Review

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Post-traumatic stress disorder: a psychiatric disorder requiring urgent attention

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Abstract: Post-traumatic stress disorder (PTSD) is a severe and heterogenous psychiatric disorder that was first defined as a mental disorder in 1980. Currently, the *Diagnostic and Statistical Manual of Mental Disorders Fifth Edition* (DSM-5) and the *International Classification of Diseases 11th Edition* (ICD-11) offer the most widely accepted diagnostic guidelines for PTSD. In both diagnostic categories, experiencing a traumatic event (TE) is the necessary criterion for diagnosing PTSD. The TEs described in the DSM-5 include actual or threatened death, serious injury, sexual violence, and other extreme stressors, either directly or indirectly. More than 70% of adults worldwide are exposed to a TE at least once in their lifetime, and approximately 10% of individuals develop PTSD after experiencing a TE. The important features of PTSD are intrusion or re-experiencing fear memories, pervasive sense of threat, active avoidance, hyperarousal symptoms, and negative alterations of cognition and mood. Individuals with PTSD have high comorbidities with other psychiatric diseases, including major depressive disorder, generalized anxiety disorder, and substance use disorder. Multiple lines of evidence suggest that the pathophysiology of PTSD is complex, involving abnormal neural circuits, molecular mechanisms, and genetic mechanisms. A combination of both psychotherapy and pharmacotherapy is used to treat PTSD, but has limited efficacy in patients with refractory PTSD. Because of the high prevalence, heavy burden, and limited treatments, PTSD is a psychiatric disorder that requires urgent attention. In this review, we summarize and discuss the diagnosis, prevalence, TEs, pathophysiology, and treatments of PTSD and draw attention to its prevention.

Keywords: animal models; comorbidity; pathophysiology; post-traumatic stress disorder; traumatic events; treatments.

Introduction

Post-traumatic stress disorder (PTSD) is a serious and prolonged psychiatric disorder that occurs following exposure to extreme stressors or traumatic events (TEs), such as combats, terrorist attacks, natural disasters, sexual assault, or even severe traffic accidents [1]. The characteristic features of PTSD are intrusion or re-experiencing fear memories, pervasive sense of threat, active avoidance, hyperarousal symptoms, and negative alterations of cognition and mood [2, 3]. Exposure to a TE is a necessary criterion for diagnosing PTSD, and exposure to such TEs increases the risk of developing PTSD within the first 3 months [4]. Although TEs are a major risk factor for PTSD, not every victim develops PTSD after experiencing TEs. Psychiatrists have long been aware of the existence of PTSD symptoms. Indeed, PTSD-like disorders were mentioned in ancient times in the recording of abnormal mental symptoms and behaviors after experiencing combat [5]. However, it was not until 1980 that the *Diagnostic and Statistical Manual of Mental Disorders Third Edition* (DSM-III) first adopted PTSD as a psychiatric disorder. The diagnostic criteria for PTSD have been refined over several decades and have been updated in the latest version of the DSM-5 [6]. Now in the DSM-5, PTSD falls under the category of "Trauma- and Stressor-Related Disorders." Moreover, due to the high comorbidities between PTSD and other mental disorders diagnosed based on DSM, the *International Classification of Diseases 11th Edition* (ICD-11), published by the World Health Organization (WHO), is also widely used to diagnose PTSD [7]. Although symptom clusters differ in certain respects, both diagnostic categories describe the symptoms of PTSD in detail.

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The psychological response and emotional reactions to TEs are determined by the characteristics of both the event and person. It has been estimated that more than 70% of people are exposed to a TE at least once in their lives, and approximately 10% of individuals develop PTSD after experiencing a TE [8, 9]. Globally, the lifetime prevalence of PTSD is 1.3%–12.2%, and the 12 month prevalence ranges from 0.2% to 3.8% [10]. The current coronavirus disease (COVID-19) pandemic can also be considered as a TE that can impact physical and mental health, with a relative high incidence of symptoms of PTSD ranging from 7 to 53.8% [11]. The clinical presentation of PTSD varies differently, and symptoms have substantial overlap between PTSD and other psychiatric diseases, such as depression, anxiety, and substance abuse [12]. Approximately, 91% of individuals diagnosed with PTSD meet the criteria for other psychiatric diagnoses [13]. Fear-based emotional reactions and long-lasting negative emotions are common symptoms in PTSD, which not only affect the life of patients and their families, but also cause heavy mental health burden. PTSD is also associated with several medical comorbidities, such as chronic pain, cardiometabolic diseases, and a heightened risk of dementia [14–16].

Since PTSD was first formally introduced in 1980, numerous studies have been published on PTSD (Figure 1), with many exploring the complex pathophysiology of PTSD in patients and animal models. Researchers have made great progress in understanding the neural circuits, molecular mechanisms, and genetic mechanisms of PTSD. In recent decades, although awareness of PTSD has increased, the gained knowledge has not yet led to enhance effects of treatments for patients with PTSD. One of the major reasons for this is the insufficient predictive power of the PTSD animal model, which limits translation from basic research to clinical applications [17]. Several animal models have been established to imitate PTSD according to its characteristics and symptoms. Indeed, physical or psychosocial stressors can be employed as trauma-like events to build a model of PTSD. However, these animal models cannot fully mimic all mechanisms and symptoms of PTSD [18]. In addition, the development of new technologies is required to establish effective mechanism-based interventions for PTSD. Because of its high prevalence and limited treatments, PTSD is a mental disorder that requires urgent attention.

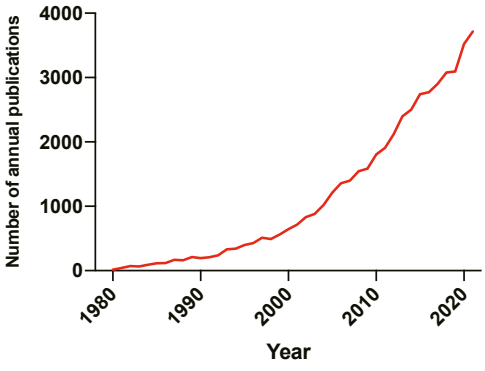

Figure 1: Yearly growth in the number of post-traumatic stress disorder publications from 1980 to 2021. The number of annual publications was obtained by searching PubMed using the search terms "post-traumatic stress disorder" and "PTSD". Online publications 1980 to 2021 are tallied. PTSD, post-traumatic stress disorder.

A brief history of PTSD

Though PTSD as a psychiatric disorder has been described since 1980, records of PTSD-like disorders have been found in literature starting from 4000 years ago. Researchers found some intrusive traumatic pictures related to exposure to dead bodies recorded in cuneiform scripts after the attack of war [19]. Similar phenomena can also be found in other recordings of people, especially soldiers, who experienced recurring intrusive memories of past battles after exposure to combat or witnessing death. PTSD-like disorders were also excessively described in fictional works and operas, such as intrusive memories of battlefields coupled with the loss of interests, loneliness and arousal, which are similar to the PTSD diagnostic criteria used today. From these records, we can deduce that warfare was the main TE causing soldiers to suffer from PTSD-like symptoms in ancient times. However, the diagnostic category for PTSD has a long history before being adopted in the DSM-III (Figure 2).

Accordingly, psychiatrists were concerned with presumed etiologies or symptom expression of these traumatic psychic injuries and termed them "soldier's heart", "irritable heart", "effort syndrome", "sunstroke", or "nostalgia" during the American Civil War (1861–1865) [20], albeit with limited progress on combat-related psychiatric injuries. Accordingly, during World War I (WWI), massive artillery bombardment killed numerous soldiers, leading to the term "shell shock", which was said to be suffered by surviving soldiers following exposure to combat [21]. Military physicians reported specific psychiatric symptoms in patients with "shell shock", including den muteness, deafness, generalized tremors, nightmares, difficulty standing or walking, jumpiness, loss of consciousness, agitation, and convulsions [22]. The concept of shell shock was the first combat-related disorder to include explicit and common psychiatric symptoms, but the relationship between

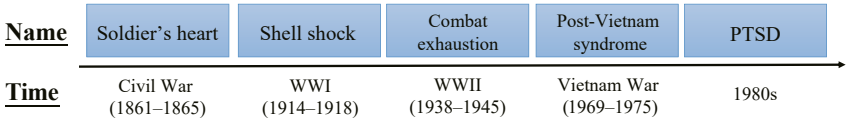

Figure 2: Different names for post-traumatic stress disorder used in different historical periods. PTSD, Post-traumatic stress disorder; WWI, World war I; WWII, World war II.

psychological trauma and war neurosis remained unclear [23]. During WWI, the term "shell shock", as a combat-related mental disorder, was common among the troops, and at least 65,000 soldiers received disability pensions on their diagnosis of shell shock after WWI [24, 25]. The term "shell shock" was then gradually replaced with terms that were "less suggestive of incapacitation" and were less of a "grievous misnomer" [26]. During World War II (WWII), "combat exhaustion" or "battle fatigue" was used to describe PTSD states instead of "shell shock" for combat psychiatric cases [20]. Similar to WWI, many soldiers left the battlefield due to psychiatric reasons, and almost 2.97% of combat veterans (n = 475,397) were classified as psychiatric casualties [27]. The prevalence rates of PTSD ranged from 1.9 to 10.8% in several Western European countries among WWII survivors, mostly in civilians [28]. Even though more than 70 years have passed since WWII, the extreme mental burden still impacts survivors' health and lives [29].

