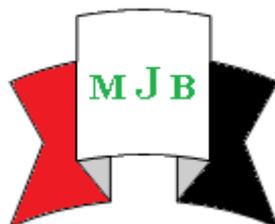# Posttraumatic Stress Disorder: History, Diagnosis and Pathogenesis: A Review Article

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Review Article

Abstract

After 2003, there is almost no day without an explosion or terrorist attacks in Iraq. The effects of repeated explosions extended to cover all aspects of life and places, where the negative effects of destruction, devastation and death continue. Consequently, the psychological and social effects are one of the most important negative effects which remain for long periods as a result of these traumatic experiences, as well as, the experiences of severe psychological stress had an evident impact on most individuals who have experienced such traumatic events. Usually, our communities have no sufficient interest in psychological care for disaster survivor, despite the fact that the psychological effects of disasters have often more impact than organic effects [1].

This review article highlights to the history, diagnosis and pathogenesis of posttraumatic stress disorder (PTSD).

Keyword: posttraumatic stress disorder, diagnosis, pathogenesis, DSM-IV, ICD–10.

اضطراب ما بعد الصدمة: تاريخه وتشخيصه وإمراضيته: مقالة مرجعية

الخلاصة

يكاد لا يمر يوم في العراق بعد عام ٢٠٠٣ دون حصول انفجار أو هجمة ارهابية. ان آثار الانفجارات المتكررة يمتد ليشمل جميع مناحي الحياة، حيث تستمر الآثار السلبية المترتبة على الدمار والخراب والموت. وبالتالي، فإن الآثار النفسية والاجتماعية هي واحدة من اهم الآثار السلبية التي تبقى لفترات طويلة نتيجة لهذه الخبرات الصادمة. وكذلك، كان هنالك تأثير واضح لخبرات الإجهاد النفسي الشديد على معظم الأفراد الذين عانوا من مثل هذه الأحداث الصادمة. وعادة فان مجتمعاتنا لا تهتم بشكل كافي في مجال الرعاية النفسية للناجين من الكوارث، على الرغم من أن الآثار النفسية للكوارث في كثير من الأحيان تكون أكثر تأثيرا من الآثار الجسدية.

يسلط هذا المقال الضوء تاريخ وتشخيص وإمراضيه اضطراب ما بعد الصدمة.

الكلمات المفتاحية: اضطراب ما بعد الصدمة، التشخيص، الامراضية، DSM-IV، ICD–10

Introduction

For an extended period of more than the past century and a half, posttraumatic syndromes have been mentioned in the medical papers under a different of names, involving railway spine, war neurosis, shell shock, soldier's heart, combat fatigue, and rape-trauma syndrome [2]. The case remained as it is until 1980, when the third edition of the Diagnostic and Statistical Manual for Mental Disorders DSM-III [6] introduced posttraumatic stress disorder (PTSD) for the first time among the anxiety disorders in the DSM classification[2].

For extensive understanding of post-traumatic stress disorder, it is

necessary to delve into the history of the discovery, historical connotations and review of literatures.

Unfortunately, the basic experiences in human history are the violence and war. Shay J. mentions that Homer's Iliad includes powerful images of war traumatization and stresses that Achilles feels with sadness, disappointed withdrawal, and feelings of guilt toward deaths of comrades; sometimes, Achilles feels as if he is dead himself and is prompted to berserk-like anger. In poetry and fiction, another examples of how to handle with traumatization, as in the story of Oliver Twist by Charles Dickens, who talk about a boy tolerating to cope with the early death of his parents[7]. Daly RJ illustrates a witness of the Great Fire of London in 1666 who wrote, "How strange that to this very day I cannot sleep at night without great fear of being over-come by fire? And last night I lay awake until almost 2 o'clock in the morning because I could not stop thinking about the fire." It is an exemplary way to describe thought intrusions here [8].

