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Review Article

PTSD: Past, present and future implications for China

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ABSTRACT

There has been a long history since human beings began to realize the existence of post-traumatic symptoms. Posttraumatic stress disorder (PTSD), a diagnostic category adopted in 1980 in the Diagnostic and Statistical Manual of Mental Disorders-III, described typical clusters of psychiatric symptoms occurring after traumatic events. Abundant researches have helped deepen the understanding of PTSD in terms of epidemiological features, biological mechanisms, and treatment options. The prevalence of PTSD in general population ranged from 6.4% to 7.8% and was significantly higher among groups who underwent major public traumatic events. There has been a long way in the studies of animal models and genetic characteristics of PTSD. However, the high comorbidity with other stress-related psychiatric disorders and complexity in the pathogenesis of PTSD hindered the effort to find specific biological targets for PTSD. Neuroimage was widely used to elucidate the underlying neurophysiological mechanisms of PTSD. Functional MRI studies have showed that PTSD was linked to medial prefrontal cortex, anterior cingulate cortex and sub-cortical structures like amygdala and hippocampus, and to explore the functional connectivity among these brain areas which might reveal the possible neurobiological mechanism related to PTSD symptoms. For now, cognitive behavior therapy-based psychotherapy, including combination with adjunctive medication, showed evident treatment effects on PTSD. The emergence of more effective PTSD pharmacotherapies awaits novel biomarkers from further fundamental research. Several natural disasters and emergencies have inevitably increased the possibility of suffering from PTSD in the last two decades, making it critical to strengthen PTSD research in China. To boost PTSD study in China, the following suggestions might be helpful: (1) establishing a national psychological trauma recover project, and (2) exploring the mechanisms of PTSD with joint effort and strengthening the indigenized treatment of PTSD.

Introduction

Since the beginning of the 21st century, natural disasters (e.g., tsunami, earthquake), terrorist attacks (e.g., 9/11 attack), public health emergencies (e.g. Ebola virus, COVID-19) and endless armed conflicts have frequently impacted the life of human beings over the globe.[1–3]

During these events, millions of people underwent traumatic experiences, such as seriously injured, almost losing lives, losing loved ones, witnessing someone's death or injury, and exposed to aversive details in traumatic scenes, etc;[4] some of the victims would develop posttraumatic stress disorder (PTSD) (also known as "the second tsunami"[5]), a mental disorder occurring after traumatic event (TE). Individuals with PTSD suffered from long-lasting physiological and psychological distress, which caused heavy

Abbreviations: PTSD: posttraumatic stress disorder; TE: traumatic event; DSM: Diagnostic and Statistical Manual of Mental Disorders; fMRI: functional magnetic resonance imaging; TSD: transient situational disturbances; WWII: World War II; ICD: International Classification of Diseases; NMDA: N-methyl-D-aspartic acid; HPA: hypothalamic-pituitary-adrenal; SNPs: single nucleotide polymorphisms; GWAS: genome-wide association studies; ACC: anterior cingulate cortex; mPFC: medial prefrontal cortex; CBT: cognitive behavior therapy; EMDR: eye movement desensitization and reprocessing; CPT: cognitive processing therapy; WET: written exposure therapy; BEP: brief eclectic psychotherapy; NET: narrative exposure therapy; SIT: stress inoculation training; PCT: present-centered therapy; IPT: interpersonal psychotherapy; N-PTRP: national psychological trauma recover project; RDoC: research domain criteria.

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burden on mental health.[6] Large and continuous efforts have been made to deepen the understanding of PTSD.[7] Here, we reviewed relevant research results and divided time course into two phases: the first one regarding the past of PTSD (studies before Diagnostic and Statistical Manual of Mental Disorders (DSM)-III), which mainly reviewed the history of studies of posttraumatic stress symptoms, with early treatments of PTSD that provided reference and key enlightenments to current therapies also included in this part; and the second one focusing on the present of PTSD (studies after DMS-III), which exhibited the improvements of researches in modern era in the epidemiology, mechanism (neural basis from functional magnetic resonance imaging (fMRI) studies, animal models and genetic studies), and treatment (coming era of cognitive behavioral therapy) of PTSD. As a summary of the present study, future implications for China, including establishing a national psychological trauma recover project, strengthening the study of mechanisms of PTSD in multiple domains and indigenizing the treatment of PTSD, were discussed.

Before introduction of the past of PTSD, we would first start with the symptoms of PTSD.

According to DSM-5,[8] diagnosis of PTSD requires reference to the following criteria: (1) traumatic experiences like experiencing sexual assault, terrorist attack, serious earthquake, fetal diseases and witness of war, shot death, etc. (premises of PTSD); and (2) presence of psychiatric symptoms of intrusion, avoidance, negative alternation of cognition and mood, and hypervigilance and hyperarousal in the following months and even years. The terms are expressed as follows:

Intrusion: Traumatic experience recurs vividly even in a non-threatened place, accompanied by strong emotions and feelings that were experienced during the TE (e.g., a veteran suddenly lay down and screamed out with pain and fear at home for he thought battle happened at near place after hearing the loud noise outside).

Avoidance: One avoids memories, thoughts, or external reminders (e.g., people and places) of TE (e.g., a car accident survivor avoided to ride or be near an automobile).

Negative alternation of cognition and mood: One tends to think negatively about him/herself towards TE (e.g., "The world is completely dangerous", "It's all my fault"), with negative emotional state (e.g., fear, horror, anger, guilt, or shame). Clinical patients will be lack of positive emotions, interests in significant activity, and ability to attach with others.

Hypervigilance and hyperarousal: One will be easily startled or irritated (e.g., startled by a slight touch on the shoulder), even with self-destructive behavior. There are also problems on concentration and sleep.

Dissociative subtype of PTSD characterized individuals who experience dissociative feelings of detachment from their body, thoughts and surroundings. It is estimated that 13%–30% of individuals with PTSD meet the criteria for the dissociative subtype.[9] PTSD symptoms could persist over decades and increased the suicide attempts,[10,11] accompanied with substance use disorder and impairments in close relationship and social function.[12,13]

Past of PTSD

From tale of Gilgamesh to PTSD

Early records of human's response and experience related to combat trauma could be dated back to the Deuteronomy and tale of Gilgamesh. The first case with chronic posttraumatic symptoms, such as blindness and illusions about a horrible warrior, caused by threat in the battlefield, was recorded in the account of the battle of Marathon by Herodotus (written in 440 B.C.). It is noteworthy that the symptoms which persisted over years were not caused by a physical wound, but by fright and witness of a comrade being killed. There are also vivid descriptions of post-battle psychiatric symptoms in the early poems written by Lucretius (De Rerum Natura) and Shakespeare (Romeo and Juliet, and Henry IV).[14,15]

> After Gilgamesh loses his friend Enkidu, he experiences symptoms of grief, as one may expect. But after this phase of mourning, he races from place to place in panic, realizing that he too must die. This confrontation with death changed his personality.[14]
>
> Sometime she driveth o'er a soldier's neck,
>
> and then dreams he of cutting foreign throats,[14]
>
> ....
>
> Why hast thou lost the fresh blood in thy cheeks;
>
> And given my treasures and my rights of thee;
>
> To thick-eyed musing and curst melancholy[15]

"vent du boulet" syndrome described individuals frightened by the wind of passage of a cannonball. From 1792 to 1815 (during French Revolutionary wars and Napoleonic wars), it was observed that some soldiers collapsed into protracted stupor after shells brushed past, although they were physically unharmed. Derealization and depersonalization could also be induced by the sound of shells. Pinel used the "cardiorespiratory neurosis" to describe the patients shocked by the events and wars of French Revolution. He tracked a case who almost drowned by falling off the horse carriage for 8 years and personality changes (e.g., more nervous and withdrawn) were found in this patient.[14]

The Industrial Revolution and the introduction of steam driven machinery had raised the possibility of civilian trauma and its related posttraumatic symptoms outside the battlefield. On railway collisions, Erichsen (Fig. 1) believed that micro lesions to the head and spine could result in severe disability due to "molecular disarrangement" or anemia of the spinal cord, against those who insisted that emotional shock was the essential cause of hysterical symptoms. From 1866 to 1882, Erichsen's serial works made these types of injuries known as railway spine or railway brain. The organic concept of railway spine became the focus of controversy because the compensations of alleged railway injuries increased after a past law in 1871, Europe. Under the trend of controlling the exaggeration, German physician Hermann Oppenheim postulated "traumatic neurosis" and popularized its use from 1884 to 1889. Charcot argued that post-traumatic symptoms were actually due to hysteria, neurasthenia or hystero-neurasthenia. But Friedmann stated that symptoms such as headache, dizziness, vasomotor instability, and intolerance to alcohol were due to disorder in intracranial circulation.[16]

Da Costa observed "cardiac malady among soldiers" when he was assigned to military hospitals, finding that some of his patients had experienced typical symptoms before enlisting. Then he used the term "irritable heart" to describe this functional disorder. In 1871, Da Costa syndrome were used to describe the soldiers presented with dyspnoea, palpitations, sharp chest pain, fatigue, migraines, diarrhoea, vertigo and insomnia after participation in the American Civil War.[17] From 1864 to 1916, a series labels were used to describe the symptoms that had similar characteristics with Da Costa syndrome, such as "muscular exhaustion of the heart", "effort syndrome", "neurocirculatory asthenia", "disordered action of the

Fig. 1. John Eric Erichsen, 1818–1896 from Evans 2010 at Headache Currents. (Cited from: Evans RW. Persistent post-traumatic headache, postconcussion syndrome, and whiplash injuries: the evidence for a non-traumatic basis with an historical review. Headache. 2010; 50:716–724. http://doi.org/10.1111/j.1526-4610.2010.01645.x).

heart", "soldier's heart", in which respiratory complaints (including breathlessness, with and without effort, and smothering sensations) are almost universal, and palpitation, chest discomfort, dizziness and faintness, and fatigue are common.[18]

During the Russian-Japanese war (1904–1905), the German physician Honigman who served in Red Cross Society of Russia firstly used the term "war neurosis" for what was previously called "combat hysteria" and "combat neurasthenia"; also, he stressed the similarity between these military cases and civilian railway accident cases reported by Oppenheim.[14]

During World War I (WWI), the psychiatrist Gaupp reported that most symptoms of psychiatric patients (e.g., den muteness, deafness, general tremor, inability to stand or walk, episodes of loss of consciousness, and convulsions) were mainly caused by fright and anxiety as a result of explosion of enemy shells and mines, and seeing maimed or dead comrades. French psychiatrist Régis also found that about one fifth of 88 cases of mental disorder showed a physical wound, but all cases encountered fright, emotional shock, and seeing maimed comrades.[14] The term "shell shock", coined by popular usage, was well received among the troops.[18]

In World War II (WWII), Bradley firstly used the term of "exhaustion" as initial diagnosis for all combat psychiatric cases.[19] Kardiner stressed the concomitance of somatic and psychological symptoms and identified traumatic neurosis as a "physioneurosis". Russian scholars described posttraumatic symptoms as "affective shock reactions", which were observed after wartime events, earthquakes, or railway accidents in the form of acute and chronic process.[20] In 1945, the acute "reactions to combat" and delayed "reactions after combat" were used by American psychiatrists in a treatise describing 65 war psychiatric cases. The US Air Force replaced the latter one with euphemism "operational fatigue".[14] A five-year follow-up report named "*Traumatic war neuroses five years later*" provided a nearly exact description of current PTSD symptoms.[21]

In DSM-I, the trauma-related stress disorders were under the category of gross stress reaction, which was replaced by transient situational disturbances (TSD) diagnostic category in DSM-II.[22] During Vietnam War, Burgess and Holmstrom investigated 92 adult female rape survivors, analyzed their patterns of reaction in acute (e.g., impact reactions, somatic reactions, and emotional reactions) and long (e.g., reorganization, motor activity, nightmares and traumatophobia) phases, and identified three types of syndromes (rape trauma syndrome, compounded reactions and silent reaction). The "traumatophobia" coined by Sandor Rado means the phobic reaction to a traumatic situation, such as fear of staying indoors or outdoors, fear of being alone, and fear of crowds.[23] After Vietnam War, almost a quarter of all soldiers from 1964 to 1973 required some form of psychological help. The increasing post-Vietnam syndrome ultimately led to the adoption of PTSD as a diagnostic category in 1980 in DSM-III.[14]