In the DSM-I and DSM-II, combat-related mental disorders were subsumed under the category of Gross Stress Reaction (GSR) and Transient Situational Disturbances (TSD), respectively [30]. However, a large number of veterans with post-combat symptoms did not meet the diagnostic criteria for these according to the DSM-I and DSM-II. In the 1970s, almost 25% of all Vietnam War veterans needed psychological assistance or therapy, even some soldiers who had experienced only "low-level" warfare [31]. Because of the high rate of neuropsychiatric diseases after experiencing the Vietnam War, researchers termed the specific trauma disorder as post-Vietnam syndrome [25]. In response to the medical, social, and financial problems induced by combat-related disorders following the Vietnam War, in 1980 the American Psychiatric Association adopted PTSD as a diagnostic category in the DSM-III [31]. However, in this version, the criteria for PTSD were largely based on studies on survivors who experienced combat [32]. In addition to combat, other TEs, such as serious traffic accidents or sexual assault, can lead to PTSD-like disorders; however, individuals with mental disorders resulting from other types of traumas may not generally be diagnosed with PTSD based on DSM-III criteria [33]. As these trauma-related disorders augmented, psychiatrists began refining and changing the definition of TEs as well as the diagnostic criteria for PTSD in subsequent versions of the DSM.

Diagnosis for PTSD

Diagnostic categories are commonly used to accurately identify mental illness by defining the symptom requirements of the disorder; however, many of the diagnostic classifications are not specific [34]. PTSD, as a psychiatric syndrome, is difficult to define, and its condition and status are difficult to diagnose due to its complex symptoms and etiology. The diagnosis of PTSD is based on several specific symptoms after exposure to a TE, and the DSM-5 and ICD-11 are the most popularly accepted criteria among all diagnostic guidelines for PTSD at present [35].

The diagnostic criteria for PTSD were first introduced in the DSM-III and refined, improved in 1987 and 2000. Currently, the DSM-5 is the latest version and is widely used for diagnosing PTSD. However, the diagnosis of PTSD in the DSM-5 remains controversial in some quarters, and this affects the ability of psychiatrists to identify PTSD. In the DSM-5, 20 symptoms of PTSD across four symptom clusters are described (Figure 3A), including five symptoms of intrusions, two of active avoidance, seven of negative alterations in cognition and mood (NACM), and six of alterations in arousal [3]. The diagnosis of PTSD requires exposure to a trauma that is accompanied by the symptoms at least one intrusion, one avoidance, two NACM, and two arousal. All of the symptoms should be persisting for more than 1 month [36]. It should be noted that some of the PTSD criteria in the DSM-5 overlap with other psychiatric diagnoses, such as depression, anxiety, sleep disturbance, difficulty concentrating, and irritability. These symptoms, included as criteria, can also be found in patients with anxiety and depression. Thus, PTSD and other mental disorders diagnosed using the DSM-5 have a high degree of comorbidity.

Unlike the DSM-5, in the ICD-11 published by the WHO in June 2018, the PTSD criteria include six symptoms under three clusters (Figure 3B): re-experiencing the TE,

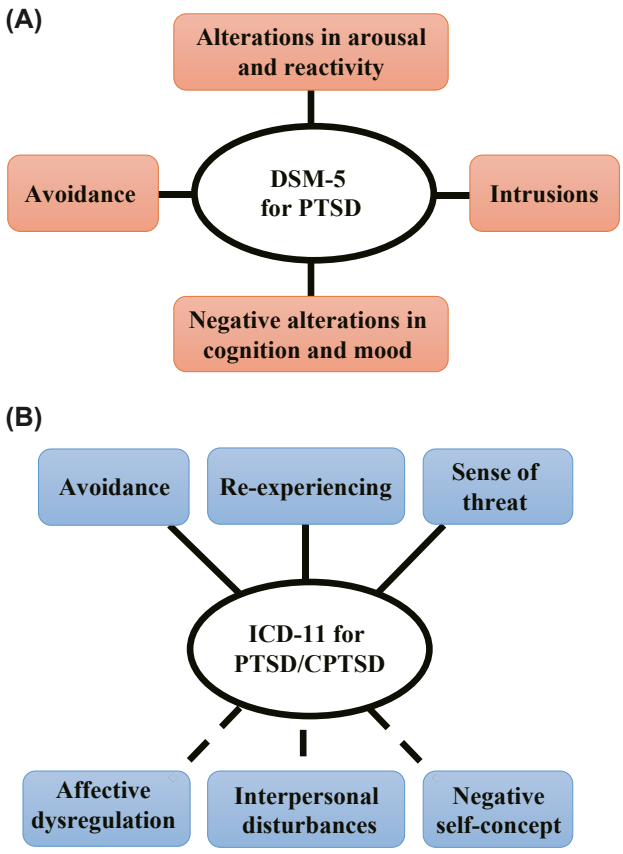

Figure 3: Symptom clusters in the DSM-5 and ICD-11 for post-traumatic stress disorder. The diagnostic criteria for post-traumatic stress disorder include four symptom clusters in the DSM-5 (A) and three symptom clusters in the ICD-11 (B). The complex post-traumatic stress disorder in the ICD-11 consists of six symptom clusters (B). CPTSD, Complex post-traumatic stress disorder; DSM-5, Diagnostic and statistical manual of mental disorders fifth edition; ICD-11, International classification of diseases 11th edition.

avoidance of traumatic reminders, and a sense of threat, with each cluster consisting of two symptoms [37]. The criteria of PTSD in the ICD-11 are explained by a minimum set of symptoms that takes the core of the post-traumatic response to minimize overlap with other disorders and enhance clinical usefulness [38]. The ICD-11 excludes many non-specific symptoms in PTSD (e.g., sleep disturbance, concentration problems, and irritability); thus, the prevalence of ICD-11 PTSD is greatly lower than that of DSM-5 PTSD [35]. The diagnosis of PTSD requires at least one symptom from each cluster in the ICD-11 [36]. The ICD-11 also proposed a sibling disorder named complex PTSD (CPTSD), meaning the PTSD with disturbances in self-organization (DSO) [39]. The DSO symptoms have three clusters (Figure 3B): affective dysregulation, negative self-concept, and interpersonal disturbances [7].

Several questionnaires for PTSD were created for PTSD to assess its diagnostic status and symptom severity; these include the Clinician-Administered PTSD Scale (CAPS), PTSD Checklist (PCL), Post-Traumatic Stress Scale (PTSS), Post-Traumatic Embitterment Disorder Self-Rating Scale (PTED Scale), Impact of Events Scale (IES), International Trauma Questionnaire (ITQ), and others (Table 1) [40–45]. Of all of these interviews, the CAPS, a psychometric measure of PTSD diagnosis and symptom severity, has become one of the most widely used diagnostic measures in both the clinic and in research since its creation in 1989 [46]. Because the CAPS was created by the USA National Center according to the criteria for PTSD in the DSM, it has been revised several times according to different versions of the DSM and was recently updated to the CAPS-5 [47]. The revised CAPS-5 streamlined the administration and simplified scoring by changing the forms of the frequency and intensity thresholds so that interviewers can quickly achieve proficiency [46]. The CAPS-5 measures PTSD symptoms through a 30-item questionnaire, with response options ranging from 0 to 4 [48]. Most clinicians and clinical researchers use the CAPS-5 as the primary diagnostic measure and gold standard for PTSD diagnosis. Additionally, the PTSS defined in the DSM-IV and the PCL for DSM-5 is used to screen patients at risk of PTSD [40]. The PTSS-14 is a refined 14-item version developed following the DSM-IV; it assesses the frequency of PTSD symptoms based on a rating scale in which a cutoff score of 45 is used for a provisional PTSD diagnosis [40, 49]. The PCL is another widely used self-report measure of PTSD created in 1990 for PTSD diagnosis according to the DSM [50]. The PCL-5 is a rating scale consisting of 20 items, and the scores are summed to assess PTSD symptom severity, with a total score of more than 33 suggesting probable PTSD [42]. The ITQ is a 28-item questionnaire that is used to assess the symptoms of PTSD and CPTSD based on the ICD-11, but only 18 items of the validated version were used in the analysis [51]. The ITQ measures reliable and clinically considerable treatment-associated alterations in ICD-11 PTSD and CPTSD symptoms, and the ITQ performs consistently with the PCL-5 in terms of sensitivity to changes [52]. Due to high comorbidities with depression and anxiety, other assessment tools, such as Hamilton Depression Rating Scale (HAM-D) and Hamilton Anxiety Rating Scale (HAM-A), are also used to facilitate the diagnosis of PTSD.

Table 1: Structured interviews or questionaries for assessing post-traumatic stress disorder symptoms.

