addition to the HPA axis, the dynorphin/kappa opioid receptor (KOR) system and the metabotropic glutamate receptor 2/3 (mGluR2/3) pathways have been suggested to have a role in the pathogenesis of PTSD [6,12,95,150-152]. The KOR system, expressed in the HPA axis and throughout the entire brain, plays a crucial role in regulating stress responses and neuroendocrine function [153-155]. Dynorphin opioid peptides are released by the corticotropin-releasing factor during stress and create the feedback loop associated with the body's stress response. Expressed on immune cells, KOR also influences the levels of IL-6 and TNF-α, two cytokines that play a crucial role in the inflammatory response. Activation of the KOR system has been implicated in adverse outcomes associated with head impact trauma [6,12]. A study by Lee *et al*. [12] investigated the effect of the selective KOR antagonist nor-binaltophimine (norBNI) on PTSD outcomes induced by single and repetitive blast trauma. Male mice were treated with 10 mg/kg norBNI 3 d before either a single or repetitive blast or sham exposure. A month after exposure, animals were subjected to measures of anxiety/compulsivity through a marble burying test, aversion behavior by a place conditioning test, habituation via an acoustic startle test, motor coordination through a rotarod test, aversion by an odorant conditioning paradigm, and photosensitivity via a photophobia reward conflict test. Increased dynorphin A immunoreactivity was observed in the entire brain of animals exposed to repetitive BSWs [12]. Mice exposed to repetitive BSWs also displayed increased concentrations of IL-5, IL-6, granulocyte colony-stimulating factor (G-CSF), C-X-C motif chemokine ligand 10 (CXCL10/IP-10), and CXCL1 levels. However, treatment with norBNI attenuated those effects. Furthermore, norBNI pretreatment prevented the upregulation of multiple other proinflammatory proteins, including IL-1α, IL-6, IL-9, IL-17, G-CSF, IFN-γ, IP-10, MCP-1, and regulated upon activation, normal T cell expressed and presumably secreted (RANTES/CCL5) in the brain following exposure to BSWs [12]. Moreover, norBNI pretreatment mitigated the behavioral changes previously observed in the blast-exposed group, including aversion to paired visual cues and odor, aversion to light, reduced marble burying, and inhibited acoustic startle habituation. Thus, blocking KOR signaling via norBNI pretreatment could mitigate several PTSD phenotypes, including aversion, anxiety, habituation, and photosensitivity, as well as suppress multiple cytokine responses [12].

Beneficial effects of inhibiting mGluR2/3 signaling

Activation of mGluR2/3, a group II mGluR, results in the inhibition of glutamate release from presynaptic nerve terminals, affecting various signaling pathways in neuroglia

and postsynaptic nerve terminals [150,151]. Furthermore, dysregulation of mGluR2/3 has been implicated in various neurodegenerative and neuropsychiatric diseases, including AD, Parkinson's disease, schizophrenia, PTSD, and depression [150], and treatment with a mGluR2/3 antagonist, BCI-838 (a prodrug for BCI-632), has been found to improve memory and reduce anxiety in AD and is currently being investigated for treating depression [151,156]. mGluR2/3 antagonists, being pro-neurogenic, can also enhance hippocampal neurogenesis, leading to improved learning and memory, as well as anxiolytic and antidepressant effects [151]. Thus, pro-neurogenic drugs like BCI-838 could potentially minimize the pathogenesis of various neuropsychiatric disorders, including PTSD [151,157-159]. Another study investigated the effects of a ketamine metabolite treatment to modulate mGluR2 signaling on PTSD emerging from blast injury. Ketamine has been investigated in various neuropsychiatric disorders, specifically refractory depression and PTSD, as a potential treatment option [95,152]. The proposed mechanism by which ketamine acts is through inhibition of glutamate NMDA receptor function, resulting in its dissociative and psychotomimetic effects. Ketamine's ability to elicit rapid effects has been linked to its impact on glutamatergic signaling in the brain [152]. *In vivo*, ketamine is rapidly metabolized and hydroxylated, resulting in the production of various metabolites known as hydroxynorketamines. Both ketamine and its metabolites have been found to modify the function of mGluR2/3, an inhibitory receptor that reduces adenylate cyclase activity and cAMP production. One ketamine metabolite, (2R,6R)-HNK, has been explicitly observed to act similarly to mGluR2/3 antagonists, exerting antidepressant-relevant actions [152]. Garcia GP *et al*. [95] investigated the effects of (2R,6R)-HNK on established PTSD-related behaviors after exposure to repetitive BSWs. The animals exposed to repetitive BSWs received a single intraperitoneal dose of (2R,6R)-HNK (20 mg/kg) or saline at 7–11 months post-exposure. Animals treated with (2R,6R)-HNK at 7, 8, or 11 months post-BSWs exposure displayed reduced anxiety, proficiency for novel object recognition, and reduced startle response [95].