> Intense anxiety, recurrent battle dreams, startle reaction to sudden or loud noises, tension, depression, guilt, and a tendency to sudden, explosive, aggressive reactions … a tendency to avoid people, fear of exposure to any type of criticism, difficulty in making decisions, and various types of sleep disturbances … The threat of annihilation and destruction that was very real and imminent under combat conditions is carried over into civilian life.[21]

Early treatment of PTSD

Forward treatment

During the Russian-Japanese war, casualties were difficult to evacuate over long distance probably due to uncompleted railway construction. Hence, Russian psychiatrists firstly developed forward psychiatric treatment which worked and was considered as the most effective method in succeeding conflicts.[14]

Five key principles for aiding psychiatric casualties

In WWI, psychiatric casualties who were treated in the frontline hospital had a better prognosis than the evacuated ones, with higher possibilities of returning to duty and lower possibilities of chronic disabilities. American physician Salmon summarized the five key principles of forward area treatment as: immediacy, proximity, expectancy, simplicity, and centrality.[24]

> Immediacy meant treating as early as possible, before acute stress was succeeded by a latent period that often heralded the development of chronic symptoms; proximity meant treating the patient near the frontline, within hearing distance of the battle din, instead of evacuating him to the peaceful atmosphere of the rear, which he would, understandably, never wish to leave; expectancy referred to the positive expectation of a prompt cure, which was instilled into the patient by means of a persuasive psychotherapy; simplicity was the use of simple treatment means such as rest, sleep, and a practical psychotherapy that avoided exploring civilian and childhood traumas; finally, centrality was a coherent organization to regulate the flow of psychiatric casualties from the forward area to the rear, and a coherent therapeutic doctrine adopted by all medical personnel.[24]

Immediacy, proximity, and expectancy also became the tenet of military psychiatry in WWII, and continued through Korea War to the Vietnam War when combat psychiatry was confronted with overwhelming mental health needs.[25]

> … takes him to a quiet place, urges him to review traumatic events, reassures him, lets him sleep overnight after a hot meal when possible, recommends medications to the general medical physicians there when appropriate, and then returns the man to duty the next morning.[25]

Electrical treatment

Electrical treatment was probably valued for its efficacy at dealing with motor symptoms such as tremor, paralysis, contractions, limping, or fixed postures. But faradization was criticized by other psychiatrists for being excessively cruel.[26]

Psychotherapy with assistance of drug

The early treatment of PTSD included individual therapy with a psychodynamic stance, “emphasizing the importance of psychoeducation as well as spelling out a role for cognitive interventions, foreshadows several critical elements of current-day trauma-focused psychotherapies”.[15]

The pressure from WWII forced psychiatrists to search time-saving techniques and promotion strategies that help patient to face traumatic memory and to uncondition him/her to it in psychotherapy. Consequently, drug assistance was adopted to alleviate physiology symptoms when facing traumatic episode in three ways:[27]

> (1) use of sedatives to secure rest; (2) use of intravenous barbiturates to promote mental catharsis, thereby assisting in the recall of a suppressed episode; (3) use of drugs acting directly on the autonomic nervous system.[25]

Grinker and Spiegel's treatise described 65 clinical cases under the cathartic treatment by using barbiturates on the reference to psychoanalytical theories.[14] Further, Heath and Sherman proposed that “relived the battle experience while under the influence of sodium pentathol”, which had advantage over ordinary sedation and hastened unconditioning without producing great discomfort when facing traumatic experience.[15]

In vivo exposure therapy

Visio-auditory exposure technique applied during WWII resembled the current *in vivo* exposure which referred to the exposure to the trauma-related situation, but more like a virtual reality-assisted exposure. Short films with sound of battlefield were graded in order of intensity and gradually shown to the participants until reaching the maximum level. After these films, pulses and blood pressures are taken. “This is followed by group discussion with the psychiatrist acting as a moderator… Patients are given simple explanations of the conditioned reflex illustrated by Pavlov's experiments”.[28] Saul et al.[29] conducted this type of treatment by increasing the intensity of the sound of the film, showing good results of extinction of conditioned reflex linked to trauma.

> The second and most fundamental point is gradualness. The showings are given every morning. At first the shades are up, the door is open. The man may even stand in the doorway and merely peek at the screen. He is free to look way or walk out any time. At first the scenes are shown silently. Only gradually is the sound introduced. Day by day the sound is increased until the volume is reached.[29]

Hypnosis

There was an urgent need to shorten the period of time required for the treatment of acute combat reaction due to a relatively high proportion of neuropsychiatric casualties and limited personnel and facilities. Hypnosis was successfully applied in forward hospitals. Kartchner and Korner[30] introduced the hypnosis patterned after Erickson and presented its advantages over narcosynthesis.

> … Under the hypnosis it was possible to control the degree of abreaction … The better a patient understood the factors involved in the production of neurosis, the more rapidly did he gain insight and obtain improvement.[30]

Group therapy

In 1947, Grotjahn[31] introduced his experience of group therapy with 25 enlisted diagnosed as acute sever anxiety states. The therapy consisted of 12 group meetings in 4 weeks.

> My main goal was to secure the emotional participation of the men. Intellectual participation is easy to get and useful as a start, but the real therapy begins only when the emotional issues are brought out.[31]

Kasanin et al.[32] treated 240 veterans of WWII who had been discharged because of neuropsychiatric disabilities with weekly psychotherapy, including group therapy, pentothal, social and environmental “therapy”, and coordination with various community resources. The follow-up study showed that among the 83 respondents, 55% had improved, 38% remained the same, and 6% became worse.

Present of PTSD

In DSM-III, DSM-IV and DSM-IV text revision, there were three core symptom clusters for PTSD: re-experience of trauma (criterion B), persistent avoidance of stimuli associated with the trauma and numbing (criterion C), and persistent symptoms of increased arousal (criterion D). In DSM-5, criterion C were further divided into "persistent avoidance of stimuli associated with the traumatic event" and "marked alterations in arousal and reactivity associated with the traumatic event".[7] Compared to DSM-5, International Classification of Diseases (ICD) defines PTSD in a narrow way by reducing the "non-specific symptoms" that overlap with symptoms of other mental disorders. Only six PTSD symptom items belong to the clusters of intrusion, avoidance, and sense of threat (two for each cluster). In a sample of trauma survivors from China (n = 1060), Cao et al.[33] found that the disagreement rate of diagnosis of probable PTSD between ICD-11 and DSM-5 was relatively high (ICD-11 *vs.* DSM-5: 43.6% (102/234 participants), but there was no significant difference on PTSD's comorbidity of major depressive disorder or generalized anxiety disorder. Six-factor models (the Anhedonia model,[34] the Externalizing Behavior model[35]) have also been proposed. Recent study showed that a seven-factor hybrid model that divided the current DSM-5 criteria into re-experiencing (B1–B5), avoidance (C1–C2), negative affect (D1–D4), anhedonia (D5–D7), externalizing behavior (E1–E2), anxious arousal (E3–E4) and dysphoric arousal (E5–E6) best described the underlying dimensionality of PTSD as defined in the DSM-5.[36]

Epidemiological features of PTSD

TE

Diagnosis of PTSD requires a pre-symptom criterion — exposure to TE. TE was defined as exposure to threatened death, serious injury or sexual violence. Such experience may occur directly or indirectly by witnessing the event, learning of such event happening to a loved one, or repeated confrontation with aversive details of TE (e.g. collecting bodies of the victims of earthquake).[8] TE is common in general populations. The national wide investigation of TE in US (1995) revealed 60.7% of men and 51.2% of women reported at least one TE. Over 15% of the samples had experienced three or more TEs.[37] Terrorist attack (e.g., 9/11 attack), natural disasters (e.g., Indian Ocean tsunami, Wenchuan earthquake), public health emergencies (e.g., Avian influenza and COVID-19) emerged frequently in last two decades, which caused continual waves of TEs in human being over the globe. A general national survey conducted from 2001 to 2012 in 24 countries with a combined sample of 68,894 adults reported that over 70% of respondents reported a TE and 30.5% were exposed to four or more TEs. The prevalence of exposure to any TE varies across countries, which was higher than 80% in the USA, Colombia, Peru and Ukraine. Unexpected death of loved one (31.4%) and witnessed death/dead body/someone hurt (23.7%) rank the first two highest prevalence rates than other TEs. TE exposure also varied on sociodemographic factors including gender, being a student or not, age, education degree, marital status, prior trauma, etc.[38]

Prevalence of PTSD

Earliest investigations found that the prevalence of PTSD in community samples ranged from 1.1% to 12.3%.[39–41] This variance might be mainly caused by different diagnostic tools, the ways of interview conducted, and the age of the participants. The first national wide face-to-face survey (n = 5877) of PTSD in general population showed that the prevalence was 7.8% (DSM-III-R criteria).[37] In 2005, the prevalence was assessed as 6.8% in a national wide subsample by using the DSM-IV criteria (n = 5692).[42] The results from Wave-2 National Epidemiologic Survey on Alcohol and Related Conditions (n = 34,653) in the US reported that the lifetime prevalence of PTSD and partial PTSD (meet Criterion B and endorse at least one symptom each from Criteria C and D in DSM-IV) were respectively 6.4% and 6.6%.[43] A cross-nation survey (n = 51,295) reported that the 12-month PTSD prevalence rate was 1.1% (ranged from 0.2% to 3.8% across countries).[44] Further analysis with expanded samples (n = 68,894) found that the burden of PTSD was 77.7 person-years/100 respondents.[6] The first national wide mental health survey in China (n = 32,552), set up in 2012, reported that the lifetime and 12-month prevalence rate were respectively 0.4% and 0.2%.[45] Regarding the highly exposed population groups, several studies found that 8%–12% first responders (police, firefighters) of 9–11 attack had a probable diagnosis of PTSD within the first 4 years.[46] The estimated prevalence of PTSD in Wenchuan earthquake survivors ranged from 9.4% to 86.2% within one year after the hit.[47] The post-deployment PTSD prevalence was estimated to be 13.2% in operational infantry units deployed to Iraq or Afghanistan.[48]

Comorbidity between PTSD and other disorders

Early investigations found that more than 60% of patients with PTSD are combined with other DSM-III disorders, especially in highly exposed groups (98.8%).[49] History of other psychiatric disorders is associated with increased risk of PTSD.[37] The investigation in the era of DSM-IV found that 61.5% of individuals with PTSD had mood disorders, 59% had anxiety disorders, and 46.6% had substance use problems.[43] It was proposed that this high comorbidity could be partly attributed to the overlap in symptom criteria. For instance, symptoms of diminished interest, restricted range of affect, sleep difficulties and difficulty concentrating are in accordance with symptoms of depression. Irritability, hypervigilance and startle overlap with symptoms of generalized anxiety disorders. Physiological reactivity also occurs in phobia. As see in Fig. 2, it is evident that PTSD has shared genetic and neurobiological underpinnings with other psychiatric disorders such as anxiety disorders and depression. Other studies have found individuals who underwent trauma had higher odds ratios for physical illness such as angina pectoris, heart failure and stroke.[50,51] Cases with four or more TEs had greater functional impairment in domains of work, home maintenance, close relationships and social life.[44]

Risk factors of PTSD

Women were more than twice as likely to have lifetime PTSD as men (10.4% *vs.* 5.0%[37] and 8.6% *vs.* 4.1%[43]). Results from Chinese population showed that the prevalence of 12-month PTSD in two genders were alike, but was based on limited confirmed cases (n = 35).[45] Regarding age, Pietrzak et al.[43] found that age above 65 years had the lowest prevalence of PTSD (12.2%). Age of 45–64 years had the highest prevalence rate (41.3%), followed by 30–44 years (31.8%), and 20–29 years (14.8%). There was a trend that the prevalence rose along with the increase of age but dropped down at the high end. It could be inferred that individuals with PTSD at an older age might have more deteriorated mental and psychical conditions compared to non-affected ones, which might lead to early death in this population. However, this could not be examined by data in early national wide investigations.[37] Compared to married ones, being widowed/separated/divorced was associated with a higher possibility of suffering from PTSD, while never being married had a lower rate. Interestingly, it was reported that being married was a protective factor for encountering TE.[38] Attributes of TE were also related to the possibility of having PTSD, including types, age of onset, persistence, and severity. Physical abuse by a spouse or partner and psychical abuse were common among those PTSD patients experiencing four or more TEs.[44] The investigations