Instrument	Contents and characteristics
Clinician-administered PTSD scale for DSM-5 (CAPS-5)	A 30-item questionnaire according to the DSM-5 diagnosis for PTSD. Frequency and intensity of symptoms are assessed by rating scales on a 4-point scale ranging from 0 (not at all) to 4 (extremely). The CAPS-5 is considered to be the gold standard for PTSD diagnosis.
PTSD checklist for DSM-5 (PCL-5)	A 20-item self-report measure according to the DSM-5 diagnosis for PTSD. A 5-point scale ranges from 1 (not at all) to 5 (extremely). A cutoff score of 33 is used for a provisional PTSD diagnosis.
Post-traumatic stress Scale-14 (PTSS-14)	A refined 14-item version developed according to DSM-IV for PTSD to assess the frequency of PTSD symptoms. A 7-point likert scale from 1 (never) to 7 (always) is used to assess the frequency of common PTSD symptoms. A cutoff value of 45 indicates presumable PTSD.
The screen for posttraumatic stress symptoms (SPTSS)	A 17-item questionnaire is designed to closely match the DSM-IV symptom criteria for PTSD. A 11-point scale ranges from 0 (never) to 10 (always) in each item.
Post-traumatic embitterment disorder self-rating scale (PTED scale)	Contains 19 items designed to assess features of embitterment reactions to negative life events.
International trauma questionnaire (ITQ)	A validated measure with 28 items corresponding to the ICD-11 diagnosis for PTSD and CPTSD; only the 18 items of the final and validated versions are used in the analysis. The ITQ measures reliable and clinically significant treatment-related changes in ICD-11 PTSD and CPTSD symptoms.
Impact of events scale (IES)	Contains 8 items organized into two symptom clusters, intrusion (four items) and avoidance (four items). IES-8 can be used in adults, children, and adolescents for assessing posttraumatic stress. A 13-item version of the IES is designed for children called Children's revised impact of event scale (CRIES-13).
Hamilton depression rating scale (HAM-D) and hamilton anxiety rating scale (HAM-A)	The most frequently used measures to assess depression and anxiety severity

Symptoms and comorbidities of PTSD

Symptoms of PTSD

Generally, patients with PTSD present psychiatric symptoms for the first 6 months after exposure to a TE. According to the DSM-5, four symptom clusters with 20 symptoms are used to diagnose PTSD: intrusive symptoms, active avoidance, NACM, and hyperarousal symptoms [3]. The duration of these psychiatric symptoms persists over months or even years, creating a heavy financial and mental health burden. The psychiatric abnormalities of PTSD can result in substantial distress or impairment in occupational or social functioning. Based on the diagnostic criteria in the DSM-5, the presence of intrusion and persistent avoidance of reminders or thoughts associated with TEs are unique psychiatric symptoms of PTSD, beginning after the first occurrence of the TE. In particular, avoidance is an indicator of the core features of PTSD, while intrusion and hyperarousal represent largely normative trauma responses [53]. Here, we describe these negative symptoms in detail.

Intrusion symptoms include intrusive distress or recollections of the TE, as well as flashbacks and nightmares [54]. Individuals with PTSD may also present marked physiological responses to trauma-related cues or reminders. As a result of these intrusive distressing symptoms, people with PTSD often exhibit active avoidance of distressing memories or external cues closely associated with TEs. One or more symptoms in these two clusters should be present to support the diagnosis of PTSD. In addition to intrusion and active avoidance, PTSD symptoms include NACM and hyperarousal symptoms. It is believed that TEs usually impair patients' cognition and mood or worsen cognitive and mental symptoms, including dissociative amnesia, distorted cognitions, and other disturbed emotional states (e.g., negative beliefs and anhedonia) [55, 56]. Patients with PTSD tend to have at least two of the seven symptoms in the NACM cluster. Symptoms

of hyperarousal, including irritable behavior and angry outbursts, reckless behavior, hypervigilance, exaggerated startle response, decreased concentration, and sleep disturbance, can also be found in patients with PTSD. Among these four symptom clusters, different symptoms are presented at different phases of PTSD; intrusion and hyperarousal symptoms always occur in the initial phases of PTSD after the TE, while the other two symptom clusters are more predominate in the chronic phases of PTSD [57]. Generally, in those exhibiting negative symptoms, steps should be taken to exclude the possibility of alcohol or drug abuse or another medical illness.

Comorbidities of PTSD

Many physiological symptoms of PTSD in the DSM-5 overlap with other psychiatric diseases, such as major depressive disorder, substance use disorders, and other anxiety disorders [12, 58, 59]. Large volumes of epidemiologic data from the National Comorbidity Survey in 1995 indicate that 59% of men and 44% of women with PTSD had three or more other psychiatric diagnoses [60]. A longitudinal epidemiological study even reported that approximately 91% of patients with PTSD also met the criteria for other psychiatric diagnoses [13]. In some cases, it is difficult to distinguish PTSD from complex psychiatric disorders due to the high degree of symptom overlap, particularly when trauma histories are uncertain.

PTSD and major depressive disorder

Among these common comorbid psychiatric disorders, depression is most likely to co-occur with PTSD after experiencing TEs, and 45%–90% of patients with PTSD can also be diagnosed with major depressive disorder (MDD) [61], though PTSD and MDD are distinct diagnoses. The NACM cluster and hyperarousal clusters are nonspecific symptoms of PTSD, so many symptoms in these two clusters directly overlap with MDD [62]. Common symptoms of PTSD and MDD include concentration difficulties, sleep problems, lack of interest and pleasure in experiencing positive emotions, avoidance and withdrawal, and impairment of cognition. Both PTSD and MDD are chronic mental disorders in which negative mood symptoms always last for several months. One comparison of DSM-5 PTSD and depression suggests that more affective and somatic depression was linked to more NACM symptoms, which in turn were related to an increased severity of PTSD [63]. Though studies on the structural relationship between PTSD and depression are inconsistent, non-diagnosed specific mood symptoms can explain their high comorbidity [63–66]. Due to the substantial overlap of symptoms, PTSD and depression are thought to commonly coexist, but they can be distinguished. First, a TE is a prerequisite of PTSD, and negative symptoms begin to present after the occurrence of the TE, while the diagnostic criteria for depression does not require a TE, and depression may exist before it. Second, depression does not include any PTSD-specific symptoms within the intrusion and avoidance symptom clusters in the DSM-5. Experienced clinicians believe that evaluating symptoms is the best way to distinguish PTSD from other diagnostic categories, especially reexperiencing the TE, hyperarousal, and avoidance tied to trauma-related cues [67]. Through rating symptom items, PTSD is easily distinguishable from other categories for clinicians through a physiological reactivity that is specific to trauma and memories of trauma.

PTSD and generalized anxiety disorder

Before the publication of the DSM-5, PTSD was considered as an anxiety-related disorder, suggesting a high degree of symptoms shared between PTSD and anxiety. Estimates of generalized anxiety disorder (GAD) in patients with PTSD ranged from 11.1 to 31.6%, which is lower than in PTSD patients with depression [64]. Relative to depression, the co-occurrence between PTSD and GAD is examined less frequently in the literature. Irritability, hypervigilance, increased startle reflex, feeling on edge, avoidance, and difficulty sleeping are shared symptoms of PTSD and anxiety disorder. Interestingly, there is currently no consensus on which factor of PTSD is more highly correlated with the factor of GAD. Dysphoria and hyperarousal have both been used to explain the interrelations between two highly comorbid disorders [64, 68]. Some patients with PTSD may present with worry, sleep disruption, and other anxiety disorder symptoms, but more subtypes of PTSD manifest as dysphoria, aggression, or dissociation [69]. The key feature of PTSD is that complex and heterogeneous symptoms of PTSD are clearly related to an experienced TE. However, PTSD symptom severity has also been related to more severe general anxiety [68].

PTSD and substance use disorder

Numerous studies report that PTSD is closely related to substance use disorder (SUD) [59, 70, 71]. SUD primarily includes alcohol use disorder and drug use disorders [72]. Individuals with PTSD are more likely to develop SUD than the normal, and this comorbidity is common among veterans [73]. Approximately 41.4% of veterans diagnosed with PTSD have a co-occurring SUD [74]. The US Department of Veterans Affairs reported that veterans who served in the post-Vietnam era (1973–1991) had the highest rates of comorbidity between PTSD and SUD [74]. The data collected by the Australian National Survey of Mental Health and Well-Being also showed that 34.4% of those with PTSD had at least one SUD, most commonly an alcohol use disorder (24.1%) [75]. In the general population, estimates of the prevalence of SUD range from 21.6 to 43.0% in patients with PTSD [76]. Abusing substances to self-medicate PTSD symptoms may lead to the high comorbidity associated with PTSD.

PTSD and acute stress disorder

Acute stress disorder (ASD) is another psychiatric disease that clinicians may confuse with PTSD due to the similarities between the causes and symptoms. Individuals with ASD often present with intrusion, avoidance, negative mood, arousal symptoms, and other dissociative symptoms after exposure to TEs [77]. Generally, clinicians distinguish between PTSD and ASD by evaluating the duration of the disturbance. Symptoms of ASD always occur immediately after experiencing a TE, and last for at least 3 days but no more than 1 month [78]. If the acute stress responses continue for more than 1 month, individuals can meet the criteria for PTSD. Clinical psychologists had hoped that ASD could predict PTSD development after patients experienced an acute TE, and thereby initiate early interventions [79]. However, ASD diagnosis cannot accurately identify people who will eventually develop PTSD, and only 1.3%–11.2% of patients with ASD develop long-term symptomatic diseases such as PTSD [77, 80].

Prevalence of PTSD

The earliest studies of PTSD mainly focused on survivors and veterans who experienced combat. It has been shown that 12.2% of male U.S. Vietnam veterans had PTSD, while the prevalence was approximately 8.5% among female veterans; 26.2% of living theater veterans met CAPS-5 criteria for PTSD [81]. Moreover, approximately 21.8% of 289,328 veterans of the Afghanistan and Iraq wars were diagnosed with PTSD during the 6 year period from 2002 to 2008 [82]. From 1985 to 2015, approximately 1.45 billion people worldwide had experienced wars, among whom approximately 1 billion were adults, and the prevalence of PTSD among these adults was 23.81% [83]. In recent years, the symptoms of PTSD have spread from war trauma to other events, the number and types of TEs have increased, and PTSD is highly prevalent following natural disasters and artificial accidents (Table 2). Indeed, 3 years after the Ya'an earthquake, the prevalence of PTSD among teenagers was 13.10% [84]. In a survey in the region of Molise in Italy, the prevalence of PTSD was 14.5% 6 months after two earthquakes in 2002 [85]. The estimated morbidity of PTSD among survivors of typhoons or hurricanes is 17.81% [86], and the total incidence of PTSD among refugees who have experienced floods is 15.74% [87]. According to a literature review and meta-analysis, the prevalence of PTSD in rescue workers worldwide is 10%, and the estimated prevalence is higher among rescue workers in Asia [88]. The lifetime prevalence of PTSD in cancer survivors is estimated at 12.6%, and the current prevalence rate is 6.4% [89]. The current COVID-19 pandemic has also caused many related people to suffer from PTSD. Indeed, 1 month after the outbreak of the COVID-19 epidemic, the prevalence rate of PTSD among undergraduate students isolated at home in China was 2.7% [90]. Moreover, the prevalence rate of PTSD among ICU nurses who treated patients with COVID-19 was 27% [91], and that of survivors infected with COVID-19 was 28% [92]. From these studies, we can find that the prevalence rate of PTSD is determined by the characteristics of both the event and person.