One of the earlier articles published in medical literature on the subject of PTSD is the article of the English surgeon Erichsenin 1866, who attributed obvious psychological abnormalities that follow railway accidents to microtraumas of the spinal cord that later led to the concept of the "railroad spine syndrome." The varied range of symptoms described involves anxiety, tiredness, irritability, defective memory, sleep disturbance, nightmares, perceptual disorders, dizziness, noise in the ear, and limbs pain. Erichsen notices that speech can also be influenced. Later the surgeons Page and Oppenheim contradicted the original connection drawn by Erichsen. Oppenheim with his study on traumatic neurosis is the first one who introduces this term and then placed the main seat

of the disturbance in the cerebrum. The term "trauma," that till then had been utilized exclusively in surgery, was thus introduced into psychiatry. Also, Oppenheim illustrates the frequent involvement of the heart in traumatic neurosis: "The abnormal excitability of the cardiac nervous system is an almost constant symptom of traumatic neurosis, only in few instances is there serious cardiac disease" [3]. Myers [9] and da Costa [10] originate the concept of "irritability of the heart" so normally in soldiers with combat experience that they gave it a term for diagnosis: "irritable heart" or "soldier's heart."

Another term commonly used in German-speaking countries around the turn of the 20th century is "Schreckneurose" which mean (fright neurosis) which was invented by Kraepelin [11], who set the personal shock in the foreground.

In the same time, another area of enhancement concerning trauma etiology began at France, where Charcot [12] and Janet [13] referred to the importance of traumatic experience for the origin of hysterical or dissociative symptoms. Janet [13] gives emphasis to the role of dissociation as the central process in the genesis of posttraumatic symptoms.

During the second half of the 19th century in Paris, an argument was presented Tardieu [14] the specialist in forensic medicine recorded the sexual abuse of children. This argument was rejected by Fournier as "pseudologiaphantastica " in children who falsely accuse their parents of incest.

The term "shell-shock" was presented into the psychiatrist literature in 1915 by the British military psychiatrist C. S. Myers [15]. After discovering that the shell-shock syndrome was found in soldiers who had not contributed in actual fighting,

he discriminated between "shell concussion", in which a neurological disturbance could obviously be recognized as a result of a physical injury, and the actual shell-shock syndrome, in which an emotional shock produced by extreme stress was considered as enough for its causation [16].

At the beginning of the 20th century, natural disasters were dealt with from a psychiatric point of view. Earthquake at Messina (1907) was investigated by Stierlin [17] and found that 25% of the victims underwent from nightmares and sleep disturbance. Also, Prasad [18] describes the emotional problems of the survivors after a disastrous earthquake in India. Adler [19] presents an excellent clinical depiction of posttraumatic consequences in the survived people of the Boston Coconut Grove fire, with emphasis on nightmares, avoidance behavior, and insomnia.

Abram Kardiner [20] in 1941 published a book entitled "The Traumatic Neuroses of War", a book that is considered as an exceptional contribution to the field of psychotraumatology with very detailed clinical descriptions. Kardiner [20] considered the amnesia as a defensive method of the personality as a whole and as a collapse of ego resources. He refers to night-mares with a threat of annihilation or very aggressive dreams. The contraction of the ego according to Kardiner [20] is the key process, it is a, an inhibitory process and represented as the primary symptom, and all others being secondary. Kardiner[20] saw, the sleep disturbances were caused by an increased susceptibility to external stimuli, preventing the patients from falling asleep, and when sleep is accomplished the dream content awakens them. Also, Kardiner [20] differentiated the normal action syndrome from its alteration through

trauma in terms of the symptomatology. This differentiation led to the term physioneurosis, emphasizing the prevalence of physiological changes. At this period, the diagnoses of "combat fatigue" or "combat exhaustion" had been also fairly popular [21].

The first edition of the diagnostic and statistical manual of mental disorders (DSM-I) [22] introduced in 1952 the diagnosis of "gross stress reaction," to describe the combat reactions after World War II and after the Korean War. The diagnosis seemed to be defensible for situations of extreme demands or stress situations which occurred as a consequence of acts of war or natural disasters which were capable of causing abnormal behavior in individuals who had previously been entirely normal.

Many psychiatric reports was published about the consequences of natural disasters during the period that followed, such as the Mississippi tornado of 1953 [23], the sinking of the Andrea Doria of 1957 [24], the Alaska earth-quake of 1962 [25] and the Bristol flood disaster of 1968 [26].

A group of specialists from the American Psychological Association published the second edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-II), at the end of the 1960s [27]. They introduced the name "Transient situational disturbance" instead of "gross stress reaction." In the mid-1970s, the lack in DSM-II of operational criteria, the diagnosis limited reliability, and many missing links led to a commission within the American Psychiatric Association to create more detailed symptom profiles. The sub-commission for "reactive disorders," then came up with the title of "posttraumatic stress disorder" as published in the DSM-III in 1980 [28].