Thus, treatment with (2R,6R)-HNK could serve as an effective therapy for individuals experiencing PTSD symptoms [95,150]. Although (2R,6R)-HNK has been used primarily in models of depression, the similarities in symptoms among PTSD, depression, and other neuropsychiatric disorders suggest that further research into (2R,6R)-HNK therapy for PTSD is warranted. Nevertheless, more studies are necessary to determine the most effective timing and dosage of the drug to observe the most substantial recovery after blast exposure.

Conclusions, limitations of studies, and future perspectives

The emergence of PTSD has been linked to various biochemical and neurological underpinnings, highlighting several therapeutic targets. Due to the nature of PTSD and its complex clinical manifestation, presentation varies considerably from person to person [3]. The heterogeneity in symptom presentation reflects underlying differences in neural circuit dysfunction, stress response systems, and individual vulnerability factors. Typically, there is a delay of 6 weeks to 12 months between the traumatic event and the symptom onset, although this latency period can vary significantly depending upon the type and severity of the trauma, as well as individual risk and resilience factors [5,7].

The causes of PTSD are vast and multifaceted, but most commonly stem from abuse and other forms of violence, including physical assault, sexual trauma, domestic violence, and childhood maltreatment [1,43,44]. Combat exposure, natural disasters, serious accidents, and witnessing death or severe injury also represent significant traumatic events that can precipitate PTSD development. This plays into the sex differences seen with PTSD. Men and women differ in both the type of trauma that they are more commonly exposed to and their stress response, with men more frequently experiencing combat-related trauma and physical assault, while women are disproportionately exposed to sexual violence and interpersonal trauma [103,104]. These differential exposure patterns, combined with biological differences in stress hormone regulation, neural processing of threat, and fear extinction mechanisms, contribute to the observed sex differences in PTSD prevalence and presentation. Although women have approximately twice the prevalence of developing PTSD in their lifetime compared with men, animal model studies have often evaluated only male subjects, limiting our knowledge of PTSD mechanisms in females and hindering the development of sex-specific therapeutic interventions [92,99].

Current treatment for PTSD combines psychotherapy and pharmacotherapy in an integrated approach tailored to individual patient needs and symptom profiles. Cognitive processing therapy, which aids patients in identifying and challenging maladaptive beliefs about their trauma, and prolonged exposure therapy, which involves gradual, repeated confrontation with trauma-related memories and situations in a safe therapeutic context, are focused on helping patients to reframe thought processes and confront trauma-linked memories to reduce avoidance and facilitate emotional processing [2,4,21]. These psychotherapies are considered first-line treatments and have shown significant efficacy ina

reducing PTSD symptoms across diverse trauma populations. Drugs such as SSRIs are used as first-line pharmacological interventions, targeting serotonergic dysfunction linked to PTSD, with prazosin being a treatment specific to trauma-related nightmares and sleep disruption by blocking alpha-1 adrenergic receptors and reducing noradrenergic hyperactivity during sleep. However, treatment response rates are suboptimal, with many patients exhibiting only partial symptom relief or treatment resistance. Furthermore, several emerging therapies are currently being tested as potential alternatives or adjuncts to conventional treatments. These include MDMA-assisted therapy, which combines the empathogenic drug with psychotherapy to increase emotional processing and reduce fear responses, and ketamine-assisted therapy, which targets glutamatergic systems to rapidly reduce depressive and dissociative symptoms. Also, several neuromodulation techniques have been employed, including transcranial magnetic stimulation and deep-brain stimulation [22-27]. Nonetheless, large-scale randomized controlled trials have yet to be conducted to fully understand their long-term effectiveness, optimal dosing strategies, safety profiles, and potential for integration into standard clinical practice.

Several animal models have been employed to comprehend mechanisms by which PTSD-like symptoms emerge and address specific epidemiological characteristics, including single-stressor, intermediate complexity, social interaction stress, predator stress, and blast exposure prototypes [74-76,78-80,83,94]. In conjunction with the type of PTSD animal model, various mechanisms have been proposed for the pathogenesis of PTSD, including dysfunctional neural circuitry, the HPA axis, neurochemical imbalance, neuroinflammatory environment, and genetic and epigenetic factors [6,12,16,31-37,95,151,152]. Other mechanisms also intersect with these 5 primary pathways, subsequently leading to PTSD symptomology. These include elevated p-Tau levels associated with cognitive dysfunction and other PTSD-related behaviors. While no specific therapies have been initiated to target elevated Tau phosphorylation levels, studies suggest that microtubule-stabilizing agents show promise but require further detailed investigation [7,142,143]. Another therapeutic target is the dynorphin/kappa opioid receptor, which acts on the HPA axis. Antagonism of this receptor has been found to attenuate some of the outcomes associated with BSWs-induced PTSD [6,12]. An additional potential mechanism is the mGluR2/3 pathway, in which antagonism of mGluR2/3 has been shown to reverse some of the adverse effects of exposure to BSWs [150,151,157-159]. These therapies aim to target specific mechanisms that current therapies for PTSD have not.