Studies have also shown that there is a significant difference in PTSD prevalence between males and females, with females generally more likely to develop PTSD than males [84, 93, 94]. Indeed, the prevalence of PTSD in women is approximately twice as high as that in men [95, 96]. In addition, the prevalence of PTSD is similar worldwide, although the trauma exposure in low-income countries is higher than that in high-income countries [97]. Globally, the lifetime prevalence of PTSD ranges from 1.3 to 12.2%, and its 12 month prevalence is 0.2%–3.8% [10]. The lifetime prevalence of PTSD among U.S. adults (n = 2953) is estimated to be 8.3% [98].

PTSD often results in a high-cost burden. A study on American veterans showed that the mental healthcare costs of depression patients with PTSD are 1381 USD higher than that of patients with depression without PTSD within 12 months, and their total healthcare costs are 20%

Table 2: Prevalence estimates of PTSD in different publications.

Publication	Traumatic events	Sample size	Diagnostic criteria	Prevalence
Marmar et al. 2015 [81]	Warfare (veterans)	1450	DSM-IV, DSM-5	Male: 12.2% Female: 8.5%
Seal et al. 2009 [82]	Warfare (veterans)	289,328	ICD-9-CM	21.8%
Acarturk et al. 2020 [103]	Warfare (refugee)	1678	DSM-5	19.6%
Scherer et al. 2020 [104]	Warfare (children and adolescents)	852	–	11.5%
Kakaje et al. 2021 [105]	Warfare (refugee)	1951	ICD-11	36.9%
Yousef et al. 2021 [106]	Warfare (university students)	833	DSM-5	28.2%
Hoppen et al. 2019 [83]	Warfare (adult survivors)	14,718	DSM-III, DSM-IV, DSM-5, and ICD-10	23.81%
Jin et al. 2018 [84]	Earthquake (children and adolescents)	3962	DSM-IV	13.10%
Priebe et al. 2008 [85]	Earthquake	1680	DSM-IV	14.5%
Wang et al. 2019 [86]	Typhoon or hurricane	43,123	DSM-III, DSM-IV, DSM-5	17.81%
Chen et al. 2015 [87]	Floods	40,600	DSM-III-R, DSM-IV	15.74%
Harvey et al. 2016 [107]	Emergency (fire-fighters)	744	DSM-IV	Current:8% Retired:18%
Berger et al. 2012 [88]	Emergency (rescuers)	20,424	DSM	10%
Bedaso et al. 2020 [108]	Car accident	423	DSM-5	15.4%
Lin et al. 2018 [109]	Car accident	6804	DSM-III-R, DSM-IV	22.25%
Abbey et al. 2015 [89]	Cancer (patients)	4189	DSM-IV	Current: 6.4% Lifetime: 12.6%
Warmerdam et al. 2019 [110]	Children with cancer (parents)	9262	DSM-IV	26%
Tang et al. 2020 [90]	COVID-19 epidemic (university students)	2501	DSM-IV	2.7%
Georgieva et al. 2021 [111]	COVID-19 epidemic	9543	DSM-5	11.4%
Caill et al. 2020 [91]	COVID-19 epidemic (ICU caregivers)	208	ICD-11	27%
Mazza et al. 2020 [92]	COVID-19 epidemic (survivors)	402	DSM-5	28%

DSM, diagnostic and statistical manual of mental disorders; ICD, international classification of dsiseases.

higher [99]. Another study on the economic cost of the PTSD population in Northern Ireland shows that the total cost of treating 1986 patients with PTSD is conservatively estimated at 172,756,062 GBP, which includes the direct cost of treating the disease and the indirect cost of lost productivity [100]. In another study, according to the data of private medical insurers in the United States, the annual cost of direct treatment for PTSD is 10,960–18,753 USD per patient, which is higher compared to matched control subjects having depression [101]. A German research database reported the total cost of patients with PTSD (within 5 years) is approximately 43,000 Euros per person, which is three times that of non-PTSD patients; 18% of this medical cost was caused by PTSD and 59% by other mental disorders, while only 19% of costs of the non-PTSD control group were caused by mental disorders [102].

Traumatic events

TEs are major risk factors for PTSD, and exposure to TEs is not only a prerequisite for the diagnosis of PTSD in the DSM-5 and ICD-11, but is also associated with other negative mental health outcomes. In the DSM-5, PTSD was reclassified into "Trauma- and Stressor-Related Disorders," suggesting that PTSD is closely related to TEs and extreme stressors. As defined in the DSM-5, TEs include actual or threatened death, serious injury, or sexual violence, which occur directly or indirectly by witnessing the event, and exposure to a traumatic stressor is the necessary criteria for diagnosing PTSD (Table 3) [112]. The CAPS and other structured interviews to assess PTSD also include questions and rating scales for TEs. Exposure to TEs is a widespread issue, the WHO World Mental Health (WMH) survey of 68,894 adults in 24 countries across six continents assessed 29 lifetime traumas and indicated that 70.4% of respondents reported at least one TE, while 30.5% adults were exposed to four or more TEs, with each person experiencing an average of 3.2 traumas [8]. The lifetime prevalence of exposure to any TE also varied by sex in that males were more likely to be exposed to different types of TE [113]. In 1995, a national health interview survey of TEs, with a sample of 5877 respondents in the US, revealed that 60.7% of men and 51.2% of women had experienced at

least one TE, showing a significant sex difference [60]. Moreover, the prevalence of TE exposure varied by country, with rates higher than 80% in Ukraine (84.6%), Peru (83.1%), USA (82.7%), and Colombia (82.7%) [8]. Even people in developed countries have a high prevalence of lifetime exposure to at least one TE, ranging from 28 to 90%.

Much progress has been made to understand the relationship between PTSD and TEs. Individuals with PTSD must experience TEs and then exhibit negative symptoms lasting for more than 1 month before being diagnosed. Exposure to a TE results in a high risk of developing PTSD, and systemic therapeutic interventions for TE exposure can successfully reduce PTSD and related symptoms [114]. Studies have also found significant associations or "dose-response" relationships between TEs (e.g., physical violence) and PTSD symptom severity. Although Criterion A in the DSM-5 defined a qualifying stressor as the gatekeeper criterion, the extent to which traumas can induce PTSD remains unclear. Despite the high rate of exposure to TEs, not everyone will go on to develop PTSD after experiencing a TE. Indeed, one study reported that approximately 10% of people exposed to TEs may suffer from clinically relevant PTSD [115]. In fact, while most people have experienced TEs in their lives, only a small minority will develop PTSD [116]. The question of who are most likely to develop PTSD after experiencing TE still puzzles psychologists. These lines of evidence indicate that, while exposure to a TE is necessary, this alone is not sufficient to induce PTSD.

Animal models of PTSD

Since PTSD was first adopted as a psychiatric disorder in the DSM-III, psychologists have paid considerable attention to it. In recent years, awareness of PTSD has grown, particularly regarding its symptoms. Nevertheless, the pathophysiology underlying PTSD remains unclear, and the efficacy of available treatments is still highly unsatisfactory. The goal of psychologists is to develop or improve effective drugs and new approaches to treat PTSD by understanding the physiological and neural mechanisms underlying the disorder. Based on the clinical characteristics of PTSD, various animal models have been established to imitate human PTSD to help researchers to better understand PTSD. Whether animal models can mimic the symptoms and pathophysiology of PTSD is a challenging scientific problem. It is essential to provide solid and validated animal models to explore the underlying mechanisms of PSTD and help to develop more reliable diagnosis and effective treatment approaches. Here, we introduce several animal models that have been widely used to imitate PTSD.

The TE serves as the gatekeeper criterion for PTSD, and a person may develop PTSD after experiencing extreme stressors. Based on the fact that traumatic experiences are necessary for developing PTSD, animal models should be exposed to trauma-like stresses to induce PTSD-like symptoms. Physical or psychosocial stressors are employed as trauma-like events to establish animal models of PTSD (Figure 4). Accordingly, physical stressors include electric shock, inescapable tail shock, restraint stress or immobilization, underwater trauma, single prolonged stress (SPS), and unpredictable variable stress (UVS), while psychosocial stressors include conditions such as social isolation, social defeat stress, and predator-based stress [117–119]. Inescapable severe stressors are applied to animals to induce prolonged PTSD-like behavior, and different stressors may lead to different negative responses or biological observations.

Table 3: Definition of traumatic event(s) in the DSM-5 and ICD-11 [3, 37].

