Journal of Experimental and Basic Medical Sciences 2024;5(3):214-221

Review

Neurobiological Insights into Post-Traumatic Stress Disorder

Öznur Demirci[1], Oytun Erbaş[1]

ABSTRACT

Post-traumatic stress disorder (PTSD) is a psychiatric condition characterized by dominant feelings of fear and anxiety, affecting memory, attention, mood, and other mental and physiological processes. Post-traumatic stress disorder, which is continuously fueled by psychological and physiological mechanisms, has associated neurobiological markers that are crucial for developing drug treatments. These markers can be detected through neuroimaging studies and the levels of specific pro-inflammatory cytokines. The primary factor creating these effects in PTSD is often related to stress. Therefore, the markers are closely linked to biological mechanisms influenced by stress. Neuroimaging studies have shown changes in the amygdala, hippocampus, ventromedial prefrontal cortex, and anterior cingulate cortex, both psychologically and physiologically. These changes are accompanied by various neurotransmitters released in different brain regions. Understanding the impacts of the disorder on the brain and body is important for developing treatment options. In this review, we have summarized the neurophysiological, neuroanatomical, and neuroendocrine cycles that may offer insights for treatment development.

Keywords: Amygdala, anterior cingulate cortex, hippocampus, trauma, ventromedial prefrontal cortex.

Post-traumatic stress disorder (PTSD) is a psychiatric condition that arises following a traumatic event, leading to excessive, uncontrolled fear and dysfunctional defensive responses in situations associated with the trauma.[1]

From a pathophysiological perspective, higher levels of cytokines such as interleukin-1 beta (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-alpha have been noted in the development and symptoms of PTSD, contributing to inflammation.[2]

Additionally, the excess of these proinflammatory cytokines affects the hypothalamic-pituitary-adrenal (HPA) axis, a region associated with acute stress, and the autonomic nervous system (ANS), which governs automatic behaviors. In the HPA region, the intense stress experienced during the PTSD process leads to irregular activation. This dysregulation in the HPA axis disrupts the negative feedback mechanism, meaning the body continuously attempts to balance the stress. As a result, this condition leads to irregular glucocorticoid levels.[3,4] However, one of the outcomes is a low cortisol level. The low cortisol contributes to the inflammation sustained by the HPA axis, as cortisol typically has an anti-inflammatory effect.[2,5,6]

On the other hand, PTSD symptoms also affect the ANS, which consists of the sympathetic and parasympathetic systems. Within the context of PTSD, heightened stress and anxiety trigger continuous activation of the sympathetic nervous system (SNS), which is responsible for the body's fight-or-flight response.[7] Additionally, the heart rate variability (HRV) mechanism plays a role in this process. The heart rate variability reflects the coordinated functioning of the sympathetic and parasympathetic systems in regulating heart rate. One effect of PTSD is increased sympathetic system activation, which raises heart rate. This results in a low HRV due to the instability in heart rhythm. Consequently, ANS struggles to balance sympathetic activation with parasympathetic activation, leading to further difficulty in regulating stress responses.[8-14]

[1]ERBAS Institute of Experimental Medicine, Illinois, USA & Gebze, Türkiye

Correspondence: Öznur Demirci. Institute of Experimental Medicine, 41470 Gebze-Kocaeli, Türkiye

E-mail: odemirci0646@gmail.com

Cite this article as: Demirci Ö, Erbaş O. Neurobiological Insights into Post-Traumatic Stress Disorder. JEB Med Sci 2024;5(3):214-221.

doi: 10.5606/jebms.2024.1095

Received : June 15, 2024
Accepted : June 21, 2024
Published online : August 29, 2024

At this point, we can also explain the brain regions involved in psychological stress in PTSD. First, the process of PTSD can be defined as a form of emotional and behavioral learning in terms of its development. In this context, we can discuss the effects on the amygdala, hippocampus, ventromedial prefrontal cortex (vmPFC), and anterior cingulate cortex (ACC).[1]