They were described as specified diagnostic criteria. In third revised edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-III-R) in 1987 [29], special classes of traumatization were described.

At Geneva, the tenth revision of the International Classification of Diseases (ICD-10) of World Health Organization (WHO) in 1991, under mental and behavioral disorders (including disorders of psychological development) introduced the clinical descriptions and diagnostic guidelines of PTSD [30].

More work was done, and more precise descriptions of the diagnosis of PTSD were listed in the fourth edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) in 1994 [31].

Diagnosis of PTSD

Nowadays, there are two types of diagnosis criteria; DSM-IV [31] and ICD-10 [30]. In both ICD–10 and DSM–IV, the diagnostic criteria for PTSD require that the person has been exposed to "a stressful event or situation of exceptionally threatening or catastrophic nature likely to cause pervasive distress in almost everyone" (according to ICD–10) and eliciting a response involving "intense fear, helplessness or horror" (according to DSM–IV) [32].

DSM-IV [31] categorized the criteria into six criterion (A-F), criterion A includes the expose to a traumatic event in which both A1 and A2 criterions were present. Criterion A1 involves "the person experienced, witnessed, or was confronted with an event or events that involved actual or threatened death or serious injury, or a threat to the physical integrity of self or others." Criterion A2 includes "the person's response involved intense fear, helplessness, or horror." Criterion A2 followed by the note "In children,

this may be expressed instead by disorganized or agitated behavior."

Criterion B involves "the traumatic event is persistently re-experienced in one (or more) of the following ways:
1. Recurrent and intrusive distressing recollections of the event, including images, thoughts, or perceptions.
Note: In young children, repetitive play may occur in which themes or aspects of the trauma are expressed.
2. Recurrent distressing dreams of the event.
Note: In children, there may be frightening dreams without recognizable content.
3. Acting or feeling as if the traumatic event were recurring (includes a sense of reliving the experience, illusions, hallucinations, and dissociative flashback episodes, including those that occur on awakening or when intoxicated).
Note: In young children, trauma-specific reenactment may occur.
4. Intense psychological distress at exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event.
5. Physiological reactivity on exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event."

Criterion C involves "persistent avoidance of stimuli associated with the trauma and numbing of general responsiveness (not present before the trauma), as indicated by three (or more) of the following:
1. Efforts to avoid thoughts, feelings, or conversations associated with the trauma.
2. Efforts to avoid activities, places, or people that arouse recollections of the trauma.
3. Inability to recall an important aspect of the trauma.
4. Markedly diminished interest or participation in significant activities.

5. Feeling of detachment or estrangement from others.
6. Restricted range of affect (e.g. unable to have loving feelings).
7. Sense of a foreshortened future (e.g., does not expect to have a career, marriage, children, or a normal life span."

Criterion D involves "persistent symptoms of increased arousal (not present before the trauma), as indicated by two (or more) of the following:
1. Difficulty falling or staying asleep.
2. Irritability or outbursts of anger.
3. Difficulty concentrating.
4. Hypervigilance.
5. Exaggerated startle response."

Criterion E includes "duration of disturbance (symptoms in Criteria B, C, and D) is more than 1 month"

Criterion F comprises "the disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.
Specify if: Acute—If duration of symptoms is < 3 months; Chronic—If duration of symptoms is ≥ 3 months
Specify if: With delayed onset—if onset of symptoms is at least 6 months after the stressor."

In Europe, the ICD-10 [30] is more popular [3]. ICD-10 attributes PTSD to "delayed and/or protracted response to a stressful event or situation (either short-or long-lasting) of an exceptionally threatening or catastrophic nature, which is likely to cause pervasive distress in almost anyone (e.g. natural or man-made disaster, combat, serious accident, witnessing the violent death of others, or being the victim of torture, terrorism, rape, or other crime)."