Fig. 2. Cross-disorder genetic relationships for stress-related disorders: the genetic bases for comorbidity. ADHD: attention deficit/hyperactivity disorder; AG: agoraphobia; BPD: bipolar disorder; GAD: generalized anxiety disorder; MDD, major depressive disorder; PD: panic disorder; PTSD: posttraumatic stress disorder; SAD: social anxiety disorder. (Cited from: Smoller JW. The genetics of stress-related disorders: PTSD, depression, and anxiety disorders. Neuropsychopharmacology. 2016; 41:297–319. http://doi.org/10.1038/npp.2015.266).

of PTSD under natural disasters and terrorist attacks found that other factors associated with PTSD were mainly in two areas: living-working condition (social support, occupation, frequent residence changes, family connection) and personality (self-esteem, nervousness, negative coping style).[46,47]

Persistence of PTSD

The symptoms of PTSD can be long-lasting. A retrospective investigation of PTSD patients (n = 459) found that the trend of proportion of recovery was high in the first 12 months, but slowed down in the next 10 years. Although there were significant differences between curves in treated and non-treated groups, the differences became minimal after 72 months (Fig. 3).[42] There was also a lack of decline of PTSD prevalence in those exposed to 9/11 attack. Among the first responders (police officers), there was little change in the first 4 years and even an increase on year 5–6; from year 6–10, the estimated PTSD rate remained stable at 10%.[46] However, studies from Wenchuan earthquake showed a trend of decline of PTSD prevalence, but a relatively high level was still showed at the longest follow-up. There was large variance of PTSD prevalence (86.2%–9.4%) among the affected residents on the early stage after hit (1–3 months). From year 5–8, the rate was estimated at 9.2%–11.8%. There were only repeated cross-sectional studies but lack of longitudinal follow-up studies. Therefore, it is difficult to determine the explicit time course of PTSD in Wenchuan earthquake.[47] In a longitudinal study of 2348 Vietnam veterans across 25 years, 16% of participants reported increased PTSD symptoms and 7.6% showed decreased symptoms. The current war-zone PTSD in male veterans was estimated to be 4.5%–11.2% based on different assessment tools.[52]

Mechanism of PTSD

TE sets the stage for the occurrence of PTSD; and for the development and maintenance of PTSD, researchers had investigated related factors at the cognitive processing, neural basis and gene. Studies using animal models also help to understand the mechanism underlying the occurrence of PTSD.

Cognitive models of PTSD

From the view of learning, a TE survivor with PTSD could acquire Pavlovian fear to any object (CS+) if it used to be related with any danger (US) and caused serious consequences (UR). Thus, several learning and memory model has been proposed to explain the course of PTSD, for example, fear generalization could explain why PTSD would fear stimulus sharing similar features with conditioned danger-cue (such as veterans from Vietnam War would fear ring tone for the bell, because the tone of the bell was related to bomb); reduced fear extinction and inhibition could explain why the symptoms of PTSD was lasting (such as veterans from Vietnam War would show war-fear even if they had returned home, because their ability to inhibit the CS-UR was impaired and fear extinction reduced) (see Lissek and van Meurs for a review).[53]

Except for learning, other cognitive models have also been proposed to explain the development and maintenance of PTSD. In an influential cognitive model raised by Ehlers and Clark (Fig. 4),[54] the authors suggested that PTSD became persistent if a TE survivor appraise the trauma and/or its sequelae in an excessively negative way and if his/her autobiographical memory was characterized by poor elaboration and contextualization, there would be priming effect of strong associative memory and strong perceptual. According to Ehlers and Clark, impaired memory and appraisal leaded to biased processing of current threat and PTSD symptoms like intrusion, high arousal and emotion alternations, and maladaptive strategies to control these symptoms might be effective in short-term; but for the long run, these strategies might have the consequence of solidifying impaired cognitive process and therefore maintaining the disorder.

In Ehlers and Clark's model, appraisal of the trauma and/or its sequelae was a core cognitive process. Individuals with persistent PTSD may overgeneralize from the TE and, as a consequence, perceive daily activities as more serious than they really are (e.g., “I cannot handle these things, bad things will happen to me”). Appraisals of the way one felt or behaved during the TE can also have long-lasting threatening implications. A number of twisted, negative thoughts about the sequelae caused by trauma can aggravate the persistence of PTSD.[55] These include interpretation of one's initial PTSD symptoms, thoughts about other people's reactions in the aftermath of trauma, and appraisal of the consequences that the trauma caused in other life domains, such as seriously body injury with pain and financial problems. Negative changes in emotional response depend on the particular appraisals in PTSD patients. For instance, perceiving potential threat leads to fear (e.g., “The world is too dangerous”) and feeling one breaking rule leads to anger (e.g., “I was not treated fairly”).

Another key element was memory of TE. It was proposed that traumatic memory is poorly elaborated and unable to be integrated into autobiographical memory base on PTSD patients,[56] which explains problematic intentional recall, and perception of current threat without danger. Patients also had strong Stimulus to Stimulus (S–S) and Stimulus to Reaction (S-R) associations for traumatic material, which makes triggering memories of the event and/or emotional responses by associated stimuli even more likely.[57] Strong perceptual priming (a form of implicit memory) also exists in stimulus connected to TE, explaining why cues of trauma are more likely to be noticed.

According to the information-processing theories, fear and anxiety may be caused by different cognitive processes, such as interpretation, memory, and attention.[58] Interpretation is similar with appraisal in Ehlers and Clark's model, thus, interpretation and memory process has been discussed in previous models. Attention

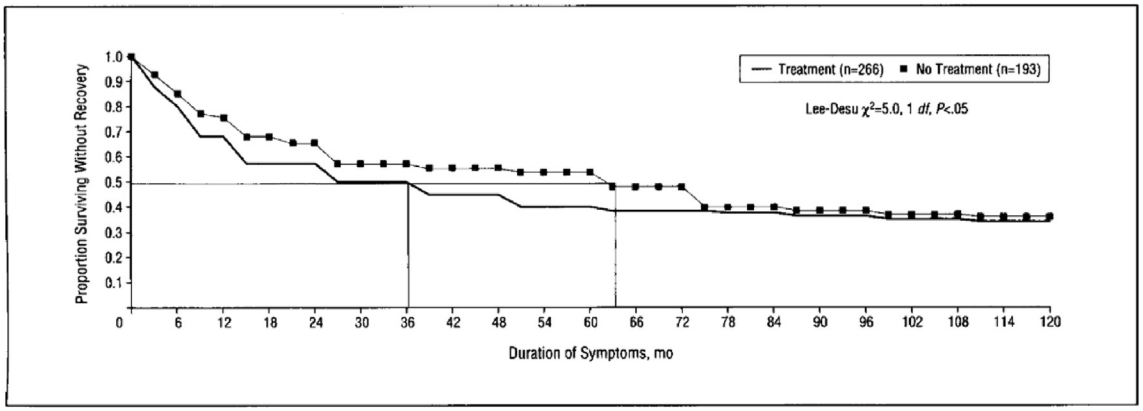

Fig. 3. Survival curves based on duration of symptoms for respondents who did and did not receive treatment for posttraumatic stress disorder (Cited from: Kessler RC, Sonnega A, Bromet E et al. Posttraumatic stress disorder in the National Comorbidity Survey. Arch Gen Psychiatry. 1995; 52:1048–1060. http://doi.org/10.1001/archpsyc.1995.03950240066012).

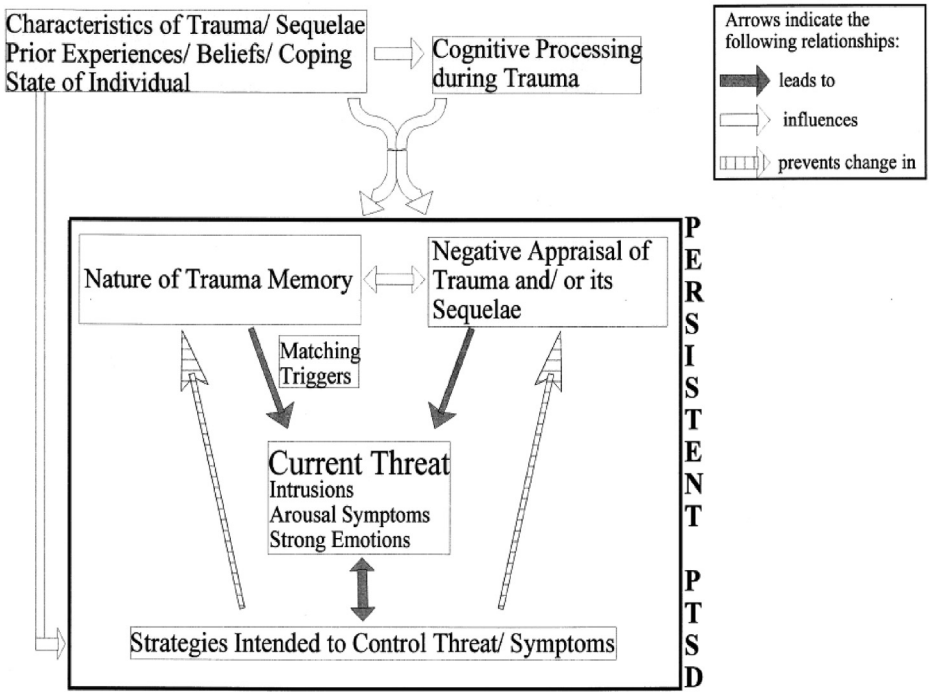

Fig. 4. A cognitive model of PTSD. (Cited from: Ehlers A, Clark DM. A cognitive model of posttraumatic stress disorder. Behav Res Ther. 2000; 38:319–345. http://doi.org/10.1016/s0005-7967(99)00123-0).

is an earlier and more basic cognitive process and several models of anxiety disorder have already seen biased attentional process as a cause as well as a consequence of anxiety (see Van Bockstaele for a review).[59] Accumulating evidence has shown that individuals with PTSD have attentional bias in that they avoid[60] or have difficulty in disengagement from threat stimuli.[61] Modification of attentional bias is an effective way to reduce PTSD symptoms.[62] Future cognitive models might consider early cognitive process in PTSD.

Animal models of PTSD

Building animal models. Animal models were used to explore the underlying physiological and neural mechanisms with the novel treatment target of PTSD in experimental conditions, offering a complementary research modality that supports clinical research. The earliest animal model for trauma-related disorders could be traced back to "learned helplessness" paradigm which was based on Pavlov's "classical conditioning".[63] Mice and rats were animals commonly used for experimental studies. To build an animal model that could fully capture the pathological features of PTSD in human is not a trivial issue. There are mainly three criteria to evaluate the eligibility of PTSD animal models. Face validity means model should have resemblance to PTSD phenomenology. For instance, stimulus should be "traumatic" to animals. Construct validity means model should show the underlying mechanisms of PTSD such as enhanced glucocorticoid negative feedback and exaggerated catecholamine release. Predict validity means treatment effect could be of predictive value, e.g. the treatment effect of later serotonin reuptake inhibitors.[64]

Symptom clusters of PTSD in DSM-5 criteria were corresponded to certain behavioral phenotypes of animal model: intrusion was equivalent to freezing and exaggerated response to mild stressor; avoidance was equivalent to anxiety behavior in the elevated plus

maze; negative alternations in cognitions and mood were corresponded to alteration of spatial memory, reduced social interactions and source consumption, and immobility in forced swim test; alterations in arousal and reactivity could be found in exaggerated startling response to acoustic stimulus, alterations of sleep, increased locomotor activity and aggressive behaviour.[65]

Animal models could be categorized into two main groups by stressors provided by experimenters [66]: physical stressors included time dependent sensitization, foot shock, underwater trauma, restraint stress, single prolonged stress, tail suspension, and chronic stress model which includes 21-day stress model, unpredictable mild stress and mild stress. Social and psychological stressors include predator-based stress, social defeat, social isolation and early life stress. The methods to build these models with their characteristics have been comprehensively reviewed.[65] To date, models with satisfactory face and construct validity were predator-based exposure, single prolonged stress, and foot shock with additional stressors (e.g., restraint, a cold swim and ether anaesthesia).[67] Those models, however, have overlooked the individual differences of the response to trauma. Thus the application of cut-off inclusion/exclusion criteria to behavioral data, which classified individuals as “extreme behavioral response”, “minimal behavioral response”, or “partial behavioral response”, has been suggested to model the variability of the individual's response to the stressors (Fig. 5).[64]