DSM-5 criteria	ICD-11 criteria
Exposure to actual or threatened death, serious injury, or sexual violence in one (or more) of the following ways: 1. Directly experiencing the traumatic event(s). 2. Witnessing, in person, the event(s) as it occurred to others. 3. Learning that the traumatic event(s) occurred to a close family member or close friend. In cases of actual or threatened death of a family member or friend, the event(s) must have been violent or accidental. 4. Experiencing repeated or extreme exposure to aversive details of the traumatic event(s) (e.g., first responders collecting human remains; police officers repeatedly exposed to details of child abuse). Note: Criterion A4 does not apply to exposure through electronic media, television, movies, or pictures, unless this exposure is work related.	Exposure to an extremely threatening or horrific event or series of events.

DSM, diagnostic and statistical manual of mental disorders; ICD, international classification of diseases.

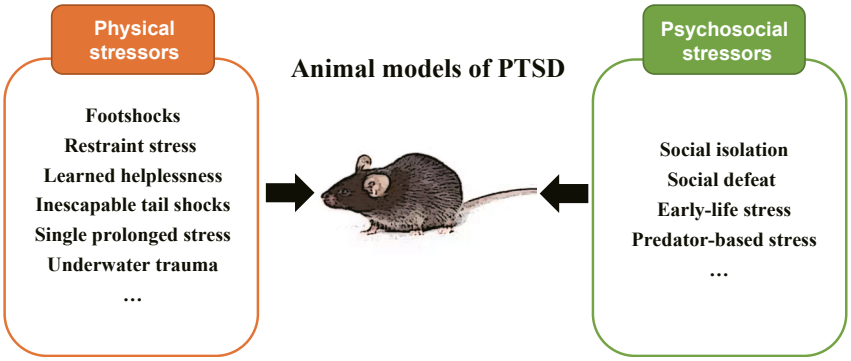

Figure 4: Physical or psychosocial stressors used to generate animal models of post-traumatic stress disorder. Physical or psychosocial stressors are employed as trauma-like events to establish animal models of post-traumatic stress disorder. Many models are defined by the type of trauma that animals are exposed to. PTSD, post-traumatic stress disorder.

Physical stressor–induced PTSD animal models

The fear condition model is established by administering inescapable foot shocks to rodent fear models and paired with conditional stimulus (e.g., tone, lights, context) [120]. This shock model can evoke fear learning and long-term sensitization of the response associated with stressors. Briefly, rodents receive a sequence of acute electric shocks accompanied by brief tones as conditional cues in shock chambers [121]. The number, intensity, and duration of shocks vary substantially between studies (e.g., 1–20 shocks, 0.3–1.5 mA, 0.5–10.0 s) [18]. The brief tone is given before electric shock so that the fear response to the tone can be evoked after successful building of the animal models, while the collection of freezing time can be used as an index of pathology to assess PTSD-like behavior. Researchers believe that fear condition models can reproduce some core behavior of PTSD, such as avoidance, anxiety, hyperarousal, aggression, intrusion, and or re-experiencing the TE. Usually, PTSD-like phenotypes of the fear condition model can persist for several weeks. Inescapable electric tail shocks are also delivered to rodents to mimic PTSD and induce some PTSD-like behavioral symptoms and biological changes [122]. The inescapable tail shock model is often established with other stressors (e.g., immobilization) to exhibit a delayed and exaggerated startle response and other neuropsychological molecular mechanisms that are observed in PTSD [123].

Immobilization or restraint stress is another common physical stressor in which rodents are attached to a board or placed in a restraint device for 15 min to 2 h [123]. Restraint stress or immobilization has been widely used to model PTSD-like anxiety and to enhance nociception, but the restraint stress is insufficient to generate the entire array of symptoms related to PTSD. Due to the limitation, restraint stress and immobilization are always combined with additional acute stressors to induce PTSD-like symptoms. In SPS paradigm, the stressors in a single continuous session include restraint stress for 2 h, forced swimming for 20 min, and exposure to diethyl ether until loss of consciousness [124, 125]. SPS models exhibit significantly increased startle responses, increased anxiety-like behavior, greater nociception, and diminished fear extinction [119]. Importantly, SPS can elevate glucocorticoid receptors expression and increase the negative feedback of the hypothalamic pituitary adrenal (HPA) axis [126].

Psychosocial stressor-induced PTSD animal models

Some psychosocial stressors, including social isolation, social defeat, and predator-based stress, can also cause PTSD-like symptoms. In the typical social defeat (SD) stress paradigm, mice are exposed to a single aggressor mouse for 5–10 min, during which time physical fighting occurs for either 1 or 5 days. After exposure to SD stress, the animals can be divided into susceptible and resilient groups based on the severity of their stress response [117, 127]. Susceptible mice subjected to SD present persisting avoidance behavior as seen in PTSD. Chronic SD is also widely used as a model of depression and anxiety due to the nonspecific symptoms of PTSD. Likewise, animals are exposed to natural and inescapable predator-stress to evoke enduring PTSD-like symptoms, including avoidance, hyperarousal, exaggerated fear response, and severe anxiety [121]. Exposure to predator-based stressors for a

brief time is also considered a trauma-like event. In predator-based stress models, rodents are exposed to natural predators or to odors of predator [117, 128].

Though several animal models have been widely used to study the mechanisms underlying PTSD, it is difficult to fully model all aspects of PTSD. Researchers have identified specific symptoms and several potential subtypes of PTSD, and animal models for PTSD employ physical, psychological, or other stressors, which can be considered a traumatic-like event, to evoke PTSD-like symptoms. Patients with PTSD exhibit numerous and heterogeneous psychiatric conditions, and different subtypes may result from distinct types of traumas. Which symptoms of PTSD need to be mimicked is an important question in animal models, given that an animal model mimics only certain features of a patient with PTSD. Simultaneously, some symptoms of PTSD, such as dissociative flashback memories, are impossible to observe in animal models. Thus, researchers should select appropriate animal models to mimic specific subtypes of PTSD according to the purpose of the study. Moreover, investigators should focus on specific types of traumas to mimic specific PTSD phenotypes, thereby increasing the validity and efficiency of PTSD. As primary scientific tools for investigating physiological and neuronal mechanisms underlying PTSD, animal models have allowed progress to be made in the study of the mechanisms of fear memory; however, these studies have yielded little improvement in effective treatments for patients with PTSD [17]. Optimizing animal models to overcome the deficiencies of previous research is a challenge. Additionally, ethical principles should be taken into consideration when delivering traumatic-like events to animals.

Mechanisms/pathophysiology of PTSD

PTSD is a complex and heterogeneous mental disorder that has received increasing attention because of its clinically significant distress, high prevalence, and major socioeconomic impact. Researchers have made great effort in understanding the mechanisms underlying PTSD, including genetic factors, molecular and neurochemical factors, cognitive factors, and neurocircuitry, using clinical data from patients or animal models of PTSD.

Neuroimaging and neurocircuitry

PTSD is characterized by dysfunctions in the brain structure and neurocircuitry. Psychiatrists use several neuroimaging techniques to detect alterations in brain structure, function and metabolism in PTSD patients. Magnetic resonance imaging (MRI) observations of patients with PTSD compared to healthy controls have revealed that the grey matter volume was largely reduced in certain brain areas, including the left anterior cingulate gyrus, left insula, right parahippocampal gyrus, the medial prefrontal cortex (mPFC), left hippocampus, left middle temporal gyrus, and right superior frontal gyrus [129, 130]. Furthermore, patients with PTSD with different types of traumas may have different correlations with cerebral deficits. Alterations in the volume and morphology of grey matter may underlie the dysfunction of fear memory and extinction in PTSD, and can also account for long-lasting cognitive impairment in individuals with PTSD. Though many findings have indicated that reductions in hippocampal volume might vary with PTSD symptom severity, there have been no consistent results on whether the volume of the hippocampus is reduced in patients with PTSD [131–133]. However, a smaller hippocampus may be a risk factor for the persistence of PTSD [134]. Moreover, several studies have reported that stress can induce the death of neurons, which may induce structural alterations in the hippocampus and amygdala [135]. As the key function of the amygdala involves emotional systems, changes in its structure may lead to the mental dysfunctions observed in PTSD. Similar changes related to stress can also be observed in the mPFC, which is linked to the fear of acquisition and extinction [136].

Clinical researchers have also used functional MRI (fMRI) and positron emission tomography (PET) to detect functional neuroimaging in patients with PTSD. The results of such investigations have shown increased activity in the amygdala, the dorsal anterior cingulate cortex (dACC), and the insular cortex, and decreased activity in the ventromedial PFC (vmPFC) and hippocampus in individuals with PTSD (Figure 5A). The amygdala is an essential part of the neurocircuitry that supports threat detection, fear learning, responses and memory [137–139]. Many studies have reported that hyperactivity of the amygdala can be detected when exposed to trauma-related stimuli or other negative stimuli [140]. Investigators speculate that the hyperactivity of the amygdala may be linked to conditioned fear learning and memory [141]. Patients with PTSD also show increased activation in the amygdala when they meet external reminders associated with TEs [139]. A more detailed meta-analyses noted that there were two distinct clusters within the left amygdala for PTSD, a hyperactivation cluster in the ventral anterior region and a hypoactivation cluster within the dorsal posterior region [142]. These findings suggest that distinct patterns of amygdala activity and connectivity should be considered in different PTSD phenotypes.