Furthermore, more commonly seen in the military population is BSW-induced PTSD. Most studies assessing links between BSW exposures and PTSD employed similar methodologies to closely simulate the BSW exposures received in a war environment. Determination of PTSD-like symptomology by assessing behavioral outcomes was also more or less comparable across different studies. However, several limitations are evident in these studies, including the inclusion of only male subjects, exposure to BSWs under anesthesia, and limited neuroimaging studies to examine p-Tau accumulation across brain regions [5,12,94]. While the available studies suggest a few promising leads for preventing or treating blast-induced PTSD, this is an area that needs further exploration. Due to variations in the initial injury to the clinical manifestations following exposure to BSWs, additional studies are required to determine the optimal time for intervention and the optimal treatment dose to minimize the adverse effects of blast injury.

In conclusion, the studies performed so far have suggested several potential mechanisms in the development of PTSD, spanning from molecular and cellular alterations, including neurotransmitter dysregulation, synaptic dysfunction, and epigenetic modifications, to circuit-level abnormalities in fear processing and extinction networks, to systems-level dysregulation of neuroendocrine and immune responses. These studies have also begun to identify potential therapeutic targets. However, further investigations are needed to fully explore the complex sequelae, including the specific neuropathological changes in multiple brain regions such as the amygdala, hippocampus, prefrontal cortex, and anterior cingulate cortex in PTSD caused by distinct factors, including combat trauma, sexual assault, childhood abuse, and natural disasters. Understanding the progression of these changes from the immediate post-trauma period via the delayed onset phase to chronic PTSD is important, as a subset of these changes may underlie the initial onset and development of PTSD, while others may represent compensatory or maladaptive responses that maintain symptoms over time. The required future studies include studies on neurobiological and behavioral changes from pre-trauma baseline through acute and chronic phases, sex-specific mechanisms and therapeutic responses, development of biomarkers for early identification of individuals at risk for chronic PTSD, evaluation of resilience factors that protect against PTSD development despite trauma exposure, and translational studies that bridge findings from animal models to PTSD patients to accelerate the development of novel, mechanism-based interventions.

Abbreviations

ACTH: Adrenocorticotropin releasing hormone
AD:Alzheimer's disease
AUD: Alcohol use disorder
BDNF: Brain-derived neurotrophic factor
BrdU: 5′-bromodoxyuridine
BSWs: Blast shock waves
bTBI: Blast-induced traumatic brain injury
CRH: Corticotropin releasing hormone
cTBI: Closed head traumatic brain injury
DSM-5: Fifth Edition of the Diagnostic and Statistical Manual of Mental Disorders
EZM: Elevated zero maze
[^{18}F] AV1451: ^{18}F-Flortaucipir
FPS: Fear-potentiated startle
GABA: Gamma-aminobutyric acid
G-CSF: Granulocyte colony-stimulating factor
HPA: Hypothalamus-pituitary-adrenal axis
IFN-γ: Interferon-γ
IL: Interleukin
kPa: Kilopascals
KOR: Dynorphin/kappa opioid receptor
LD: Light/dark emergence
LORR: Loss of righting reflex
MCP-1: Monocyte chemoattractant protein-1
mGLuR2/3: Metabotropic glutamate receptors 2/3
MRI: Magnetic resonance imaging
mTBI: Mild traumatic brain injury
NMDA: N-methyl-D-aspartate
NOR: Novel object recognition
norBNI: Nor-binaltophimine
psi: Pounds per square inch
PCL-5: PTSD Checklist for DSM-5
PET: Positron emission tomography
PFC: Prefrontal cortex
pTBI: Penetrating traumatic brain injury
PTSD: Post-traumatic stress disorder
SSRI: Selective serotonin reuptake inhibitor
TBI: Traumatic brain injury
tDCS: Transcranial direct current stimulation
TI: Tonic Immobility Questionnaire
TMS: Transcranial magnetic stimulation
TNF-α: Tumor necrosis factor-α

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Authors' contributions

FN drafted the first version of the manuscript text and table. AKS provided feedback, made edits, and added text to the initial draft. FN then revised the drafts. FN and AKS further edited and finalized the manuscript text and table. All authors read and approved the final manuscript.

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The authors declare that they have no competing interests.

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