Amygdala

Due to the amygdala's role as the region where emotions, particularly fear, are represented, there is increased activity in the amygdala in the symptoms of PTSD.[15,16] In individuals with PTSD, it has been found that there is excessively high amygdala activity in response to both trauma-related stimuli and normal fear-inducing stimuli.[17,18] On the other hand, it is also believed that high amygdala activity is associated with inflammation.[19]

Ventromedial Prefrontal Cortex

The ventromedial prefrontal cortex exhibits low activity in the presence of PTSD, while its high activity has been found to have a preventive effect against PTSD. Therefore, it can be identified as a biomarker for PTSD.[20,21] During the development phase of PTSD, the vmPFC is highly active in fear learning. However, as PTSD symptoms become more pronounced over time, the activity of the vmPFC decreases.[22,23]

Finally, it is believed that the varying levels of vmPFC activity in PTSD are also related to inflammation, similar to the activity observed in the amygdala.[24]

Anterior Cingulate Cortex

The anterior cingulate cortex, which is associated with emotional evaluation and threat perception, shows increased activity in the persistence of PTSD and plays a role in fear responses.[25-27] Therefore, the increase in activity of ACC, particularly the dorsal anterior cingulate cortex, is a sustaining factor for PTSD.[28,29]

Additionally, it has been found that the increased activity of the ACC and amygdala has a positive correlation with dysregulated inflammatory cytokine levels.[30,31]

It can be inferred that in PTSD, there is high activation in regions associated with emotional experience and expression, while regions representing emotional regulation show relatively lower or dysregulated activation. In relation to this condition, it can be easily inferred that unregulated emotions also affect memory.

Hippocampus

The hippocampus, known as the center of memory, also encompasses emotional memory.[32] In relation to PTSD, it is known that stress can lead to memory recall issues. In terms of the hippocampus, this situation results in a decrease in the activity of neurogenesis, which refers to the formation of new neurons that can occur throughout life in the hippocampus.[33,34]

In PTSD, the consequences of this result in problems with memory and, consequently, learning difficulties.[35,36]

THE HPA AXIS AND INFLAMMATION IN POST-TRAUMATIC STRESS DISORDER

The hypothalamic-pituitary-adrenal axis is a system that is affected in its functioning during stress. As mentioned above, this system is a physiological stress mechanism and is thought to explain the symptoms of PTSD.[37]

The effect of stress in this axis begins with the production of corticotropin-releasing hormone (CRH). Following the arrival of CRH at the anterior pituitary, the secretion of adrenocorticotropic hormone begins. Meanwhile, the arrival of CRH at the adrenal gland alters the balance of glucocorticoid hormones. The continuity of this cycle results in an increase in the amount of glucocorticoids, which leads to inflammation.[38,39] However, as mentioned above, the level of cortisol, a glucocorticoid, decreases in this context.[2,5,6]

The decrease in cortisol levels may indirectly contribute to inflammation because cortisol can reduce SNS activity. Since increased SNS activity can lead to inflammation, cortisol typically has a protective effect; however, due to low cortisol levels in PTSD, inflammation cannot be effectively suppressed. The increase in SNS activity begins with the release of catecholamines from the SNS region stimulated by the secretion of CRH in the HPA axis.[2]

Among these catecholamines, norepinephrine can lead to an increase in the levels of pro-inflammatory cytokines, making the rise in SNS activity a potential cause of inflammation. This is due to the increased stimulation of the β2-adrenergic receptor, which mediates the release of norepinephrine during heightened HPA activation associated with stress. As a result, the levels of pro-inflammatory cytokines such as IL-1β and IL-6 in macrophages increase.[40]

There is research indicating that inflammation is also elevated in other psychiatric disorders that may be associated with stress.[41,42]

In summary, elevated levels of CRH under stress can increase inflammation both through the SNS pathway and by affecting the HPA axis, thereby contributing to heightened inflammation.[2,40] In other words, these two mechanisms are closely related to each other

FINDINGS FROM NEUROIMAGING STUDIES IN POST-TRAUMATIC STRESS DISORDER

In PTSD, the amygdala, hippocampus, and prefrontal cortex, which normally play a coordinated role in effectively coping with fearful and threatening stimuli, are involved in learning and managing fear. Fear learning occurs through classical conditioning. In this process, the unconditional stimulus, which is the fear-inducing stimulus, directly reaches the amygdala and elicits the feeling of fear.[41]