Enlightenments from animal models. The results of studies using animal models have contributed to the understanding of brain circus dysfunction in PTSD. A recent study has found that pre-trauma neural circuit functions in olfactory and stress-related brain areas could predict vulnerability in predator scent model of PTSD.[68] Variation in cortico-amygdala circuitry has been found able to explain the individual differences in the fear extinction which is a tractable and translational assay of PTSD. Several pathways have been identified (Fig. 6).[69] For instance, the pathway of infralimbic cortex via certain intercalated cell masses to medial central amygdala was associated with effective extinction,[70] while the pathway of lateral amygdala to basal amygdala to central amygdala was associated with poor extinction and persistent fear.[71] The most unraveled molecular mechanism in fear extinction was N-methyl-D-aspartic acid (NMDA) receptor which plays a critical role that mediates the glutamatergic signaling and synaptic plasticity.[67,69] There were mainly two forms of avoidance behaviors in rodent animal: freezing (passive avoidance) and active avoidance.[72] The variance of these two behaviors lies in two pathways. The pathway for the former is from lateral amygdala to the central amygdala and then to neurons within the periaqueductal grey in midbrain,[73] while the active avoidance requires signaling from the lateral amygdala to the basal amygdala and then to the shell of the nucleus accumbens.[74] Meanwhile, the infralimbic cortex was also key to active avoidance. In addition, corticotropin-releasing hormone-expressing and somatostatin-expressing subpopulations within the central amygdala neuronal were respectively correlated to the two avoidance.[75] Neurocircuitries that corresponded to each symptom cluster in PTSD-like animal model have been comprehensively reviewed, which were further transferred to the understandings in neural mechanism of PTSD in human.[72]

Another major contribution of the animal model studies is the findings in the molecular biological processes which could explain PTSD pathophysiology and provide new targets for intervention. In the hypothalamic-pituitary-adrenal (HPA) axis, the hippocampal glucocorticoid receptors had a key role in the development of PTSD-like phenotype,[76] and high-dose glucocorticoid administration was companied by c-FOS expression changes in the dorsal CA1 and ventral dentate gyrus regions of hippocampus.[77] Abnormal levels of vmPFC glutamate and hippocampal NMDA receptor have been reported in PTSD animal models such as single prolonged stress.[78] The use of D-cycloserine, the NMDA receptor modulator, could prevent stress-induced changes in fear extinction; and the NMDA receptor antagonist blocked the effects of stress-induced phosphorylated cAMP response element-binding protein-like immunoreactivity in areas implicated in fear behavior.[79] Other findings included the critical role of 5-HT system in the dorsal raphe nucleus, hippocampus, and amygdala, and the effect of noradrenergic transmission on the arousal symptoms and brain-derived neurotrophic factor–TrkB tyrosine kinase signaling in the development of PTSD symptomatology.[67]

Genetics of PTSD

Family and twin studies. Leen-Feldner et al.[80] (reviewing over 10,000 studies that evaluated children of parents with PTSD) concluded that posttraumatic stress symptoms of parents related to negative offspring outcomes, including psychological problems (e.g., internalizing/externalizing) and biological alterations (e.g., HPA-axis function). A recent study showed that hair cortisol concentration level of the refugee mothers could predict the post-traumatic symptom levels of their children.[81] However, a study that investigated a sample of 125 mothers who experienced TE and their children found that maternal PTSD was not directly associated with child's negative psychological outcome. Instead, child's and mother's exposure to family violence was associated with the child's negative outcomes of mental health and experience.[82]

Twin studies could identify genetic effects by comparing disorder concordance rates between genetically identical and non-identical twin pairs. Heritability (denoted h^2) ranges from 0 (no contribution of genetic variation to phenotypic variation) to 100% (phenotypic variation entirely attributable to genetic variation). Previous twin studies found PTSD ($h^2 = 0.28–0.46$) and trauma exposure ($h^2 = 0.20–0.60$) were both heritable and genetically correlated ($rg = 0.76–0.89$).[83–85] A recent study with 3318 male twin pairs (1936 monozygotic and 1382 dizygotic twin pairs) enrolled in Vietnam Era Twin Registry reported that the heritability of PTSD and resilience were 49% and 25%, respectively. PTSD and resilience were negatively correlated and over 50% of this correlation was attributable to a single genetic factor. In addition, a model which defined a broader spectrum of traumatic stress was developed and showed higher heritability.[86]

Candidate gene studies. There were some implications that single nucleotide polymorphisms (SNPs) (TaqIA, rs6277) of the dopamine receptor D2 (*DRD2*) region were associated with chronic PTSD, although relevant studies had inconsistent outcomes. Investigators found a variable number tandem repeat that correlated with the risk of PTSD in those exposed to trauma, separately in dopamine transporter gene (*DAT1*) and dopamine receptor D4 gene (*DRD4*).[87] In the discovery sample of 364 veterans and 127 nonveteran partners, Wolf et al.[88] found that four SNPs (rs2134655, rs201252087, rs4646996, and rs9868039) of dopamine receptor D3 (*DRD3*) gene were associated with PTSD. But in replication samples (601 trauma-exposed African American participants), researchers only found that rs2251177 was nominally associated with PTSD in men.

The most widely studied gene of PTSD in serotonergic system is *SLC6A4* which encodes the serotonin transporter (5-HTT). The short allele (S) and A/G SNP (rs25531, further dividing it into La and Lg) of 5-HTT promoter region (*5-HTTLPR*) were suggested as risk factors for PTSD. But a meta-analysis with 12 studies found that there was no association between *5-HTTLPR* and PTSD ($z = 1.64$, $p = 0.10$). Association only existed between SS genotype and PTSD in high trauma-exposed participants.[89] A prospective cohort study with 133 U.S. Army soldiers reported *5-HTTLPR* had a moderator effect

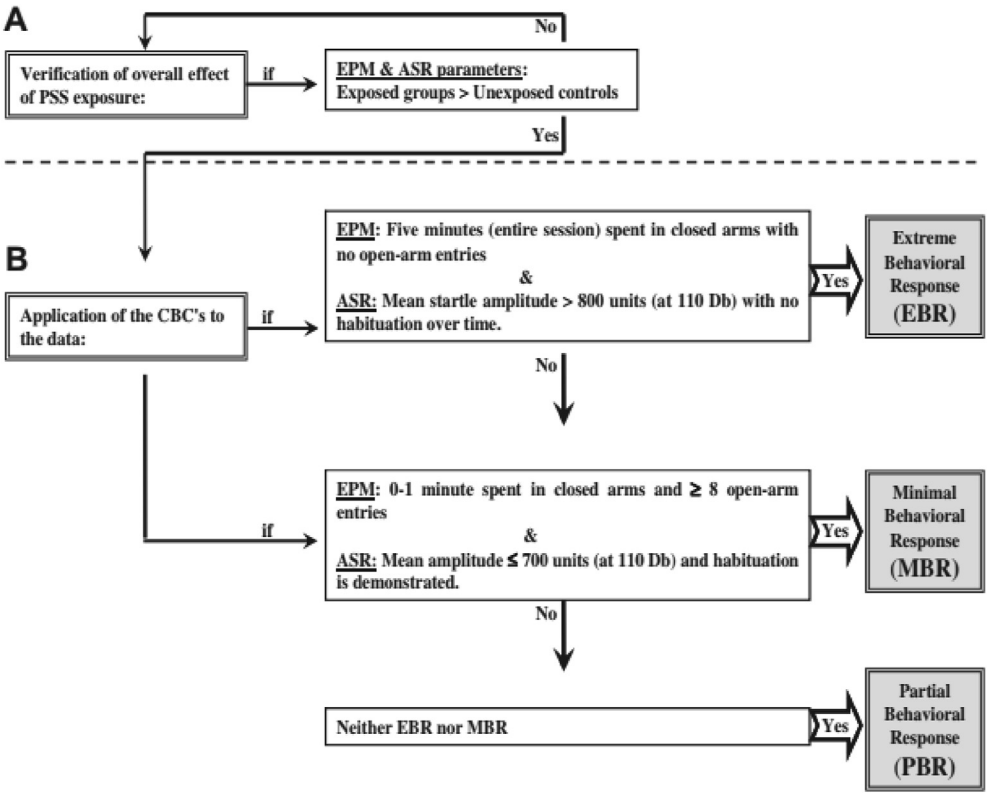

Fig. 5. The cut-off behavioral criteria algorithm. ASR: acoustic startle response; EPM: elevated plus maze (Cited from: Cohen H, Kozlovsky N, Alona C et al. Animal model for PTSD: from clinical concept to translational research. Neuropharmacology. 2012; 62:715–724. http://doi.org/10.1016/j.neuropharm.2011.04.023).

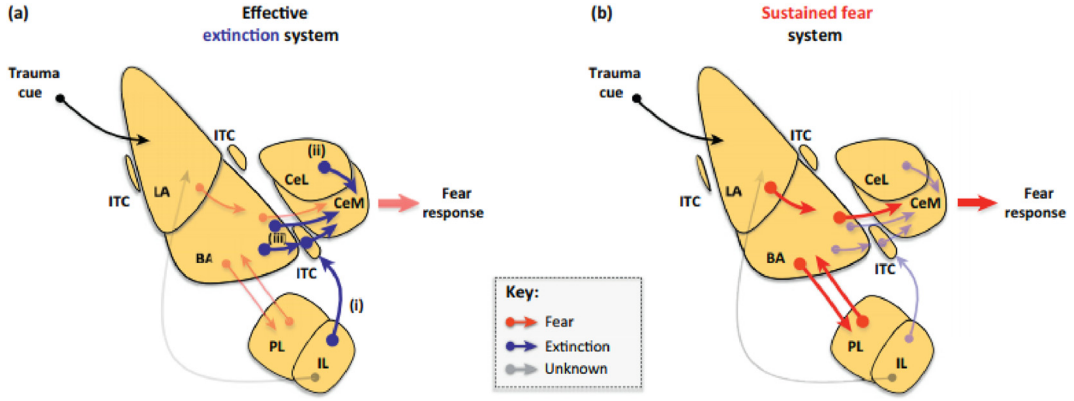

Fig. 6. Pathways associated with effective fear extinction and poor fear extinction. (Cited from: Holmes A, Singewald N. Individual differences in recovery from traumatic fear. Trends Neurosci. 2013; 36:23–31. http://doi.org/10.1016/j.tins.2012.11.003).

between level of war zone stressors and symptoms of emotional disturbance.[90] Gene–environment (G × E) interaction effect of *5-HTTLPR* on PTSD were also found in several samples who experienced childhood and adulthood trauma.[87] Another SNP of serotonergic system is rs6311 in 5-hydroxytryptamine (serotonin) receptor 2A (*5-HT2A*), with G allele increasing the risk of PTSD.[91] New findings suggested that *5-HT2A* gene variants (SNP: rs977003 and rs7322347) significantly moderated the association between PTSD severity and default mode network connectivity.[92]

The gene product of *FKBP5*, FK506 binding protein 51, is a co-chaperone regulator which inhibits the glucocorticoid receptor activity. Previous studies suggested that the role of *FKBP5* could moderate the effect of adversity and trauma on risk of PTSD and was associated with pathologic changes of stress-related disorders in brain.[93,94] Two recent meta-analysis researches have concluded a significant G × E effect of *FKBP5* interacting with trauma exposure on PTSD,[95,96] but the included studies were all with samples of early life time trauma exposure except one study.[97] There were four examined variants including rs1360780, rs3800373, rs9296158, and rs9470080. Zhang et al.[98] investigated HPA axis genes in 1132 Chinese earthquake survivors. G × E effect of *FKBP5* (rs3800373) was correlated with PTSD in women and SNP (rs2267715) in

corticotropin-releasing hormone receptor 2 was significantly associated with PTSD severity. *ADCYAP1R1* encoded the pituitary adenylate cyclase-activating polypeptide receptor PAC-R1. Pituitary adenylate cyclase-activating polypeptide is a hypothalamic neuropeptide which modulates a variety of neurohormones including corticotropin-releasing hormone. One study reported that *ADCYAP1R1* was associated with PTSD in female participants and a SNP (rs2267735) had both main effect and gene-environment interaction with trauma on the risk of PTSD.[99] Further research has found that this SNP was correlated with the expression of PAC-R1 in human and the neural change, which were intimately related to PTSD.[100]