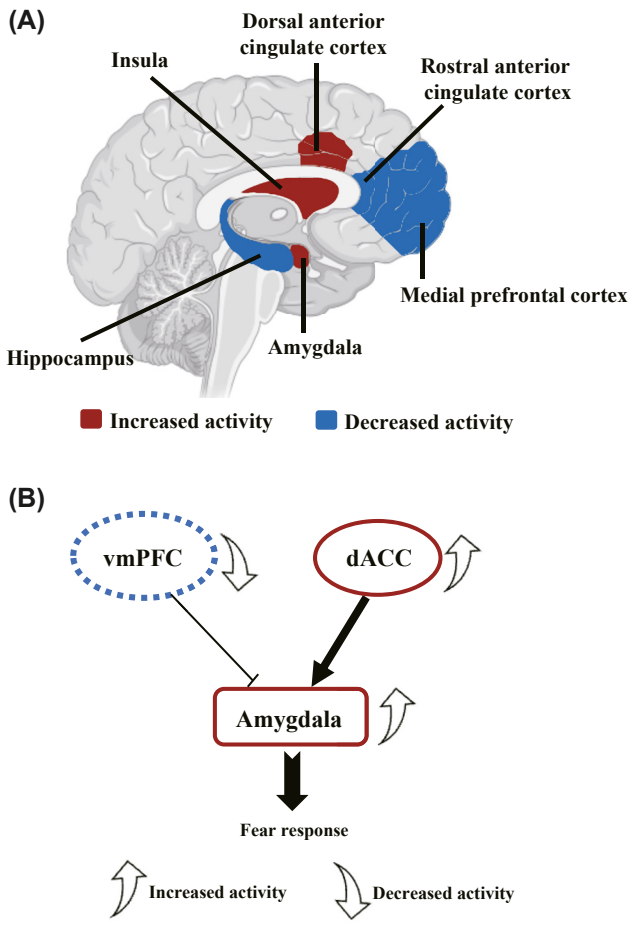

Figure 5: Abnormal activities of brain regions in patients with post-traumatic stress disorder.
(A) Functional neuroimaging shows increased activity in the amygdala, dACC and insular cortex; and decreased activity in the mPFC, rACC and hippocampus in patients with PTSD. dACC: Dorsal anterior cingulate cortex; mPFC: Medial prefrontal cortex; rACC: Rostral anterior cingulate cortex. (B) Hypoactivity of the vmPFC results in the inability of the cortex to inhibit amygdala, and hyperactivity of the dACC contributes to the increased activity of amygdala in patients with PTSD, and then the amygdala outputs to other emotional nucleus associated with fear conditioning after integrating information. PTSD, post-traumatic stress disorder; vmPFC, ventromedial prefrontal cortex; dACC, dorsal anterior cingulate cortex.

Moreover, it has been reported that the vmPFC can regulate amygdala activity and suppress the fear response [143]; thus, the vmPFC also plays a crucial role in the fear-related network. Indeed, subjects with PTSD show decreased activation in the vmPFC compared to controls during emotional tasks associated with trauma-related stimuli or even non-trauma-related stimuli [144]. Decreased vmPFC activation may lead to a failure to regulate the activity of the amygdala and facilitate fear learning progression. Thus, increasing the activity of the vmPFC may be an approach for treating PTSD. Furthermore, both the vmPFC and dACC are related to emotion regulation [145]. The activity of the dACC is increased during fear conditioning and recalling of extinction learning, especially in patients with PTSD compared to control groups [146]. Dysfunction of the dACC is positively associated with the severity of PTSD symptoms; thus, increased dACC activity may be a biomarker reflecting the familial risk of developing PTSD after trauma [147]. The hippocampus, which plays a critical role in forming conscious threat expectations, facilitates conditioned fear learning [148]. Patients with PTSD exhibit reduced hippocampal activity during fear learning and other declarative memory tasks, which appears to underlie the disruption of fear learning and memory processes [141]. Although the hippocampal activity is not consistent in patients with PTSD compared to control groups, these disparate results may be due to researchers not using the same paradigms or analyses in different studies [147]. Stronger evidence should be provided to identify the activity of the hippocampus in patients with PTSD. Nonetheless, there is no doubt that dysfunction of the hippocampus results in cognitive impairment and difficulty in fear extinction. The hippocampus plays important roles in the initial storage of fear memories and in integrating memories during retrieval [149]. Moreover, dysfunction of the hippocampus may lead to cognitive and memory impairments in patients with PTSD. Studies have reported that negative stress can impair neurogenesis in the dentate gyrus (DG) and decrease long-term potentiation (LTP) in the CA1 region and dendritic retraction in the CA3 [150, 151]. We mentioned above that a smaller hippocampus may be a risk factor for PTSD, though whether abnormal hippocampal activity in patients with PTSD is related to reduced hippocampal volume remains to be studied. Patients with PTSD also showed increased activation of the insular cortex during recall of fear memories [152]. However, the activation of the insular cortex is not specific to PTSD.

Functional neuroimaging studies have shown that patients with PTSD have hyperactivity during emotional processing in certain brain areas, including the bilateral amygdala, parahippocampal gyrus, insula, inferior parietal lobule, midcingulate, and precuneus; whereas hypoactivation including the inferior occipital gyrus, vmPFC, the rostral anterior cingulate cortex (rACC), parahippocampal gyrus, lingual gyrus, dorsal amygdala and anterior hippocampus, orbitofrontal cortex, putamen, middle occipital gyrus, dorsomedial prefrontal cortex, and midcingulate [142]. Furthermore, these reported changes in activity are closely associated with PTSD severity. These findings, including abnormal structure and function in brain regions, suggest that neural circuits and networks are dysfunctional in patients with PTSD. The amygdala has

been reported to be a key limbic structure for recognizing dangerous stimuli and coordinating fear responses, with activity modulated by higher cortical influences [147]. Hypoactivity of the vmPFC is associated with increased amygdala activity, which results in the inability of the cortex to inhibit the amygdala in patients with PTSD [153]. Further, the activities of other regions in the cortex (e.g. the rACC and inferior frontal cortex) are also reduced in individuals with PTSD during re-experiencing symptoms [154]. These decreased activities in the cortex demonstrate the inability of top-down cortical inhibition in response to fear learning and memory [149]. The neural circuit linking the mPFC and amygdala plays crucial roles in both the acquisition and extinction of fear. Several studies have reported that mPFC-amygdala circuits are involved in encoding fear extinction [153, 155–157]. Similar observation can also be found in animal models of PTSD. Indeed, fear extinction reduces the efficacy of excitatory synaptic transmission in projections from the mPFC to the amygdala, while inhibitory responses remain unchanged [158]. Such a dysregulation of cortex-limbic neurocircuitry is related to the inability to extinguish fear and may produce intrusive symptoms [159], such as flashbacks, recurring and involuntary intrusive memories, and distressing dreams. As for the avoidance symptoms, human-based PTSD research has shown limited success in establishing the neurobiological underpinnings of trauma-cue avoidance. The amygdala is a highly conserved nucleus in the limbic system, in which microcircuits mediate fear acquisition, expression, and extinction [160]. The amygdala complex consists of several interconnected subnuclei with distinct anatomical and physiological features, including the basolateral amygdala (BLA), the lateral amygdala (LA), the basal amygdala (BA), and the central nucleus of the amygdala (CeA) [161]. Using rodent models, researchers have shown that signals for active avoidance are transmitted from neurons within the LA to the BA and then to neurons within the shell of the nucleus accumbens (NAcS) [162]. Likewise, passive freezing responses are signaled from the LA, but are transmitted to the CeA and then to the periaqueductal gray (PAG) [163]. Thus, the LA is the primary input site for sensory information from the sensory cortex and thalamus to the amygdala, following which the amygdala outputs to other emotional nuclei associated with fear conditioning after integrating information [164, 165]. Amygdala inhibitory microcircuits may also be involved in mediating fear extinction [166, 167]. The functions and mechanisms of the amygdala complex need to be further investigated in animal models and patients with PTSD. Persistent negative emotions, such emotional networks, are disrupted in patients with PTSD, and an extensive network of cortical and subcortical regions is related to emotional experience, such as the link between the frontal cortex and amygdala [168]. Likewise, negative mood can also decrease activities of both the anterior cingulate cortex (ACC) and thalamus. In general, patients with PTSD exhibit negative mood because of not only suffering from PTSD but also comorbidity with depression and anxiety. Many brain regions associated with emotional progress, including the BLA, CeA, NAc, VTA, ACC, dmPFC, and orbitofrontal cortex, appear to respond to the traumatic stimuli [169]. Dysfunction in this reward processing may result in an inability to feel happiness or other positive experiences. Hyperactivity in the amygdala and the bed nucleus of the stria terminalis (BNST) and hypoactivity in the mPFC and ventral hippocampus are also observed in patients with PTSD with arousal symptoms [170]. Several lines of evidence from rodents have reported that the neural circuits, BLA-NAc, BLA-BNST, mPFC-BLA, and mPFC-CeA, are all involved in anxiety and hypervigilance [157, 171, 172].

In recent years, structural and functional neuroimaging techniques have improved our understanding of the neural correlates of PTSD. Dysfunctions of brain regions and neural circuitry related to PTSD are widely accepted, but this knowledge has not yet facilitated effective treatment of PTSD. Therefore, the development of an effective treatment for clinic patients based on these studies remains a challenging topic.

Molecular mechanisms

The HPA axis is the primary hormonal mediator in response to stress, and cortisol is the primary effector molecule of the HPA axis [173]. The hippocampus, mPFC, and amygdala, all of which are affected by intense stress, can release corticotropin releasing hormone (CRH) acting on neurons in the hypothalamus to activate the HPA axis, which in turn activates adrenal glands to release glucocorticoids such as cortisol [174]. Circuiting cortisol exerts many biological effects in response to stress and produces negative feedback on the HPA axis by banding to glucocorticoid receptors (GR) in the hypothalamus and pituitary. PTSD and other mental disorders are linked with alterations pertaining to the HPA axis, although there are distinct differences among illnesses [175].