On the other hand, there is a phenomenon that explains the avoidance behavior towards trauma reminders, such as environments and sounds, which is one of the symptoms of PTSD. The environmental context conditioned to the fear-inducing stimulus in the hippocampus, along with external stimuli like sounds, is recorded in declarative memory for retrieval and use when necessary. At this point, it appears that there are strong connections between the amygdala and hippocampus in the context of fear conditioning in PTSD.[42-46]

The prefrontal cortex (PFC) also participates in this cycle, as there is a cognitive background for behaviors related to the expectation of threat and danger. Within this loop, the amygdala activates the ANS following stimulation by the fearful stimulus, and from this point, it reflects on the physiological stress cycle.[41]

In PTSD, the amygdala's excessive activity explains the heightened feelings of fear and reactions, as well as sensitivity to reminder stimuli.[47,48]

Functional Connections Between the Amygdala, Hippocampus, and Prefrontal Cortex in PTSD

Post-traumatic stress disorder is associated with fear learning, which leads to a decrease in hippocampal activity. Although hippocampal activity is involved in the functioning of declarative memory related to fear of objects or situations, other declarative memory activities also decline.[49-51]

It has been found that patients with PTSD exhibit reduced activation in both the right and left hippocampus during recall tests.[52] On the other hand, fear conditioning is also associated with the joint functioning of the amygdala and hippocampus.[41,42]

The prefrontal cortex contributes to PTSD through the different functions of its three distinct regions. The vmPFC is a region that helps regulate emotions mediated by the amygdala. In patients with PTSD, however, the activity of the vmPFC is reduced. As a result, emotional regulation in the amygdala may become more challenging for individuals with PTSD.[53] The other two regions are the dorsolateral prefrontal cortex (dlPFC) and the dorsomedial prefrontal cortex (dmPFC). The dmPFC is heavily involved in fear acquisition and acquired fear responses. Therefore, it may exhibit high activity during the fear-learning phase in patients with PTSD.[54,55] It is believed that the dmPFC is inversely related to behavioral tendencies that lead to emotional expectations in PTSD.[56]

There are also structural changes in the brain caused by PTSD. First, there is a negative correlation between reduced hippocampal volume and PTSD symptoms. This correlation is consistent with the decreased neurogenesis activity in the hippocampus associated with PTSD. Similarly, there is neuronal loss in the amygdala in patients with PTSD. Both regions show lower volumes in individuals with PTSD. These changes in the amygdala and hippocampus are believed to be a result of stress.[57-63]

For the prefrontal cortex, particularly in dlPFC and dmPFC, a reduction in gray matter volume indicative of neuronal loss has been observed. Considering the functions of these regions can help explain the failures in learning processes and emotional regulation seen in patients with PTSD. Additionally, structural changes have been noted in the connections between the vmPFC and amygdala, as well as between the dlPFC and dmPFC. Neuroimaging findings have revealed alterations in white matter volume in the uncinate fasciculus, the connection bundle between the vmPFC and amygdala, in individuals with PTSD. This situation may disrupt the PFC's role in regulating emotions in the amygdala.[41] In line with this finding, patients with PTSD exhibit low vmPFC activation in conjunction with high amygdala activation. Another link between the vmPFC and dmPFC highlights the connection between emotional regulation and learning. One of the disrupted structures in PTSD is

the cingulum bundle that forms this connection. In summary, the damage to the connections in these areas impairs both emotional regulation and learning activities. All of these factors may help explain some of the symptoms of PTSD.[64-66] Finally, the severity of PTSD symptoms and whether they onset in childhood or adulthood can differentiate the structural and functional conditions of these regions.[41,67]

NEUROTRANSMITTERS IN POST-TRAUMATIC STRESS DISORDER

The brain regions and circuits mentioned involve various neurotransmitters. One of these neurotransmitters, triggered by stress through the stimulation of the adrenal gland in the HPA axis in relation to PTSD, is glutamate. Under normal circumstances, glutamate strengthens brain connections and contributes to learning and memory activities. However, the continuous activation of the HPA axis due to post-traumatic stress leads to an excessive increase in glutamate levels.[68] This condition has been found to lead to oxidative stress.[69]