ICD-10 [30] documents PTSD symptoms as "episodes of repeated reliving of the trauma in intrusive memories ("flashbacks") or dreams, occurring against the persisting background of a sense of "numbness"

and emotional blunting, detachment from other people, unresponsiveness to surroundings, anhedonia, and avoidance of activities and situations reminiscent of the trauma. Commonly there is fear and avoidance of cues that remind the sufferer of the original trauma. Rarely, there may be dramatic, acute bursts of fear, panic or aggression, triggered by stimuli arousing a sudden recollection and/or re-enactment of the trauma or of the original reaction to it. There is usually a state of autonomic hyperarousal with hypervigilance, an enhanced startle reaction, and insomnia. Anxiety and depression are commonly associated with the above symptoms and signs, and suicidal ideation is not infrequent. Excessive use of alcohol or drugs may be a complicating factor."

ICD-10 [30] specifies the duration of PTSD symptoms by "the onset follows the trauma with a latency period which may range from a few weeks to months (but rarely exceeds 6 months). The course is fluctuating but recovery can be expected in the majority of cases. In a small proportion of patients the condition may show a chronic course over many years and a transition to an enduring personality change."

Diagnostic guidelines of PTSD in ICD-10 [30] mention that "This disorder should not generally be diagnosed unless there is evidence that it arose within 6 months of a traumatic event of exceptional severity. A "probable" diagnosis might still be possible if the delay between the event and the onset was longer than 6 months, provided that the clinical manifestations are typical and no alternative identification of the disorder (e.g. as an anxiety or obsessive-compulsive disorder or depressive episode) is plausible. In addition to evidence of trauma, there must be a repetitive, intrusive

recollection or re-enactment of the event in memories, daytime imagery, or dreams. Conspicuous emotional detachment, numbing of feeling and avoidance of stimuli that might arouse recollection of the trauma are often present but are not essential for the diagnosis. The autonomic disturbances, mood disorder, and behavioral abnormalities all contribute to the diagnosis but are not of prime importance."

Pathogenesis of PTSD

PTSD symptoms are currently postulated to reflect the pathological changes in neurobiological stress-response systems, or failure of neurobiological systems to recover from, or adapt to extreme stressors [33]. Some of neurobiological investigations in PTSD have concentrating on stress-regulating neuroendocrine systems, such as for instance the hypothalamic-pituitary-adrenal (HPA) and hypothalamic-pituitary- thyroid axes (HPT) [34, 35]. Other studies have focusing on the neurotransmitters and neuropeptides that connect and regulate brain regions involved in fear and stress response [36]. (Figure 1).
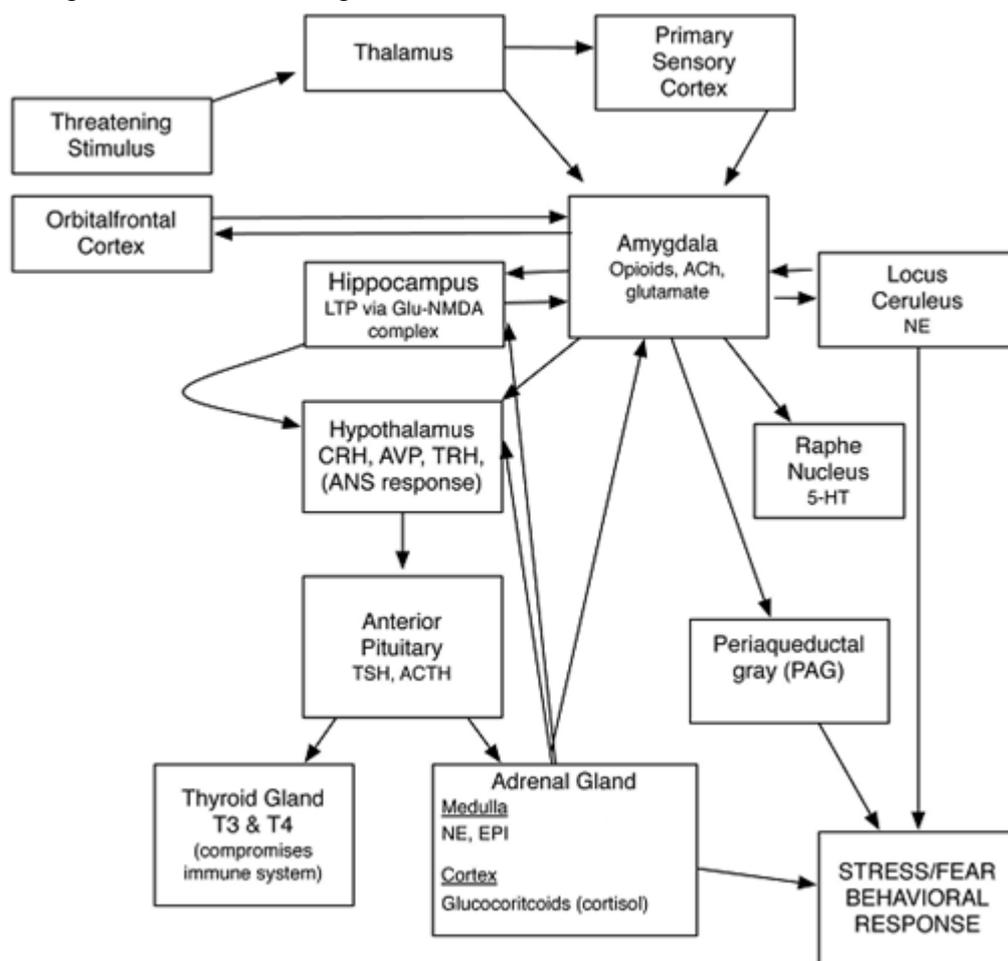