Other investigated genetic polymorphisms in other systems include locus coeruleus/noradrenergic systems (Neuropeptide Y gene, *NPY*; Dopamine betahydroxylase gene, *DBH;* Catechol-O-methyltransferase gene, *COMT*; γ-aminobutyric acid A receptor, α2, gene *GABRA2*), endocannabinoid system (cannabinoid receptor 1 gene, *CNR1*), oxytocin system (oxytocin receptor gene, *OXTR*), opioidergic system (opioid receptor-like 1 gene, *OPRL1*), monoaminergic system (vesicular monoamine transporter 2, encoded by *SLC18A2*), neurotrophins (brain-derived neurotrophic factor gene, *BDNF*), lipoproteins (Apolipoprotein E gene, *APOE*), regulators of G-protein signaling (*RGS2*), and C-reactive protein (encoded by *CRP*).[87,101–106]

Genome-wide association studies (GWAS). There have been inconsistent conclusions about the association between retinoid-related orphan receptor gene and PTSD symptoms, which might be attributed to the heterogeneity among different samples.[101] Based on results from GWAS, Lowe et al.[107] subsequently found that SNP rs893290 of retinoid acid related orphan receptor gene significantly predicted the characteristic of trajectory in individuals with high posttraumatic stress. This SNP also had G × E effect with childhood physical abuse. Other significant association with PTSD identified from GWAS include tolloid-like 1 gene, the cordon-bleu WH2 repeat protein gene, phosphoribosyl transferase domain containing 1 gene (*PRTFDC1*), and lincRNA gene *AC068718.1*. Their effects await further examination in replication samples. Notably, Flaquer et al.[101] examined mitochondrial genome, which functioned in cellular stress responses to external stimulus and was further linked to psychiatric disorders, and found that two variants were significantly associated with PTSD. Some researches could not find genome-wide significant SNP, only with interesting genes that potentially explained the pathology of PTSD.[108,109]

A GWAS with more than 165,000 US veteran identified eight distinct significant regions relevant to intrusive re-experiencing symptoms of PTSD, including three had p values $< 5 \times 10^{-10}$ (*CAMKV, KANSL1, TCF4*).[110] A meta-analysis of GWAS from multi-centers with large samples identified PTSD-related genome-wide significant loci which were specific to ancestry populations and gender, including 2 loci in European (rs34517852 and rs9364611), 1 (rs115539978) in African-ancestry, and three (rs571848662, rs148757321, and rs142174523) in men.[111] Another large-scale GWAS including 11 multiethnic studies found shared genetic risk between PTSD and schizophrenia along with other psychiatric disorders. However, no SNP exceeded genome-wide significance.[112] Genetic characteristics of PTSD in current review are summarized in Table 1.

Neural basis of PTSD

Here, we reviewed the neural basis of PTSD from the perspective of neutral function and studies using fMRI were mainly reviewed.

Resting-state fMRI and PTSD. Resting-state fMRI (rs-fMRI) is a widely used tool to investigate connectivity within brain in the absence of any controlled experimental paradigm. Studies showed that PTSD patients have widespread deficits in both the low-level perceptual and the higher-order cognitive networks. Eighteen chronic Wenchuan earthquake-related PTSD patients and 20 healthy survivors were investigated by rs-fMRI, and the results showed that the deficits of the auditory network and sensory-motor network were related to clinical severity in these earthquake-related PTSD patients.[113] The low-level perceptual network forms the basis for the flashbacks and nightmares which relate to the traumatic moments in PTSD.[114] As for the higher-order cognitive network, anterior cingulate cortex (ACC) was shown to have reduced connectivity with different brain areas in rs-fMRI studies in PTSD.[115–117] In addition, increased activation in hippocampus, amygdala, and reduced activation of the medial prefrontal cortex (mPFC) was significantly observed in PTSD compared to healthy individuals.[118,119] MRI studies showed that smaller hippocampal volume may also be a risk factor for developing PTSD.[120] Diminished medial prefrontal function was a reliable neural marker of PTSD and made contribution to trauma-related resilience and may be a reflection of the self-relevant nature of the traumatic stimuli and signify a deficiency in emotional self-awareness during traumatic memory recall.[113,121] However, such results have not been wholly consistent. For example, some studies have reported the increased activation of amygdala, while others have not.[113] Different sample size, the demographic and clinical characteristics of the patients, and the set of control group may be responsible for the variability of results.

Task-state fMRI and PTSD. Task-state fMRI is a functional MRI-based technique that involves specific tasks. Several recent task-based fMRI studies have highlighted an abnormal activation in specific regions involving the low-level perceptual (auditory, visual, somato-motor) network in PTSD patients.[122,123] Previous task-based neuroimaging in PTSD has provided support for altered activity within different brain region while engaging in Stroop task,[124] oddball emotional task,[125] N-back task,[126,127] and Go/No-Go task,[128,129] Think/No-Think task,[130] etc. Similarly, the degree and region of activation depends on task parameters and subject parameters. One study using fMRI based on the affective Stroop task found that greater PTSD symptom severity scores were associated with increased activation in amygdala, dorsolateral prefrontal, lateral frontal, inferior parietal cortices and dorsomedial frontal cortex/dorsal anterior cingulate cortex (dmFC/dACC).[124] Furthermore, the mPFC, including the perigenual ACC and supramarginal gyrus, has been reported to show reduced activation in PTSD versus controls during emotional tasks (Fig. 7).[67,131,132] Another emotional Stroop task conducted in sexually-abused women with PTSD found that no ACC activation was observed. However, another fMRI study showed lower activation in the rACC region in PTSD patients during a Go/No-Go task.[133] Moreover, the PTSD-related area may not work separately to drive and maintain the symptoms. For example, a recent study showed that compared to non-PTSD, the individuals who suffered from TE and was diagnosed as PTSD showed reduced functional coupling between memory and control system. The impaired brain connectivity might be underlying the failure of suppressing unwanted memory and lead to intrusive symptoms in PTSD.[130] In all, such research has provided neural perspective for the development of PTSD and some new insights into better intervention.

fMRI and PTSD recovery/treatment. Exploration of the underlying brain mechanisms of PTSD can provide theoretical basis for the early intervention, offering measures that can help detect the early onset. To the best of our knowledge, a greater hippocampal volume is associated with PTSD treatment response as MRI results

Table 1
Summary of genes significantly associated with PTSD from current review.

Study type	Findings				
Family study	Parental PTSD and trauma exposure increased the risk of offspring PTSD.				
Twin study	There were moderately heritabilities of PTSD and trauma exposure.				
	System	Gene	Main effect	GXE effect	Related loci/variant
Candidate gene	Dopaminergic system	*DRD2*	✓	–	TaqIA, rs1800497, rs6277
		DAT1	✓	–	VNTR
		DRD4	✓	–	VNTR
		DRD3	✓	–	rs2134655, rs201252087, rs4646996, rs9868039
	Serotonergic system	*SLC6A4*	✓	✓	VNTR, rs4795541, rs25531
		5-HT2A	✓	–	rs6311
	HPA axis	*FKBP5*	–	✓	rs1360780, rs3800373, rs9296158, rs9470080
		CRHR2	✓	–	rs2267715
		CRHR1	–	✓	rs4458044
		ADCYAP1R1	✓	✓	rs2267735
	Other systems	*APOE*	✓	–	APOE 2 allele
		OPRL1	✓	–	rs6010719
		CRP	✓	–	rs1130864
		SLC18A2	✓	–	rs2267735
		RGS2	✓	–	rs4606
GWAS	Nuclear genome	*RORA*	✓	–	rs8042149, rs17303244
		TLL1	✓		rs6812849, rs1503292, rs7691872
		COBL	✓	✓	rs406001, rs382903, rs450378
		AC068718.1 (lincRNA gene)	✓	–	rs10170218
		PRTFDC1	✓	–	rs6482463
	Mitochondria genome	*MT-ATP8*	✓	–	mt8414
		MT-ND5	✓	–	mt12501

DRD2: dopamine receptor D2; DRD3: dopamine receptor D3; DRD4: dopamine receptor D4; DAT1: dopamine transporter 1; SLC6A4: Solute Carrier Family 6, member 4; 5-HT2A: 5-hydroxytryptamine receptor 2A; FKBP5: FK506 binding protein 51; CRHR1: corticotrophin-releasing hormone receptor 1; CRHR2: corticotrophin-releasing hormone receptor 2; ADCYAP1R1: (pituitary) adenylate cyclase activating polypeptide receptor 1; APOE: Apolipoprotein E; OPRL1: opioid receptor-like 1; CRP: C-reactive protein; SLC18A2: Solute Carrier Family 18, member 2; RGS2: regulators of G-protein signaling 2; RORA: receptor related orphan receptor alpha; TLL1: Tolloid-like 1; COBL: cordon-bleu; PRTFDC1: phosphoribosyl transferase domain containing 1; MT-ATP8: mitochondrial ATP synthase subunits 8; mitochondrial NADH (nicotinamide adenine diphosphate hydride) dehydrogenase subunits 5; VNTR: Variable Number Tandem Repeat; G × E: gene-environment interaction.

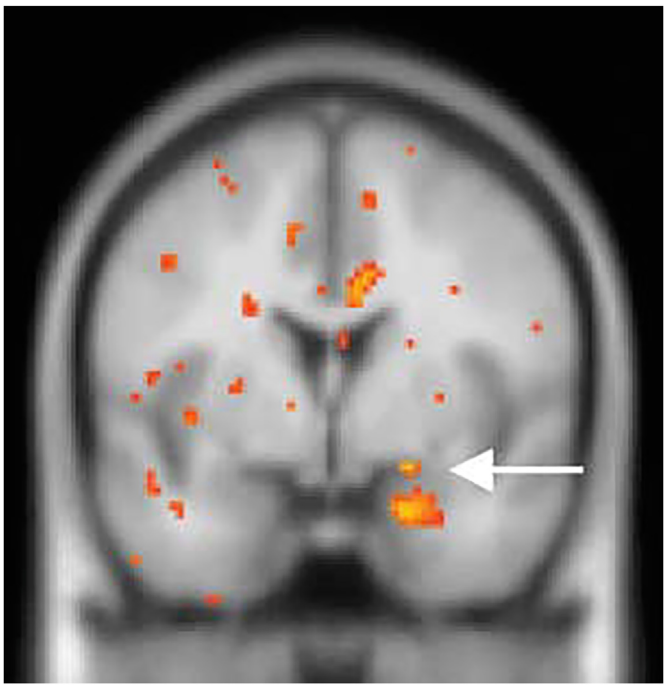

Fig. 7. The fMRI displays activation of fearful *vs.* happy facial expressions in amygdala ($z = 3.14$; Montreal Neurological Institute [MNI] coordinates, +22, +2, −14 [arrow]; and $z = 3.03$; MNI coordinates, +22, 0, −26) that were greater in PTSD group (N = 13) *vs* control groups ($n = 13$) (Cited from: Shin LM, Wright CI, Cannistraro PA et al. A functional magnetic resonance imaging study of amygdala and medial prefrontal cortex responses to overtly presented fearful faces in posttraumatic stress disorder. Arch Gen Psychiatry. 2005; 62:273–281. http://doi.org/10.1001/archpsyc.62.3.273).

indicated.[134] Similarly, PTSD patients underwent rs-fMRI before and after completing 10-session prolonged exposure (PE) in which patients narrated a detailed trauma account (imaginal exposure) and confronted trauma reminders (*in vivo* exposure) to extinguish trauma-related fear responses in one study.[135] Results showed increased resting-state functional connectivity of the basolateral amygdala and centromedial amygdala with the orbitofrontal cortex, and hippocampus-medial prefrontal cortex (mPFC) among patients with PTSD (Fig. 8), indicating that enhanced connectivity of amygdala and hippocampus rsFC with prefrontal cortical regions following PE could underlie improved capacity for inhibition and re-evaluation of threat, and heightened memory encoding and retrieval ability, respectively. Another research explored psychological and brain connectivity changes following trauma-focused cognitive behavior therapy (CBT) and eye movement desensitization and reprocessing (EMDR) treatment in single-episode PTSD patients.[136] It was observed that both EMDR and trauma-focused CBT exerted a beneficial effect on PTSD symptomatology, and both treatments had common dissociable effects on brain connectivity, with the overlap being represented by decreased connectivity between visual cortex and temporal lobe regions in the left hemisphere, and increased connectivity between bilateral superior frontal gyrus and right temporal pole regions. Additionally, the effect of real-time fMRI neurofeedback, which was an emerging approach for treating mood and anxiety disorders, on resting-state functional connectivity in combat veterans with PTSD was investigated, also providing the importance of imaging treatments. What is more, a recent study showed that treatments focused on the memory control system might also be a viable option to complement standard psychological interventions and help patients to gain a better control over their memories during therapy.[130] The importance of fMRI as an imaging biomarker in PTSD recovery will increase unceasingly, and more related studies are warranted.