Another catecholamine neurotransmitter is epinephrine, which is released during the processes of the HPA axis and the SNS. Epinephrine causes an increase in heart rate, respiration, and attention levels, putting the body in a state of arousal. The heightened arousal in PTSD patients also explains the symptoms of PTSD. Similarly, norepinephrine, which has a similar effect, is continuously released as a result of SNS activation due to PTSD symptoms, contributing to the state of hypervigilance observed in individuals with PTSD.[68]

Serotonin (5-HT;5-hydroxytryptamine) is a neurotransmitter released to compensate for traumatic stress and has a calming effect on the individual. Due to the chronic stress induced by PTSD, depletion of 5-HT may occur during the course of the disorder. As a result, individuals suffering from PTSD are no longer able to experience relief following traumatic stress.[68,70]

Therefore, it can be said that this contributes to the progression of the disorder. Finally, the change in dopamine in PTSD occurs in the mesocortical region, one of the three areas where dopamine is projected. The stress induced by PTSD leads to elevated levels of dopamine in the medial prefrontal cortex. Considering the effects of dopamine, this appears consistent with symptoms such as hypervigilance and persistent rumination about the traumatic event.[71]

POTENTIAL THERAPEUTIC MECHANISMS FOR POST-TRAUMATIC STRESS DISORDER

The function of the endocannabinoid (eCB) system is linked to the HPA axis, which is related to traumatic stress. This system plays a role in mitigating the effects of excessive stress in PTSD and can potentially prevent the hyperactivity of the HPA axis, thereby reducing outcomes associated with HPA hyperactivity, such as inflammation and glutamate excess.[72]

One of the receptors in the eCB system, cannabinoid receptor type 1 (CB1), is a heteroreceptor and thus can influence the release of other neurotransmitters. However, like many other systems, the eCB system is also disrupted in patients with PTSD. The idea of its potential therapeutic role in PTSD comes from studies suggesting that nightmares and sleep disturbances related to trauma are associated with dysfunction in the eCB system. These studies specifically show that activation of CB1 receptors alleviates sleep and nightmare issues in PTSD patients.[73-75]

Another treatment option is ketamine, a substance that acts as a glutamate receptor antagonist, which may alleviate PTSD symptoms. As mentioned earlier, due to the hyperactivity of the HPA axis, glutamate levels increase, leading to oxidative stress. Ketamine, by acting as a glutamate antagonist, can inhibit the excessive release of glutamate.[76]

Like ketamine, the hormone oxytocin, which has the potential to inhibit HPA axis activation, could also be considered as a treatment option. Oxytocin alleviates learned fear responses that contribute to the development of PTSD, meaning it helps reduce amygdala activity. Intranasal administration of oxytocin has been found to reduce excessive amygdala activation in individuals with PTSD, thereby alleviating symptoms.[77]

Potential Therapeutic Effects of Brain-Derived Neurotrophic Factor

Another potential option that could modify fear learning, which plays a crucial role in the development of PTSD, and induces extinction is related to the presence of brain-derived neurotrophic factor (BDNF), a protein found in the nervous system. Brain-derived neurotrophic factor plays a crucial role in the development, survival, and neurogenesis of the nervous system. Additionally, it plays a role in learning.[78,79]

Brain-derived neurotrophic factor, with this characteristic, also contributes to the activity of the prefrontal cortex, hippocampus, amygdala, and ACC,

all of which are associated with PTSD. Therefore, it is a protein structure that may offer potential for PTSD treatment. Specifically, the receptor for BDNF, tropomyosin-related kinase B (TrkB), plays a crucial role. The function of TrkB in the hippocampus and BDNF levels is important in fear learning. A decrease in BDNF protein levels and TrkB signaling in the hippocampus may lead to memory problems and reduced neurogenesis in individuals with PTSD. Additionally, increasing BDNF connections and using TrkB agonists may help with fear extinction learning by supporting vmPFC activity.[80,81]