Figure 1 Neurotransmitters and HPA Axis in Stress/Fear Response. [37].

These fear and memory circuits include the prefrontal cortex, hippocampus, amygdala, and brainstem nuclei.[37].

Acute stressors activate the HPA. Neurons in the hypothalamic paraventricular nucleus (PVN) secrete corticotrophic-releasing hormone (CRH) that stimulates the production

of adrenocorticotropic hormone (ACTH) in the pituitary gland, and the release of glucocorticoids such as cortisol from the adrenal cortex. The hippocampus and prefrontal cortex inhibit the HPA axis, whereas the amygdala and brainstem monoamines stimulate the PVN to start this flow. Although acute stressors activate the HPA, the bulk of studies in combat veterans, refugees, and holocaust survivors with PTSD have found decreased blood concentrations of cortisol [37-39]. Studies show that hypocortisolism in PTSD occurs in the context of sustained increases in CRH levels, suggesting increased sensitivity of the HPA axis to negative feedback from cortisol [40, 41]. The majority of PTSD studies have also demonstrated reduced volume of the hippocampus, the brain region responsible for inhibition of the HPA [42]. Together, these findings propose that PTSD may reflect chronic sensitization of the HPA axis to the stressors effects [38]. Recent studies have proven that low cortisol levels during exposure to traumatic stressors predict PTSD development. Since glucocorticoids also interfere with the retrieval of traumatic memories, they may ultimately prove to be effective treatment for PTSD. CRH may similarly play a role in conditioned fear response, increased startle, and hyperarousal; consequently, antagonism of CRF receptors may prove to be an effective approach to PTSD treatment [37].

Catecholaminergic activity increases during stress, and research findings propose that catecholaminergic dysfunction, especially in norepinephrine [1]. Norepinephrine is one of the principle mediators of the stress response in the central nerve system (CNS), and may play a role in the development of specific PTSD symptoms [36].

Noradrenergic cell bodies of the locus ceruleus are responsible for production of the majority of CNS norepinephrine and through extensive branching project to the major brain regions involved in the stress response including the prefrontal cortex, amygdala, hypothalamus, periaqueductal gray, and thalamus [37]. Converging evidence from animal models of fear conditioning and neuromolecular and neuroimaging techniques propose that norepinephrine interacts with CRH to initiate the fight or flight response involving increased heart rate, blood pressure, and skin conductance in the peripheral nervous system and also enhanced arousal and vigilance and facilitated encoding of fear-related memories in the CNS. Glucocorticoids appear to inhibit this response [43]. In the peripheral nervous system, adrenal activation during exposure to stressors results in release of norepinephrine and epinephrine from the adrenal medulla and from sympathetic nerve endings. This hyperactivity may contribute to the core autonomic hyperarousal and re-experiencing symptoms [1]. Hyperactivity of the sympathetic branch of the autonomic nervous system has been proved in various PTSD specimens and is similarly exhibited by patients with PTSD in response to reminders of traumatic experiences [44, 45].