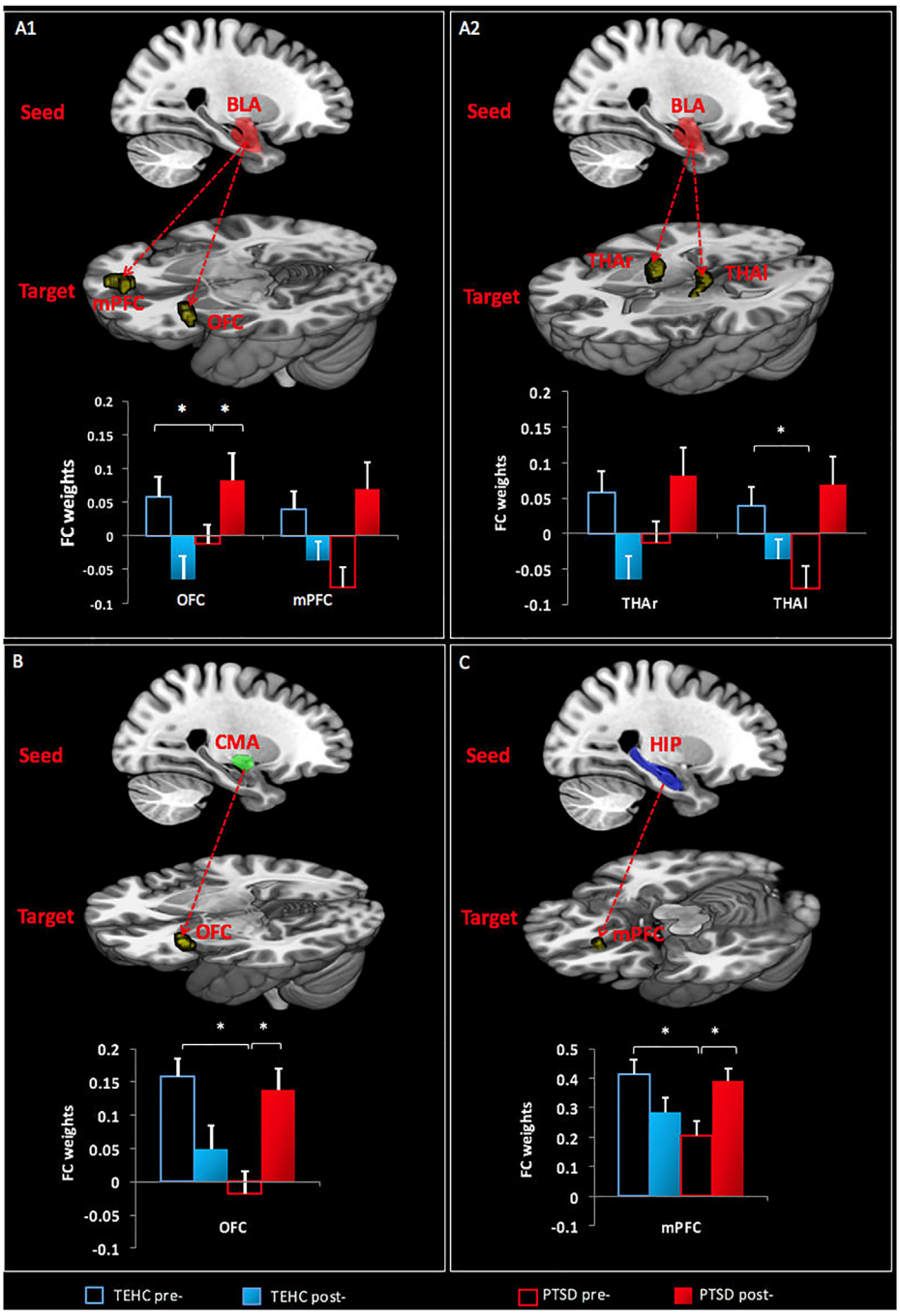

Fig. 8. Group-by-time interactions regarding functional connectivity of: (A1) BLA (red cluster)-mPFC and −OFC; (A2) BLA (red cluster)-THA (right and left); (B) CMA (green cluster)-OFC; and (C) Hippocampus (HIP; blue cluster)-medial Prefrontal cortex (mPFC). Arrows represent rsFC between seeds and target regions (yellow clusters). The y-axis represents rsFC strength. Corrected $p < 0.05$. BLA: basolateral amygdala; CMA: centromedial amygdala; OFC: orbitofrontal cortex, mPFC: hippocampus-medial prefrontal cortex (Cited from: Zhu X, Suarez-Jimenez B, Lazarov A et al. Exposure-based therapy changes amygdala and hippocampus resting-state functional connectivity in patients with posttraumatic stress disorder. Depress Anxiety. 2018; 35:974–984. http://doi.org/10.1002/da.22816).

Current treatment of PTSD

Trauma focused therapy

PE. PE was developed on the exposure technique which has showed confirmed efficacy in veterans and civilians with PTSD, and the emotional process theory has been postulated by Foa and Kozak.[137,138] The theory suggested that exposure could effectively interfere and rebuilt the pathological fear structure (fear response and untruthful idea related to unthreatened stimulus) which are falsely formed under extreme stress in traumatic situation. Treatment starts with psychoeducation, breathing training, the use of subjective distress scale, the development of a fear and avoidance hierarchy for *in vivo* exposures. The primary focus of therapy is on in-session imaginal exposure to the traumatic experience. Patients are asked to recall the traumatic scene and describe it aloud as they are imagining it, using present tense and vivid detail. Homework included breathing practice, reading material for psychoeducation, *in vivo* exposure with recording, listening to the in-session tape (especially the part of imaginal exposure). The efficacy of PE on PTSD has been evidenced by a series of randomized

controlled trial (RCTs) from samples of military, civilian and adolescent PTSD patients,[139,140] and has been recommend by recently published PTSD treatment guidelines.[141,142] Further, telehealth and virtual reality has been incorporated into PE procedure to treat military personnel with PTSD. Treatment outcomes were promising but not superior to standard PE.[143–145] Intensive PE treatment program also yielded a significant treatment effect at posttreatment and follow-up and had a very low dropout rate.[146–148]

Cognitive processing therapy (CPT). CPT, developed by Resick and Schnicke,[149] was also built on emotional processing theory. CPT was originally designed for trauma associated with sexual assault and later extended to other trauma types. Treatment consists of psychoeducation, exposure, and cognitive techniques. Exposure was conducted through writing down the traumatic experience and its meanings. Patients are asked to reread these writings and record impact of the trauma multiple times to formulate new understanding and evaluations of trauma. Cognitive technique targets on the maladaptive appraisals, or "stuck-points" (negative and distorted believes about self and others, e.g., other people cannot be trusted), through cognitive restructuring worksheets, Socratic questioning and discussion, around themes of safety, trust, power/control, esteem, or intimacy.[150] CPT was also an evidence-based treatment of PTSD and recommended as the firstline psychotherapy by treatment guidelines.[141,142] A recent randomized trial including 103 participants found that CPT with augmentation of repetitive transcranial magnetic stimulation showed greater treatment effects on PTSD than CPT alone, both for posttreatment and follow-ups.[151]

EMDR. EMDR characterized by its unique form of exposure, was developed by Shapiro for PTSD treatment. During the sessions, patients are asked to recall the traumatic scene and describe it orally. Meanwhile therapist starts finger movements and tells patients to follow it with eye movements. This process is believed to facilitate the reprocessing of traumatic memory. After the anxiety symptoms triggered by traumatic scene reduced, patients are trained to form new adaptive belief about trauma until they truly believe it.[152] EMDR has also been proved effective on PTSD treatment by randomized trials and recent study reported that there are no significant differences between PE and EMDR except that PE had a higher rate regarding full remission of PTSD.[153] A single-armed trial incorporated EMDR and PE into an intensive program (16 sessions in 8 days) and found significantly declined PTSD symptoms with controlled dropout rate.[146]

Specific cognitive behavior therapies for PTSD. Specific cognitive behavior therapies for PTSD refer to the treatments that adopt techniques from CBT, such as exposure and cognitive re-structing, and target on the symptoms of PTSD, but with distinguished difference on the form of manualized CBT-based therapy such as PE and CPT. Several trials have shown that those therapies had substantial treatment effect on PTSD since the beginning of 21 centuries and guidelines from Department of Veterans Affairs of the U.S. also strongly suggest their use.[141] In 2018, a randomized contrail compared a brief written exposure therapy (WET, 5 sessions) *vs.* CPT (12 sessions) and the results showed that WET was noninferior to CPT on PTSD improvements and had significantly fewer dropouts.[154]

Brief eclectic psychotherapy (BEP). BEP was firstly designed in the Netherlands during 1980s, which contains therapeutic elements derived from diverse psychotherapy such as CBT and psychodynamic treatment. Prior to the main parts of the BEP is the psychoeducation in session one when therapists teach patients knowledge about PTSD and motivate them to engage into therapy. The first phase is imaginal exposure (session 3–6), with the involvement of writing tasks and mementos (things related to TE, to stimulate the imaginal exposure). The second phase is cognitive constructing which also refers to meaning and integration. On the part of farewell, patients are asked to finish a symbolic ritual appropriate to his framework and trauma, meaning that he/she has left his/her TE behind. Previous studies found that the effect size of BEP is comparable to the best forms of CBT on PTSD treatment.[155,156] A study in 2012 directly compared the PTSD treatment efficacy between BEP and EMDR, and found that both treatments were effective but EMDR had a sharper decrease on symptom scores.[157]

Narrative exposure therapy (NET). Similar to PE, NET was developed partly based on the emotional processing theory and learning and fear conditioning. The key component of NET is imaginal exposure which was derived from the testimonial therapy and characterized a chronological narrative of the patient's life. In NET, patients are often asked to create a timeline of his life and acknowledge remarkable points which represent the important event of their lives. Patients are able to relive the traumatic experience by using autobiographical narrative which is finally reorganized into coherent one and wrote down by the therapist, accompanied with the alternation of cognitions related to trauma. It was considered that NET might have advantages on patients with complex traumas, such as asylum seekers and refugees.[158] The results from previous randomized trials have supported the efficacy of NET but with limited number of participants.[159] A recent study enrolling 29 participants found that NET did not achieve better PTSD alleviation than present-centered therapy at posttreatment and differences diminished at follow-up, with a lower dropout rate in NET.[160]

Non-trauma-focused therapy

Stress inoculation training (SIT). SIT which was adapted by Kilpatrick and colleagues from Meichenbaum's anxiety management procedures as firstly adopted to treat rape survivors on post-DSM era.[150] It contains three primary treatment elements: (1) behaviorally based psychoeducation to explain and normalize fear and avoidance behaviors; (2) guided hierarchical *in vivo* exposure assignments to target rape-related phobias (e.g., strange men, darkness); and (3) training in other behavioral and cognitive behavioral coping strategies including breathing exercise, deep muscle relaxation, thoughts stopping, cognitive restructing, self-guided dialogue, cover-modeling, and role playing. Nevertheless, early researches aimed to alleviate fear and anxiety in rape survivors rather than PTSD. SIT showed higher efficacy on PTSD than control group (support counseling or waitlist) but could not outperform some exposure-based therapy such as PE and NET.[161,162]

Mindfulness-based therapy. Mindfulness which grows rapidly in recent years has been known as the purposefully directed awareness of present moment in a non-judgment manner. Structural and functional changes in several brain regions (such as hippocampus, prefrontal cortex, and amygdala) by mindfulness training are considered related to the fear extinction.[163] Mindfulness is also effective at alleviating anxiety and depress symptoms that consistently accompanied with PTSD. Mindfulness-based stress reduction consisting of 8 weeks of 2-h to 2.5-h group sessions has a variety of courses of mindfulness meditation, yoga, discussion about stress and coping, weekly homework assignments and daily mindfulness practice. Mindfulness-based cognitive therapy incorporates the

elements from mindfulness-based stress reduction and CBT.[164] Patients in mantram repetition therapy are asked to choose a mantram (meaningful words that can bring peace, such as My God and My All) and practice silent repetition to interrupt the stress response.[165] Mindfulness or meditation-based therapies are important complementary therapies for PTSD and have been widely used in military.[166–168] A systematic review has report an a statistically significant effect size (small to medium range) of mindfulness-based therapy on PTSD treatment (Fig. 9).[169]

Present-centered therapy (PCT). PCT was a supportive therapy which focuses on the current life problem (e.g., manifestation of PTSD). PCT starts with an introduction and then takes major parts of sessions to discuss about the daily difficulties. The last session includes reviewing the accomplishment during the therapy and making plans for the future. PCT was frequently set as an active control group (to control for nonspecific therapeutic factor so that observed effects of an interested therapy, such as PE or CPT, could be attributed to its specific effects beyond the benefits of good therapy) in PTSD treatment studies and showed significant efficacy. Previous trials have found that PCT was not comparable to the firstline trauma-focused therapy on PTSD treatment, while a recent trial reported that there was no significant difference between PE and PCT.[148,170] Polusny et al.[171] found that the mindfulness-based stress reduction group demonstrated a greater improvement in PTSD symptom severity than PCT but with no significant difference on the loss of PTSD diagnosis.