In conclusion, PTSD is characterized by issues in learning, memory, emotional response, regulation, and sleep disturbances. It affects the structural and functional properties of regions such as the hippocampus, amygdala, and PFC. Many systems associated with these regions are also directly or indirectly impacted. Among these systems, the HPA axis notably influences neurotransmitter balance and can also increase inflammation. The levels of neurotransmitters such as dopamine, 5-HT, glutamate, and epinephrine change. The SNS, which participates in the stress response alongside the HPA axis, similarly contributes to the cycle by promoting inflammation. Dysregulation of HRV also contributes to SNS dysfunction, creating a vicious cycle. These factors can be considered components of the physiological stress cycle in PTSD. On the other hand, PTSD is also associated with psychological stress and trauma learning. The hippocampus, amygdala, and PFC play significant roles in acquiring fear responses to trauma. Brain-derived neurotrophic factor, which is involved in learning, also contributes to the activity of these regions. However, when PTSD develops, the reduced activity of the PFC and the emergence of learning and memory issues in the hippocampus lead to decreased BDNF levels. Conversely, increasing BDNF levels may help reverse issues related to fear acquisition and memory difficulties in PTSD. Excessive glutamate, resulting from HPA axis hyperactivity, has been suggested to contribute to the formation of psychological stress. This condition may be mitigated by ketamine agonists. Another form of psychological stress involves amygdala hyperactivity, and in this case, oxytocin administration could be a viable option. The eCB system activity may help prevent HPA axis overactivity and the disruption of homeostasis.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding

The authors received no financial support for the research and/or authorship of this article.

REFERENCES

1. Quinones MM, Gallegos AM, Lin FV, Heffner K. Dysregulation of inflammation, neurobiology, and cognitive function in PTSD: an integrative review. Cogn Affect Behav Neurosci. 2020 Jun;20:455-80.
2. Hori H, Kim Y. Inflammation and post-traumatic stress disorder. Psychiatry Clin Neurosci. 2019 Apr;73:143-53.
3. Pan X, Wang Z, Wu X, Wen SW, Liu A. Salivary cortisol in post-traumatic stress disorder: a systematic review and meta-analysis. BMC Psychiatry. 2018 Oct 5;18:324.
4. van Zuiden M, Kavelaars A, Geuze E, Olff M, Heijnen CJ. Predicting PTSD: pre-existing vulnerabilities in glucocorticoid-signaling and implications for preventive interventions. Brain Behav Immun. 2013 May;30:12-21.
5. Coutinho AE, Chapman KE. The anti-inflammatory and immunosuppressive effects of glucocorticoids, recent developments and mechanistic insights. Mol Cell Endocrinol. 2011 Mar 15;335:2-13.
6. Daskalakis NP, Cohen H, Nievergelt CM, Baker DG, Buxbaum JD, Russo SJ, et al. New translational perspectives for blood-based biomarkers of PTSD: From glucocorticoid to immune mediators of stress susceptibility. Exp Neurol. 2016 Oct;284:133-40.
7. Tan G, Dao TK, Farmer L, Sutherland RJ, Gevirtz R. Heart rate variability (HRV) and posttraumatic stress disorder (PTSD): a pilot study. Appl Psychophysiol Biofeedback. 2011 Mar;36:27-35.
8. Kemp AH, Quintana DS, Felmingham KL, Matthews S, Jelinek HF. Depression, comorbid anxiety disorders, and heart rate variability in physically healthy, unmedicated patients: implications for cardiovascular risk. PLoS One. 2012;7:e30777.
9. Lehrer PM, Gevirtz R. Heart rate variability biofeedback: how and why does it work? Front Psychol. 2014 Jul 21;5:756.
10. Thayer JF, Yamamoto SS, Brosschot JF. The relationship of autonomic imbalance, heart rate variability and cardiovascular disease risk factors. Int J Cardiol. 2010 May 28;141:122-31.
11. Bandelow B, Baldwin D, Abelli M, Bolea-Alamanac B, Bourin M, Chamberlain SR, et al. Biological markers for anxiety disorders, OCD and PTSD: A consensus statement. Part II: Neurochemistry, neurophysiology and neurocognition. World J Biol Psychiatry. 2017 Apr;18:162-214.
12. Dennis PA, Watkins LL, Calhoun PS, Oddone A, Sherwood A, Dennis MF, et al. Posttraumatic stress, heart rate variability, and the mediating role of behavioral health risks. Psychosom Med. 2014 Oct;76:629-37.