Serotonin or 5-hydroxytryptamine (5-HT) of neurons originating in the dorsal and median raphe nuclei also project to the amygdala, the hippocampus, and the prefrontal cortex, and mediate anxiogenic responses via 5-HT2 receptors, whereas neurons from the median raphe facilitate extinction learning (i.e., the suppression of responses associated with fear memories) via 5-HT1A receptors [46].

VII

Similarly, γ-Aminobutyric acid (GABA) inhibits the CRF/ norepinephrine circuits, mediating fear and stress responses through the inhibitory actions of the GABA$_A$ (an ionotropic receptor and ligand-gated ion channel)/benzodiazepine (BZ) receptor complex. Decreased BZ receptor density or affinity may contribute to the pathophysiology of PTSD in a non-specific manner [47, 48].

Glutamate is the primary excitatory neurotransmitter in the brain. Glutamate binds to a number of excitatory amino acid receptors including the N-methyl-D-aspartate (NMDA) receptor. The glutamate/NMDA receptor system is thought to be critical to the process of long-term potentiation and memory consolidation (including traumatic memories). The partial NMDA receptor antagonist *d*-cycloserine has been shown to facilitate extinction of fear in animal models and in phobic human subjects receiving exposure therapy. Its role in facilitating exposure-based therapies for patients with PTSD is an area of active study [49].

Other neuropeptides implicated in the pathophysiology of PTSD involve neuropeptide Y (NPY) and the endogenous opioids, where opioid system dysfunction is seen in the avoidance/numbing and hyperarousal symptoms of PTSD [1]. Elevated levels of NPY have been demonstrated in combat veterans without PTSD compared with veterans with PTSD [50]. Due to the fact that NPY reduces the release of norepinephrine from sympathetic nerve cells and inhibits CRF/norepinephrine circuits involved in the fear response, it has been proposed that NPY may play a protective role or contribute to recovery from PTSD [51].

Dopamine is involved in control of locomotion, cognition,

affect, and neuroendocrine secretion. Preclinical studies reveal that the mesocortical/mesoprefrontal and mesolimbic systems appear to be the dopaminergic neuronal systems most vulnerable to the effects of stress [52, 53]. Clinical results that support a role for dopamine in the stress response and in PTSD involve the high rates of psychotic symptoms observed among individuals with PTSD [54] and the abnormally high levels of urinary dopamine (in addition to cortisol and norepinephrine) in children with PTSD after years of severe maltreatment [55].

Exposure to trauma can result in immune dysregulation, implicating the immune system in PTSD pathophysiology. Cytokine profiles in PTSD are similar to those observed in clinical chronic psychological stress models, although differences are noted in other immune parameters [56]. The pathophysiology of PTSD also may involve dysfunction of the innate immune inflammatory system. PTSD patients have been found to exhibit high levels of circulating inflammatory markers such as C-reactive protein and interleukin-6 (IL-6), suggesting dysfunction of the innate immune inflammatory system [57]. Similarly, women with PTSD also show increased nuclear factor-κB (NF-κB) pathway activity compared to controls and was positively correlated with PTSD severity. These findings suggest that enhanced inflammatory system activity in participants with PTSD is observable at the level of NF-κB, and that in general decreased immune cell glucocorticoid sensitivity may contribute to increased NF-κB pathway activity [58].

Neuroimaging studies on brain structure and function indicated that the persons with PTSD may have alterations in brain regions central to the neurobiological fear response, specifically, the amygdala and the

hippocampus [59, 60]. These structures are components of the limbic system, the area of the brain involved in the regulation of emotions, memory, and fear. The amygdala plays a role in threat assessment, fear conditioning, and emotional learning, and the hippocampus is implicated in learning, memory consolidation, and contextual processing. PTSD can be likened to a conditioned fear response, whereby an extreme threat becomes paired with a constellation of situational triggers, resulting in an abnormal fear response [1].

The researches of past two decades have focused on the role of specific CNS regions in the development of PTSD. Results of reduced hippocampal volumes have been reported in magnetic resonance imaging (MRI) studies [61-63]. Neuroimaging evidence similarly supposes decreased hippocampal function [64], and flashback intensity has been linked to cerebral blood flow in this region [64]. The amygdala has been implicated in PTSD in findings from MRI and single photon emission computerized tomography (SPECT) studies [66,67]. Functional MRI studies demonstrate alterations in other CNS regions in PTSD, including the anterior cingulate gyrus, the thalamus, and the medial frontal cortex [68-70].

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