Interpersonal psychotherapy (IPT). Interpersonal psychotherapy (IPT) focuses on the impact of trauma on individual's interpersonal relationships. IPT emphasizes affective attunement, recognizing, naming, and expressing one's feelings in non-trauma-related interpersonal situations. Therapist guides the patient to realize the relevance between PTSD symptoms and interpersonal problems such as role disputes and transitions. Therapist also helps the patient to have a more realistic assessment of the relationship and encourages the pursuit of satisfying relationships and activities. In the end phase, the patient and therapist will discuss about the treatment gains, future plans and feeling about ending.[172] Schaa et al.[173] used NET and IPT to treat Rwandan with PTSD in a randomized sequence with 26 participants and found no significant group differences between those two psychotherapies at posttreatment, but 71% of IPT participants still fulfilled PTSD criteria (only 25% in NET). Markowitz et al.[174] enrolled 110 (PE: $n = 38$; IPT: $n = 40$) unmedicated patients with PTSD and compared the efficacy between PE and IPT. Results showed that IPT was not inferior to PE, even with a higher response rate (63% *vs.* 47%).

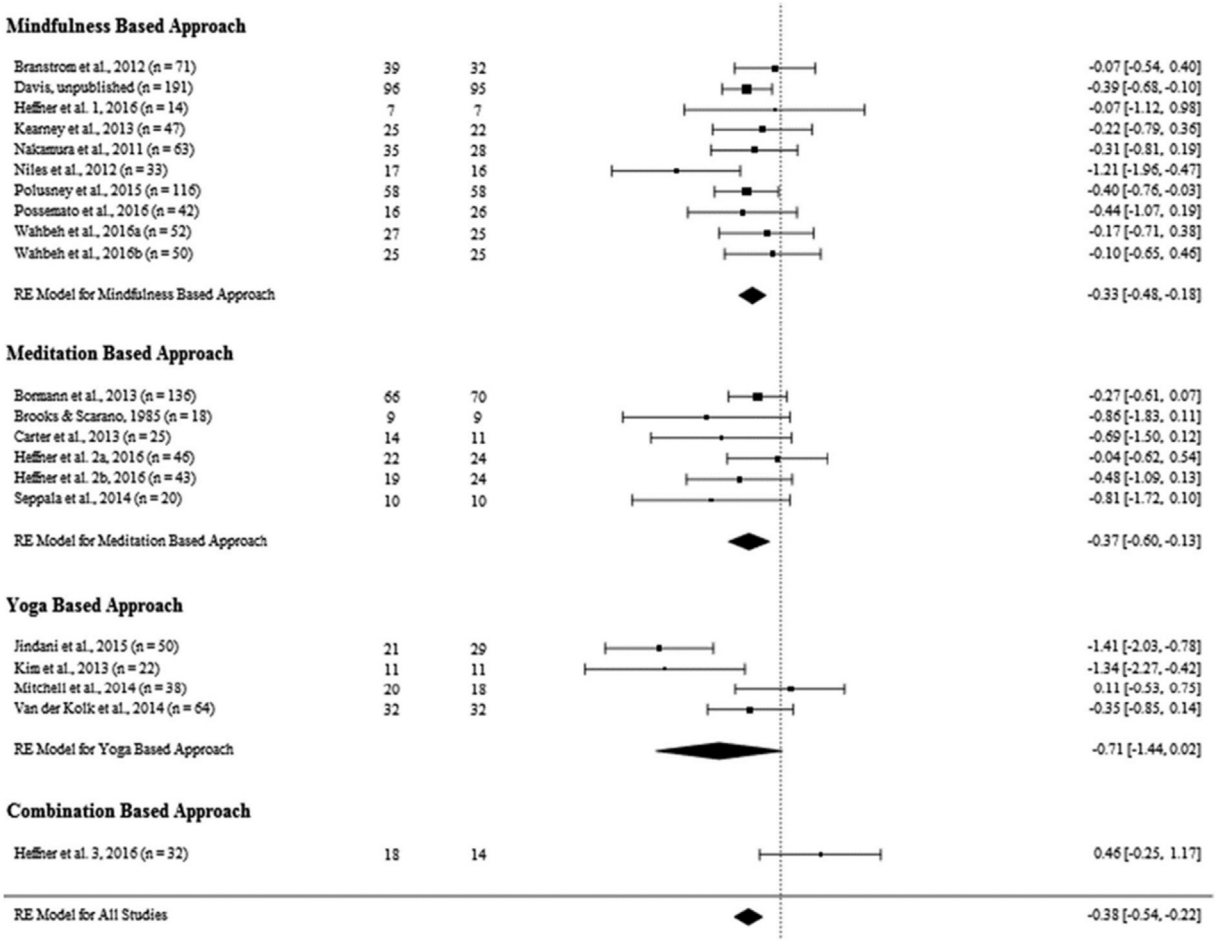

Fig. 9. Forest plot of treatment effect of mindfulness-based therapy (including mindfulness-based stress reduction, mindfulness-based cognitive therapy and mantram repetition therapy) on PTSD (Cited from: Gallegos AM, Crean HF, Pigeon WR et al. Meditation and yoga for posttraumatic stress disorder: A meta-analytic review of randomized controlled trials. Clin Psychol Rev. 2017; 58:115–124. http://doi.org/10.1016/j.cpr.2017.10.004).

Pharmacotherapy

Early pharmacotherapy for PTSD suggests the use of tricyclic antidepressant and monoamine oxidase inhibitors but their efficacy lacks evidence. Later selective serotonin reuptake inhibitors became the main stream with sertraline and paroxetine being approved by the U.S. Food and Drug Administration for PTSD treatment for confirmed efficacy in large-scale RCTs.[15] Recent trials still support that Sertraline and Paroxetine are efficacious on PTSD but there is less advantage when compared to the firstline trauma-focused psychotherapy (such as PE), especially when considering patients' preferences.[175,176] There is also solid evidence that Venlafaxine had efficacy for PTSD, which is comparable to Sertraline and Paroxetine.[177,178] Majority of previous trials have shown that Fluoxetine is an effective pharmacotherapeutic agent for treating PTSD, especially on arousal and numbing symptom subcategories.[179,180] When compared to EMDR, Fluoxetine has less improvements on PTSD and depression symptoms.[181]

Early randomized trial has found that Prazosin was effective on reducing PTSD symptoms especially in distressing dreams and sleep disturbance.[182] However, a recent study which enrolled 304 participants from VA medical center found that there were no significant differences between Prazosin group and placebo group in the change of PTSD symptoms and sleep quality,[183] which was similar to the results from other former studies.[184,185] Recent study found that oxytocin had preventive and treatment effect of PTSD,[186] enhanced the empathy and emotion regulation of PTSD patients,[187,188] and related to brain process which was beneficial for the readjustment, such as enhancing neural processing of monetary reward and loss,[189] or dampening amygdala reactivity towards emotional stimulus.[190]

Emerging effective agents have been explored since the beginning of 21st century. Nabilone, a synthetic cannabinoid, is effective at reducing symptoms of recurring and distressing dream in PTSD patients.[191] McAllister et al.[192] reported patients with a history of PTSD, traumatic brain injury, or both conditions who were treated in Methylphenidate (a stimulant that augments cerebral dopaminergic and noradrenergic function) group had significant lower PTSD symptom scores than placebo group, along with greater improvements cognitive complaints and postconcussive. Ganaxolone is a synthetic 3β-methylated derivative of allopregnanolone and GABAergic neuroactive steroid. One RCT compared its efficacy of PTSD treatment with placebo and found that there was no significant difference between groups, which might be due to underdosing.[193] Large number of evidences support the role of neuropeptide Y in the regulation of stress and anxiety-related behaviors. Sayed et al.[194] found that neuropeptide Y was well tolerated and a higher dose was associated with a greater improvement of PTSD symptoms. Intravenous Ketamine has been proved to have significant treatment effect on PTSD and be well-tolerated, but results from long-term follow-ups were lacked.[195] N-acetylcysteine was also effective on alleviating PTSD symptoms in a relatively small sample ($n = 35$).[196]

Psychopharmacotherapy

The combination of psychotherapy and pharmacotherapy were considered to achieve the maximized treatment effect on PTSD. Early studies have reported that PE combined with selective serotonin reuptake inhibitors (Sertraline and Paroxetine) had advantages over monotherapy in short term,[197,198] but recent studies with larger samples found that there was no significant superiority in this combined therapy.[176,199] However, Sertraline combined with another CBT, seeking safety, yielded a significantly larger long-term treatment effect than seeking safety plus placebo in PTSD patients with alcohol use disorders.[200] Zhou et al.[201] found that the PE combined with pharmacotherapy had generally significantly lower posttreatment PTSD symptom severity than PE alone. PTSD patients with substance dependence were treated via PE with drug assistance, such as Naltrexone or Varenicline.[202,203] The 3,4,-methylenedioxmethamphetamine, the acute effects of which has euphoria, increased extroversion and empathic social interaction, could facilitate reprocessing of traumatic memory in exposure without patients overwhelmed by negative emotions elicited by memories, but needs to be used under careful supervision.[204] Recent trials have supported that the 3,4,-methylenedioxmethamphetamine with adjunctive psychotherapy is effective and tolerated in reducing PTSD symptoms.[205,206] A systematic review using individual participant data found that D-cycloserine was associated with a small augmentation effect on exposure-based therapy on patients with anxiety, obsessive-compulsive, and PTSD.[207] However, when focusing on PTSD specifically, recent studies showed that D-cycloserine did not enhance the overall treatment effect when combined with exposure therapy, but had a higher response rate and might be effective at those who had severer PTSD symptoms.[208–210] While Alprazolam might have better adjunctive effect than D-cycloserine on treating PTSD veterans with virtual reality exposure therapy.[209] Trauma reactivation therapy could achieve better efficacy in PTSD patients when combined with pre-activation of propranolol, a beta-adrenergic blocker which played a role of blocking the reconsolidation of traumatic memory.[211] Yohimbine HCl (an alpha-2 adrenergic receptor antagonist) was associated with facilitated fear extinction in animal and humans. A pilot randomized trial found that Yohimbine augmentation to PE reduced the objective subjective arousal during exposure in treatment responders, but did not promote the improvement of PTSD symptoms compared to PE alone.[212] The treatment effect sizes of PTSD in various therapies from current review are summarized in Table 2.[139,170,213–217]

Treatment guidelines for PTSD.

1. Department of Veterans Affairs/Department of Defense (VA/DOD). VA/DOD Clinical Practice Guideline for the Management of Posttraumatic Stress Disorder and Acute Stress Disorder (version 3.0). 2017 (https://www.healthquality.va.gov/guidelines/MH/ptsd/).
2. American Psychological Association (APA). APA Clinical Practice Guideline for the Treatment of PTSD. 2017 (http://www.apa.org/ptsd-guideline).
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7. Institute of Medicine. Treatment of PTSD: Assessment of the evidence. The National Academies Press, Washington, DC. 2007.

Table 2
Treatment effect size of PTSD in various therapies from current review.