For the first time, a clinic psychiatrist reported that cortisol concentrations in 24 h urinary were significantly decreased in Vietnam combat veterans with PTSD compared to other patients without PTSD [176]. Following this, multiple studies have reported that the hypoactivity of

HPA axis and reduced cortisol levels can be found in patients with PTSD, although conflicting data also exist, suggesting that the cortisol levels in patients with PTSD remain normal [175, 177, 178]. Interestingly, one study reported that the CSF cortisol levels, not plasma cortisol levels, were higher in veterans with PTSD [179]. However, the increased GR sensitivity enhances the negative feedback of the HPA axis (Figure 6), which is most consistent in patients with PTSD, possibly due to an adaptation of the HPA axis induced by decreased levels of circulating cortisol [177]. Further, some HPA axis-related genes and their products, including *NR3C1* and *FKBP5*, are also involved in the hypoactivity of the HPA axis in patients with PTSD [175, 180]. Thus, low cortisol levels may represent a risk factor for developing PTSD following exposure to TEs [181].

Similar to depression, immune dysregulation and inflammation are associated with PTSD [182]. In line with this, numerous blood inflammatory markers, including IL-1β, IL-6, TNF-α, and CRP, are significantly elevated in patients with PTSD [183]. Moreover, proinflammatory cytokines are also altered in response to immune activation in patients with PTSD relative to controls [184]. The altered inflammatory system may be associated with the hypoactivity of the HPA axis and low circuiting cortisol levels induced by PTSD. Thus, glucocorticoids (e.g., hydrocortisone and dexamethasone) represent potential anti-inflammatory treatments for PTSD [185, 186]. Stress-induced altered interactions between the immune system, HPA axis, and sympathetic nervous system may play a key role in the etiology of PTSD [187].

Abnormal neurotransmitters can also be observed in patients with PTSD. One study reported that high levels or reactivity of norepinephrine (NE) in patients with PTSD is associated with decreased neuropeptide Y (NPY) and α_2-noradrenergic neuron receptors, which inhibit NE release [188]. The hyperreactivity of the amygdala in patients with PTSD can also induce noradrenergic system hyperreactivity [189]. Moreover, increased activity of the noradrenergic system is positively related to long-term memory for trauma-related stimuli [190]. In additional to NE, GABA has also been reported to be associated with PTSD. Studies have shown that low plasma GABA levels may be a risk factor for the development and maintenance

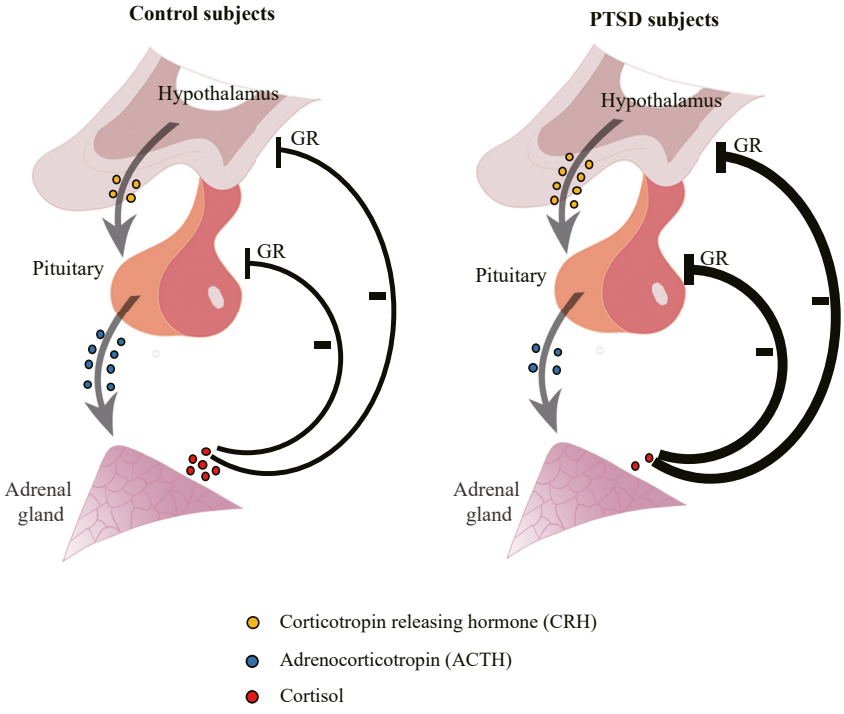

Figure 6: Hypoactivity of the hypothalamic-pituitary-adrenal axis in patients with post-traumatic stress disorder. CRH concentrations in cerebrospinal fluid are higher in PTSD compared to control subjects. But patients with PTSD show enhanced cortisol feedback inhibition of ACTH secretion at the level of the pituitary in PTSD and a blunted ACTH response to CRH. Low circulating levels of cortisol may lead to an adaptation of the HPA axis to increase GR sensitivity and increase negative feedback inhibition of the HPA axis. PTSD, post-traumatic stress disorder; CRH, corticotropin releasing hormone; ACTH, adrenocorticotropin; GR, glucocorticoid receptors. (Figure modified from Yehuda et al. 2015 [180].)

of PTSD [191, 192]. In patients with PTSD, a decrease in cortical GABA concentrations was observed, although conflicting results have also been reported [188, 193, 194]. Thus, the relationship between PTSD and GABA concentrations should be further investigated. Other studies also suggest that PTSD is related to abnormalities in BDNF, NPY, serotonin (5HT), and 17β-estradiol [195–198].

PTSD is a complex psychiatric condition involving multiple mechanisms, and, as a result, it is difficult to clearly explain the molecular mechanisms and specific pathogenesis of PTSD. In previous studies, many researchers have investigated the molecular mechanisms related to PTSD and found a few effective drugs for PTSD, including glucocorticoids, 17β-estradiol, NPY and SSRIs [188]. We hope that by exploring the novel molecular mechanisms underlying PTSD, new potential drug targets and more effective treatments will be developed in the future.

Genetic factors

Genes are the most widely acknowledged contributors to the etiology of psychiatric diseases. Specific DNA variations have been identified to be associated with mental disorders and related symptoms. Twin studies are commonly used to examine whether genetic factors are associated with psychiatric disorders including PTSD, MDD and anxiety, and in PTSD, such experiments suggest that vulnerability to PTSD is heritable [199]. Further genetic studies may provide key clues to these individual differences in vulnerability to PTSD. Several studies have also reported that offspring may have an increased risk of developing PTSD if their parents suffer from PTSD, and this association may show a dose-response relationship [200–202]. A subset of genes associated with PTSD have been reported in candidate gene studies and genome-wide association studies (GWAS). Numerous genes involved in neurotransmitter- and neuropeptide-related genes may be associated with PTSD, including *SLC6A4, HRT2A, SLC6A3, DRD3, NPY, CNR1, RGS2,* and *OPRL1,* while *ADCYAP1R1* and *FKBP5* are known to be related to neuroendocrine function [203–205]. Furthermore, *FKBP5*, as a glucocorticoid receptor co-chaperone, has been extensively studied. Indeed, previous studies have shown that genetic variation in *FKBP5* leads to an increased risk of developing PTSD after childhood trauma, while polymorphisms in *FKBP5* can be used as a predictor of PTSD symptoms in adults [206]. Briefly, the gene product of *FKBP5* can inhibit GR activity by several mechanisms, while variation and epigenetic regulation (*e.g.*, DNA demethylation) in *FKBP5* can moderate the risk of developing PTSD after experiencing a TE [207]. In another strategy, a GWAS identified five common variants associated with PTSD, including *RORA, TLL1, COBL, PRTFDC1, AC068718.1* [204]. Additionally, several studies have reported that a genetic variant BDNF (Val66Met) polymorphism is associated with fear extinction [208]. The BDNF (Val66Met) polymorphism can modulate stress susceptibility as well as stress-related neuropsychiatric endophenotypes [195]. Though candidate gene studies and GWAS have reported numerous genes largely related to PTSD, the molecular genetic basis of PTSD remains unclear. Despite the limitations of genetic studies for PTSD, the Psychiatric Genomics Consortium (PGC) is conducting meta-analyses of genetic data obtained from patients with PTSD [209]. We anticipate that great progress will be made in identifying PTSD-related genes to improve treatments for PTSD in the future.

Treatments for PTSD

PTSD is associated with high levels of medical usage given its propensity to cause significant distress and severe symptoms. Developing effective treatments for patients with PTSD is an important topic that needs further research. Physicians have found that forward-area treatment is an effective method for combat-related disorders, and summarized five key principles (immediacy, proximity, expectancy, simplicity, and centrality) first used in WWI, and then later during WWII, the Korean War, and the Vietnam War [22]. Soldiers with combat-related disorders treated with this method had a good prognosis and were more likely to return to duty. With increasing knowledge about PTSD, several treatments (Figure 7), including psychotherapy, pharmacotherapy, and neuromodulation, have been used to improve the mental health of patients with PTSD. Importantly, prevention and early intervention are the best approaches.