13. Shah AJ, Lampert R, Goldberg J, Veledar E, Bremner JD, Vaccarino V. Posttraumatic stress disorder and impaired autonomic modulation in male twins. Biol Psychiatry. 2013 Jun 1;73:1103-10.
14. Williamson JB, Porges EC, Lamb DG, Porges SW. Maladaptive autonomic regulation in PTSD accelerates physiological aging. Front Psychol. 2015 Jan 21;5:1571.
15. Hermans EJ, Battaglia FP, Atsak P, de Voogd LD, Fernández G, Roozendaal B. How the amygdala affects emotional memory by altering brain network properties. Neurobiol Learn Mem. 2014 Jul;112:2-16.
16. Linnman C, Zeffiro TA, Pitman RK, Milad MR. An fMRI study of unconditioned responses in post-traumatic stress disorder. Biol Mood Anxiety Disord. 2011 Nov 1;1:8.
17. Rauch SL, van der Kolk BA, Fisler RE, Alpert NM, Orr SP, Savage CR, et al. A symptom provocation study of posttraumatic stress disorder using positron emission tomography and script-driven imagery. Arch Gen Psychiatry. 1996 May;53:380-7.
18. Rauch SL, Whalen PJ, Shin LM, McInerney SC, Macklin ML, Lasko NB, et al. Exaggerated amygdala response to masked facial stimuli in posttraumatic stress disorder: a functional MRI study. Biol Psychiatry. 2000 May 1;47:769-76.
19. Muscatell KA, Dedovic K, Slavich GM, Jarcho MR, Breen EC, Bower JE, et al. Greater amygdala activity and dorsomedial prefrontal-amygdala coupling are associated with enhanced inflammatory responses to stress. Brain Behav Immun. 2015 Jan;43:46-53.
20. Hughes KC, Shin LM. Functional neuroimaging studies of post-traumatic stress disorder. Expert Rev Neurother. 2011 Feb;11:275-85.
21. Kühn S, Gallinat J. Gray matter correlates of posttraumatic stress disorder: a quantitative meta-analysis. Biol Psychiatry. 2013 Jan 1;73:70-4.
22. Brown VM, LaBar KS, Haswell CC, Gold AL; Mid-Atlantic MIRECC Workgroup; McCarthy G, Morey RA. Altered resting-state functional connectivity of basolateral and centromedial amygdala complexes in posttraumatic stress disorder. Neuropsychopharmacology. 2014 Jan;39:351-9.
23. Sripada RK, King AP, Garfinkel SN, Wang X, Sripada CS, Welsh RC, et al. Altered resting-state amygdala functional connectivity in men with posttraumatic stress disorder. J Psychiatry Neurosci. 2012 Jul;37:241-9.
24. Kim YK, Amidfar M, Won E. A review on inflammatory cytokine-induced alterations of the brain as potential neural biomarkers in post-traumatic stress disorder. Prog Neuropsychopharmacol Biol Psychiatry. 2019 Apr 20;91:103-12.
25. Fani N, Jovanovic T, Ely TD, Bradley B, Gutman D, Tone EB, et al. Neural correlates of attention bias to threat in post-traumatic stress disorder. Biol Psychol. 2012 May;90:134-42.
26. Demirci Ö, Erbaş O. Dementia Risk After Traumatic Brain Injury. JEB Med Sci 2023;4:180-6.
27. Tang YY, Ma Y, Fan Y, Feng H, Wang J, Feng S, et al. Central and autonomic nervous system interaction is altered by short-term meditation. Proc Natl Acad Sci U S A. 2009 Jun 2;106:8865-70.