Type	Therapy	Treatment effect size
Trauma-focused psychotherapy	Prolonged exposure[a]	Hedges' g = 1.08 (posttreatment); 0.68 (follow-up)
	Cognitive processing therapy[b]	Hedges' g = 1.24 (posttreatment); 0.90 (follow-up)
	Eye movement desensitization reprocessing[c]	SMD = 1.40
	Brief eclectic psychotherapy	Not available
	Narrative exposure therapy[c]	SMD = 1.31
Non-trauma-focused psychotherapy	Stress inoculation training[d]	SMD = 1.26 (posttreatment); 0.40 (follow-up)
	Mindfulness-based therapy[e]	Hedges' g = 0.44
	Present-Centered Therapy[f]	SMD = 0.84
	Interpersonal Psychotherapy[d]	SMD = 0.15 (posttreatment); 0.25 (follow-up)
Pharmacotherapy	Sertraline[c]	SMD = 0.20
	Paroxetine[c]	SMD = 0.44
	Fluoxetine[c]	SMD = 0.28
	Venlafaxine[d]	SMD = 0.32–1.78
Psychopharmacotherapy	MDMA assisted psychotherapy[g]	Hedges' g = 1.17

Effect size chose meta-analytic data of therapy *vs.* control or randomized control trials. Positive value meansthe therapy performed better than control.
PTSD: post-traumatic stress disorder; SMD: standardized mean difference.
[a] From Powers et al., 2015.
[b] From Asmundson et al., 2019.
[c] From Forman-Hoffman et al., 2018.
[d] From Lee et al., 2016.
[e] From Hopwood and Schutte 2017.
[f] From Belsher et al., 2019.
[g] From Amoroso and Workman 2016.

Future implications for China

There is some debate that symptoms of PTSD might vary in different countries. For instance, special symptoms with culture characteristics have been found in Latinos, indicating that culture might has an influence on PTSD symptoms and lead to various prevalence rates in difference countries.[218] However, in a comprehensive review of culture differences in PTSD, the authors concluded that evidence showing cross-cultural validity of diagnosis of PTSD in DSM-5 was substantial.[219] Also, according to ICD-11, the widely used diagnostic criteria in China, traumatic experiences is also the premise of PTSD and in line with DSM-5, PTSD is characterized by re-experience of trauma, hyperarousal and avoidance. However, the new diagnosis of complex PTSD (CPTSD) is added in ICD-11. Except for the above three symptoms, CPTSD also shows the symptoms of negative alternations in cognitions and mood and conflicting relationships.[220] ICD-11 distinguishes CPTSD from PTSD, however, there is large overlap between the two subtypes.

Both in DSM-5 and ICD-11, and both in China and western countries, PTSD is a serious mental disorder that could affect patients' social adaption and health. However, in China, relatively little attention has been paid to PTSD and the understanding of the disorder is poor. In order to move forward, national-level projects focusing trauma recovery, exploring mechanisms in depth and to indigenize PTSD treatment should be considered.

Establishing a national psychological trauma recover project (N-PTRP)

There was far less investigations and experimental studies of PTSD in China before 2008 when major earthquake hit Wenchuan, Sichuan. The emerge of natural disasters and emergencies (NDE, e.g., epidemics, earthquakes) made it urgent to strengthen the study of psychotraumatology. However, up to now, there is still a lack of any currently available database documenting posttraumatic stress symptom/PTSD in China. In the past two decades, there were very few studies systematically investigating the prevalence of PTSD in general population after the occurrence of major public trauma. The number of studies with a follow-up more than 2 years was limited, with relatively small sample sizes. The scattered and repeated cross-sectional studies were not enough to precisely describe the prevalence and trajectory of PTSD in China under the influence of NDE. Moreover, it is unknown if those who developed PTSD after NDE received effective treatment for rehabilitation. To address this issue in the future, N-PTRP under the support of the nation needs to be built to include the individuals who experience NDE for further assessment of posttraumatic mental health, long-term follow-up, psychological intervention, and provide shared database for research.

N-PTRP will mainly fill the gap of large-scale and longtime longitudinal study of PTSD in China. Learning from the trauma research program from other countries, such as National Vietnam Veterans Longitudinal Study in US, N-PTRP can include clusters of individuals into document immediately after they experiencing major trauma at the same period of time, e.g., earthquake, public health emergencies, and combat or military deployment. Meanwhile, the personal information and history of health status are simultaneously collected. This method is effective on controlling the level of traumatic exposure and the time after experiencing trauma. Long-term follow-up is launched after inclusion to monitor the occurrence and severity of PTSD symptoms, and treatment condition on those participants. The establishment of N-PTRP made it possible to conduct prospective study to answer "why only a proportion of people experiencing trauma finally develop PTSD". Specifically, the comprehensive investigation of N-PTRP allows predesigned high-quality longitudinal studies with large samples to examine the predicative factors of PTSD, such as life-working conditions and personalities, attachment style, sleep quality, and coping methods. Ultimately it is believed that the N-PTRP can provide critical reference for policies and managements of PTSD in China.

Regarding general epidemiological study of PTSD in China, more researches are needed to understand the relationships among comorbidity, PTSD and trauma, and the psychopathological differences caused by direct and indirect experience of trauma. The investigation of prevalence of mental disorders, including PTSD, in China has been conducted across country in large sample.[45] However, there is still need to understand other characteristics related

to PTSD in Chinese population, including TEs, age of onset, and persistence.

Joint effort to explore mechanisms of PTSD

The fundamental research of PTSD can provide key targets for prevention and intervention. However, this type of study in China awaits further promotion. To explore the mechanisms of PTSD under cultural specificity of China, joint efforts are needed to describe pathogenesis in new frame of concept, optimize animal models for experimental studies, find specific genetic loci, and understand neural basis in depth.

Research Domain Criteria (RDoC) concept defines 5 domains of observable behavior and neurobiological measures that have common underlying neurobiological circuits for mental disorders: negative valence, positive valence, cognitive processes, social processes and arousal, which were all intimately related to the pathology of PTSD. Each domain is highly translatable between human and animal models for those domains were analyzable on different levels, from genes and molecules to behaviours.[221] Studies using animal models under RDoC framework can provide better understanding of how alternations of circus were linked maladaptive behaviours of PTSD and complementary guidance of intervention targets.

Future animal models should incorporate individual and sex differences, and risk factors into consideration (Fig. 10). Cut-off behavioral criteria have modeled the situation in human that only a proportion of people exposed to trauma has developed PTSD, but is different from the diagnosis in human that analyzing and comparing the performances of the exposed individuals to normal ones. Behavioral profiling was adapted from cut-off behavioral criteria and on the referring to the performance to a controlled group. An affected individual has to fall out of the defined norm in several parameters, which is approximate to diagnose in human. This method can effectively help researchers to differentiate animals to 'affected' and 'non-affected' group and further investigate the risk and protective factors involved in the response to stressors.[222]

For now, very few genetic variants have been clearly identified for PTSD. GWAS findings from China and other Asian countries are needed to further understand the genetic cross-ethnic differences of PTSD. However, more in-depth research in this field has prospects for clinical translation. First, it is believed that genetic findings can be applicable for early identification of risk factors and improve prevention strategies for PTSD. An important path lies in the exploration of aggregate genetic effects on the vulnerability of PTSD by using polygene risk scores. More comprehensive evaluation should incorporate genetic variants, other biomarkers and environmental factors. Second, genetic studies can provide new targets for pharmacologic treatments. In particular, GWAS will provide proof-of-concept exploration of genetic loci that have therapeutic relevance. Such findings have been reported in other disorders (e.g., *DRD2* of schizophrenia). Although several loci (e.g., *FKBP5*) and pathways (e.g., glucorticoid receptor function) have been identified significantly associated with stress and fear responses in PTSD, the translation of genetic findings to therapeutic strategies for PTSD still await robust genetic associations. Third, genetic findings, combined with individual preference, personal history and other biological indications, can contribute to dividing PTSD patients into etiologically-based subgroups to match the most effective treatment. This "individualized treatment" is helpful to enhance response and remission rate, and reduce dropout rate.[101]

Given the risk of developing PTSD and its main symptoms were related with impaired brain structures or functions, MRI findings must take the knowledge of clinical features and potentially underlying pathophysiology of PTSD into consideration. Future studies could further explore the functional connectivity underlying other symptoms in PTSD. Finding more links between brain imaging and genetic markers in individuals with PTSD is also needed, to understand dysregulated gene pathways that affect neural systems which underlie PTSD in depth.

Strengthening the indigenization on treatment of PTSD

At present, there are limited comparative studies examining the efficacy of evidence-based psychotherapies of PTSD which have been well adapted in Chinese context, e.g., narrative therapy and EMDR.[223,224] However, RCTs studying the difference among PTSD-specified psychotherapy, treatment as usual, and blank control (e.g., waitlist) are still absent. Traditional medicine of China (e.g., acupuncture) has shown its effect on PTSD treatment,[225] but very little is discussed on indigenization of west-born psychotherapies. CBT-based psychotherapy of PTSD has its root in European countries and the U.S. Whether this type of technique is suitable for PTSD treatment in Chinese population still waits further confirmation by solid evidence, such as large-scale randomized trials in Chinese population. Indigenization is indispensable during the process of certain psychotherapy merging into the PTSD treatment in China. Following points might be considered in indigenization (1) the basic setting of a psychotherapy (e.g., number of sessions,

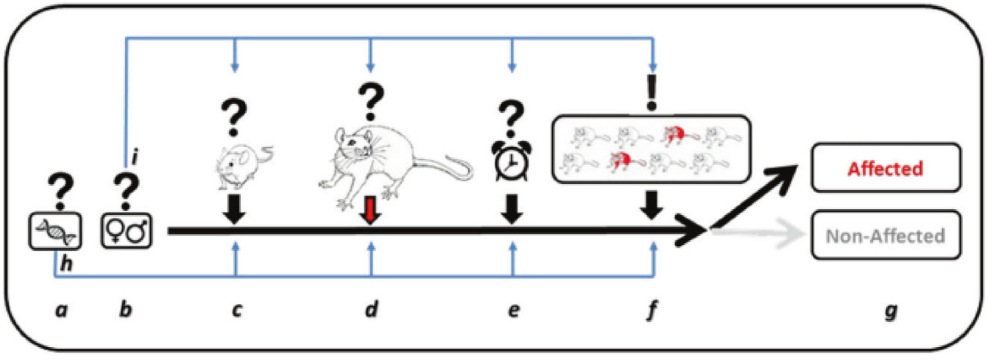

Fig. 10. Several principles should be considered when building PTSD animal model with high ecological validity. (a) heterogeneous genetic background; (b) sex differences; (c) predisposing factors; (d) choice of trauma and its parameters; (e) age of exposure, time after exposure; (f) separating individual animals into affected and non-affected groups by individualized analysis rather than analyzing the averages of exposed and non-exposed groups; (g) studying the drug effect on affected groups rather than averaged severity of specific symptoms. (Cited from: Richter-Levin 2018. Richter-Levin G, Stork O, Schmidt MV. Animal models of PTSD: a challenge to be met. Mol Psychiatry. 2019; 24:1135–1156. http://doi.org/10.1038/s41380-018-0272-5).

time for each session, modules for the therapy): might be modified; (2) the script for the therapies should be translated according to cultural background and experience from practical situations; and (3) materials for patients (e.g., homework) and therapist (e.g., forms for recording) should be transformed into forms catering to habits of native people. Curative elements of effective psychotherapy should be further examined by dismantling trials, finding out which part of evidenced-based therapies is truly effective under specific cultural context. Another option for indigenization is intensive-short-term program which might prosper in the future for its low dropout rate and treatment effect comparable to the spaced programs.[146,147] In addition, when incorporated with virtual-reality technique and exposure therapy, this program might be highly adaptive to military populations. To make psychotherapists more accessible, online treatment through cell phone APP or telehealth software in computer is worth considering in coming years. Medication will still be widely prescribed in majority of PTSD patients. However, large and more trials are in need to confirm the efficacy of pharmacological agent in use, both for novel ones and those believed effective but with insufficient evidence.[15] Future researches in neurobiology of fear extinction and fear learning provide potential targets for development of novel pharmacotherapy for PTSD. Exposure therapy combined with an adjunctive agent which has effects on facilitating fear extinction or/and alleviating physical and psychological distress is expected to be the promising mainstream treatment.

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Ethical statement

Not applicable, as this is a review.

Declaration of competing interest

The authors declare that they have no conflicts of interest.

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