Psychotherapy

Psychotherapies, including trauma-focused and non-trauma-focused psychotherapies, are generally recommended as first-line treatments and show great clinical benefits in the treatment of PTSD [210]. Trauma-focused treatments, especially cognitive behavioral therapies (CBTs), are generally accepted as the most effective means to ameliorate conditioned fear responses and regulate negative emotion. Furthermore, trauma-focused CBTs include exposure-based CBT and cognitive-based CBT [211]. Exposure-based CBT, such as prolonged exposure (PE) therapy and eye movement desensitization and

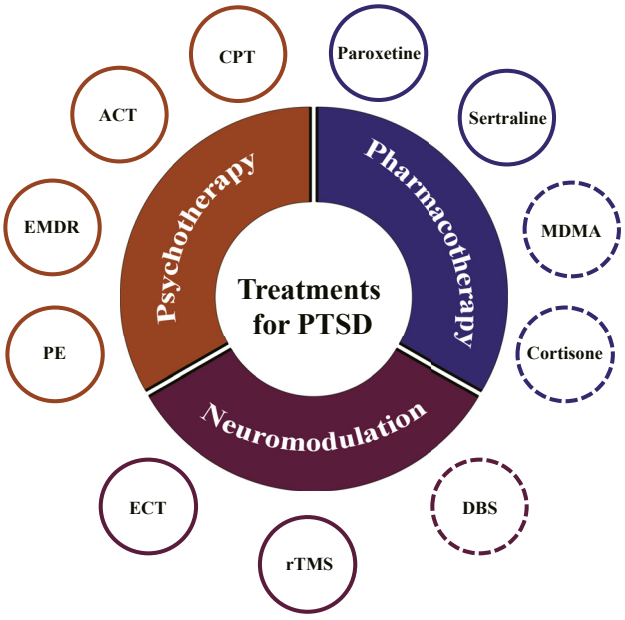

Figure 7: Common treatments for post-traumatic stress disorder. Psychotherapies are first-line treatments for PTSD. A combination of psychological therapy and pharmacotherapy can enhance treatment outcomes for PTSD. Sertraline and paroxetine are the only two FDA-approved drugs to treat PTSD. Neuromodulation has been used to reduce symptoms of refractory PTSD. The effect of treatments labeled with dotting wheel needs to be further studied. PTSD, Post-traumatic stress disorder; PE, prolonged exposure; EMDR, Eye movement desensitization and reprocessing; ACT, Acceptance and commitment therapy; CPT, Cognitive processing therapy; MDMA, 3, 4,-Methylenedioxmethamphetamine; ECT, Electroconvulsive therapy; rTMS, Repetitive transcranial magnetic stimulation; DBS, Deep brain stimulation.

reprocessing (EMDR), are used to facilitate fear extinction through multiple exposures to trauma-related stimuli or reminders and thoughts [212]. Accordingly, PE and EMDR treatments are effective, safe, and feasible for patients with PTSD [213]. Cognitive-based CBT, including cognitive processing therapy (CPT) and acceptance and commitment therapy (ACT), can effectively reduce negative evaluations of the self and of others (e.g., shame, guilt, mistrust) [214]. Generally, individuals with PTSD receive weekly psychotherapies, and may require several months or even years until symptoms are alleviated [215]. This shortcoming limits the efficacy of psychotherapeutic treatments. Additionally, psychotherapies are recommended for early intervention, but may be less effective in combat-related PTSD [216].

Pharmacotherapy

Due to the high degree of comorbidity between PTSD and MDD or anxiety, psychiatrists initially used antidepressants to reduce negative mood symptoms. Antidepressants, particularly selective serotonin reuptake inhibitors (SSRIs), not only relieve symptoms of depression but also improve specific symptoms of PTSD (*e.g.*, nightmares). Sertraline and paroxetine, both as SSRIs, are the only two FDA-approved drugs to treat PTSD [217]. Although SSRIs are an effective treatment for PTSD, there is little evidence to support dysregulation or deficiency of the serotonin system in patients with PTSD. Moreover, anti-adrenergic drugs have also received attention because of the evidence for noradrenergic dysregulation in PTSD. Therefore, the α_1 receptor antagonist prazosin has been used to reduce the frequency and severity of nightmares and symptoms of hyperarousal, but with limited capacity [218, 219]. According to the dysfunction of the HPA axis in patients with PTSD, psychiatrists began using low dose cortisone or glucocorticoid receptor antagonists for treating PTSD [185, 220]. These approaches have shown great efficiency in patients with PTSD but should be further investigated. Furthermore, hydrocortisone, but not SSRIs, may be useful in preventing the onset of PTSD [211, 221]. In recent years, new pharmacologic drugs have been developed to treat PTSD; these include ketamine and 3, 4,-methylenedioxmethamphetamine (MDMA), both of which have an antidepressant effect in patients with MDD [222–224]. Of particular note, avoidance and depressive symptoms are exacerbated by the use of benzodiazepines for PTSD, thought to be due to their strong sedative, addictive, and dissociative properties [219, 225]. Currently, no single particular medication treats all symptomatic clusters of PTSD. The combination of both psychological therapy and pharmacotherapy can enhance the treatment outcomes for PTSD [226]. However, psychotherapy and pharmacotherapy have little effect in patients with refractory PTSD, which is especially common among combat veterans with PTSD [227]. Neuromodulation techniques may be promising treatments for these patients.

Neuromodulation

Several non-invasive neuromodulation technologies, such as electroconvulsive therapy (ECT) and repetitive transcranial magnetic stimulation (rTMS), are used as treatments for severe MDD, but there is no conclusive evidence that they are able to reduce specific symptoms in PTSD [228, 229]. Several studies reported that these neuromodulations can produce effective treatments in patients with refractory depression and co-occurring PTSD [230–232]. Deep brain stimulation (DBS) is an invasive neuromodulation that has been approved to reduce symptoms in movement disorders, such as Parkinson's disease, essential tremor, and

dystonia [233, 234]. In recent years, DBS has also been used to improve psychiatric disorders, particularly obsessive-compulsive disorder (OCD) and treatment-resistant depression (TRD) [235, 236]. Preclinical studies suggest that high frequency stimulation (HFS) delivered at different targets, including the amygdala, ventral striatum, hippocampus, and mPFC, may improve PTSD-like behavior in rodent models [237–241]. These results suggest that DBS is a potential approach for treating refractory PTSD. To date, three patients with refractory PTSD have benefited from DBS. In human clinical research, two male combat veterans with severe PTSD received DBS in BLA, and one female with PTSD received DBS in the mPFC and uncinate fasciculus (Table 4) [242, 243]. After long-term DBS, the CAPS scores were significantly reduced in all three patients, with encouraging follow-up results. Currently, there are 2 ongoing clinical trials of DBS for PTSD: DBS of the amygdala for combat PTSD (NCT02091843) in USA and DBS for treatment refractory PTSD (NCT03416894) in Canada [244]. Though DBS is a promising treatment for PTSD, its effect and mechanism need to be further studied.

Perspectives

Over 70% of people worldwide are exposed to a TE at least once in their lifetime, and approximately 30.5% experience four or more TEs, with an average of 3.2 experienced per person [8]. Presently, TEs include endless armed conflicts, natural disasters, public health emergencies, violent crime, and severe traffic accidents. It is estimated that approximately 10% of individuals will develop PTSD after experiencing a TE, and the global lifetime prevalence of PTSD ranges from 1.3% to 12.2% [10]. The prevalence of PTSD is increasing, particularly during the current COVID-19 pandemic [248]. As PTSD is associated with considerable economic costs and high levels of medical usage, it is important to recognize the consequence of its occurrence. The China Brain Project is aimed for both basic research on neural mechanisms underlying cognition and translational research for the diagnosis and intervention of brain diseases [249]. PTSD, as a severe and heterogenous psychiatric disorder, is in the interest of the China Brain Project.

In recent years, researchers have made great effort in biological studies of PTSD, involving genetic factors, molecular mechanisms, and abnormal neural circuits. However, exposure therapy and SSRIs have limited efficacy in the treatment of patients with PTSD, and new rapid and safe drugs or approaches need to be developed. Though increased knowledge of PTSD is gained from patients and animal models, few translational outcomes are available for treating patients with PTSD. Recent studies suggest that ketamine, MDMA, and DBS are possible promising treatments for patients with PTSD. Patients with PTSD need novel treatments with more effective, safe, and repaid outcomes.

Most importantly, prevention and early intervention are the best approaches for treating PTSD. Prevention might be divided into primary prevention (before the TE) and secondary prevention (after the TE). Avoiding exposure to TEs is an effective way to prevent PTSD, though it is likely impossible to predict the occurrence of TEs. Further, psychosocial training is applicable for particular individuals with a high risk of TE exposure, which can enhance resilience and help individuals reduce stress responses and fear learning after exposure to TEs [250]. Individuals exposed to the TE often present ASD symptoms before the diagnosis of PTSD, during which the development of chronic PTSD can be prevented by secondary

Table 4: Publications about post-traumatic stress disorder patients received deep brain stimulation.

Publications	Patients	Traumatic event	DBS target	Stimulation parameters	Follow-up time	Reductions
Langevin et al. 2016 [242]					8 months	37.8% reduction in CAPS scores
Koek et al. 2017 [245]	1 male	Gulf war	Bilateral BLA	Right side 1.4 V, 60μs, 160 Hz; Left side 0.7 V, 60μs, 160 Hz	15 months	48% reduction in CAPS scores, but hospitalization for depression and suicidality
Koek et al. 2019 [246]					4 years	40% reduction in CAPS scores
Koek et al. 2019 [247]	1 male	Iraq war	Bilateral BLA	1.2 V, 60μs, 130 Hz	7 months	>30% reduction in CAPS scores
Hamani et al. 2020 [243]	1 female	Domestic abuse	Bilateral mPFC and uncinate fasciculus	6.5 mA, 90μs, 130 Hz	6 months	100% reduction in CAPS scores

prevention. Psychotherapies and pharmacotherapies, including propranolol and hydrocortisone, are recommended for early intervention after exposure to TEs [214, 251]. In the future, early diagnosis of PTSD and novel interventions to prevent PTSD are prospective.

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