28. Bromis K, Calem M, Reinders AATS, Williams SCR, Kempton MJ. Meta-Analysis of 89 Structural MRI Studies in Posttraumatic Stress Disorder and Comparison With Major Depressive Disorder. Am J Psychiatry. 2018 Oct 1;175:989-98.
29. van Rooij SJ, Kennis M, Vink M, Geuze E. Predicting Treatment Outcome in PTSD: A Longitudinal Functional MRI Study on Trauma-Unrelated Emotional Processing. Neuropsychopharmacology. 2016 Mar;41:1156-65.
30. Muscatell KA, Moieni M, Inagaki TK, Dutcher JM, Jevtic I, Breen EC, et al. Exposure to an inflammatory challenge enhances neural sensitivity to negative and positive social feedback. Brain Behav Immun. 2016 Oct;57:21-29.
31. Slavich GM, Way BM, Eisenberger NI, Taylor SE. Neural sensitivity to social rejection is associated with inflammatory responses to social stress. Proc Natl Acad Sci U S A. 2010 Aug 17;107:14817-22.
32. Dere E, Pause BM, Pietrowsky R. Emotion and episodic memory in neuropsychiatric disorders. Behav Brain Res. 2010 Dec 31;215:162-71.
33. Niibori Y, Yu TS, Epp JR, Akers KG, Josselyn SA, Frankland PW. Suppression of adult neurogenesis impairs population coding of similar contexts in hippocampal CA3 region. Nat Commun. 2012;3:1253.
34. McEwen BS. Stress and hippocampal plasticity. Annu Rev Neurosci. 1999;22:105-22.
35. Levy-Gigi E, Kéri S, Myers CE, Lencovsky Z, Sharvit-Benbaji H, Orr SP, et al. Individuals with posttraumatic stress disorder show a selective deficit in generalization of associative learning. Neuropsychology. 2012 Nov;26:758-67.
36. Vasterling JJ, Duke LM, Brailey K, Constans JI, Allain AN Jr, Sutker PB. Attention, learning, and memory performances and intellectual resources in Vietnam veterans: PTSD and no disorder comparisons. Neuropsychology. 2002 Jan;16:5-14.
37. Engel S, Klusmann H, Laufer S, Kapp C, Schumacher S, Knaevelsrud C. Biological markers in clinical psychological research - A systematic framework applied to HPA axis regulation in PTSD. Compr Psychoneuroendocrinol. 2022 Jun 9;11:100148.
38. Yaprak G, Çini N, Atasoy ÖB, Uyanikgil Y, Erdogan MA, Erbaş O. Administration of low dose intranasal ketamine exerts a neuroprotective effect on whole brain irradiation injury model in wistar rats. Radiat Environ Biophys. 2024 Aug;63:323-36.
39. Çavusoglu T, Erbas O, Karadeniz T, Akdemir O, Acikgoz E, Karadeniz M, et al. Comparison of nephron-protective effects of enalapril and GLP analogues (exenatide) in diabetic nephropathy. Exp Clin Endocrinol Diabetes. 2014 Jun;122:327-33.
40. Tan KS, Nackley AG, Satterfield K, Maixner W, Diatchenko L, Flood PM. Beta2 adrenergic receptor activation stimulates pro-inflammatory cytokine production in macrophages via PKA- and NF-kappaB-independent mechanisms. Cell Signal. 2007 Feb;19:251-60.

41. Harnett NG, Goodman AM, Knight DC. PTSD-related neuroimaging abnormalities in brain function, structure, and biochemistry. Exp Neurol. 2020 Aug;330:113331.
42. Selden NR, Everitt BJ, Jarrard LE, Robbins TW. Complementary roles for the amygdala and hippocampus in aversive conditioning to explicit and contextual cues. Neuroscience. 1991;42:335-50.
43. Harnett NG, Shumen JR, Wagle PA, Wood KH, Wheelock MD, Baños JH, et al. Neural mechanisms of human temporal fear conditioning. Neurobiol Learn Mem. 2016 Dec;136:97-104.
44. Marschner A, Kalisch R, Vervliet B, Vansteenwegen D, Büchel C. Dissociable roles for the hippocampus and the amygdala in human cued versus context fear conditioning. J Neurosci. 2008 Sep 3;28:9030-6.
45. Erbas O, Yilmaz M. Metoprolol and diltiazem ameliorate ziprasidone-induced prolonged corrected QT interval in rats. Toxicol Ind Health. 2015 Dec;31:1152-7.
46. Phillips RG, LeDoux JE. Differential contribution of amygdala and hippocampus to cued and contextual fear conditioning. Behav Neurosci. 1992 Apr;106:274-85.
47. Patel R, Spreng RN, Shin LM, Girard TA. Neurocircuitry models of posttraumatic stress disorder and beyond: a meta-analysis of functional neuroimaging studies. Neurosci Biobehav Rev. 2012 Oct;36:2130-42.
48. Hayes JP, Hayes SM, Mikedis AM. Quantitative meta-analysis of neural activity in posttraumatic stress disorder. Biol Mood Anxiety Disord. 2012 May 18;2:9.
49. Carrión VG, Haas BW, Garrett A, Song S, Reiss AL. Reduced hippocampal activity in youth with posttraumatic stress symptoms: an FMRI study. J Pediatr Psychol. 2010 Jun;35:559-69.
50. Hayes JP, LaBar KS, McCarthy G, Selgrade E, Nasser J, Dolcos F; VISN 6 Mid-Atlantic MIRECC workgroup; Morey RA. Reduced hippocampal and amygdala activity predicts memory distortions for trauma reminders in combat-related PTSD. J Psychiatr Res. 2011 May;45:660-9.
51. Milad MR, Pitman RK, Ellis CB, Gold AL, Shin LM, Lasko NB, et al. Neurobiological basis of failure to recall extinction memory in posttraumatic stress disorder. Biol Psychiatry. 2009 Dec 15;66:1075-82.
52. Carrión VG, Haas BW, Garrett A, Song S, Reiss AL. Reduced hippocampal activity in youth with posttraumatic stress symptoms: an FMRI study. J Pediatr Psychol. 2010 Jun;35:559-69.
53. Motzkin JC, Philippi CL, Wolf RC, Baskaya MK, Koenigs M. Ventromedial prefrontal cortex is critical for the regulation of amygdala activity in humans. Biol Psychiatry. 2015 Feb 1;77:276-84.
54. Milad MR, Pitman RK, Ellis CB, Gold AL, Shin LM, Lasko NB, et al. Neurobiological basis of failure to recall extinction memory in posttraumatic stress disorder. Biol Psychiatry. 2009 Dec 15;66:1075-82.
55. Rougemont-Bücking A, Linnman C, Zeffiro TA, Zeidan MA, Lebron-Milad K, Rodriguez-Romaguera J, et al. Altered processing of contextual information during fear extinction in PTSD: an fMRI study. CNS Neurosci Ther. 2011 Aug;17:227-36.
56. Aupperle RL, Allard CB, Grimes EM, Simmons AN, Flagan T, Behrooznia M, et al. Dorsolateral prefrontal cortex activation during emotional anticipation and neuropsychological performance in posttraumatic stress disorder. Arch Gen Psychiatry. 2012 Apr;69:360-71.
57. Ding J, Han F, Shi Y. Single-prolonged stress induces apoptosis in the amygdala in a rat model of post-traumatic stress disorder. J Psychiatr Res. 2010 Jan;44:48-55.
58. Magariños AM, Verdugo JM, McEwen BS. Chronic stress alters synaptic terminal structure in hippocampus. Proc Natl Acad Sci U S A. 1997 Dec 9;94:14002-8.
59. Vyas A, Mitra R, Shankaranarayana Rao BS, Chattarji S. Chronic stress induces contrasting patterns of dendritic remodeling in hippocampal and amygdaloid neurons. J Neurosci. 2002 Aug 1;22:6810-8.
60. Gilbertson MW, Shenton ME, Ciszewski A, Kasai K, Lasko NB, Orr SP, et al. Smaller hippocampal volume predicts pathologic vulnerability to psychological trauma. Nat Neurosci. 2002 Nov;5:1242-7.
61. Villarreal G, Hamilton DA, Petropoulos H, Driscoll I, Rowland LM, Griego JA, et al. Reduced hippocampal volume and total white matter volume in posttraumatic stress disorder. Biol Psychiatry. 2002 Jul 15;52:119-25.
62. Erdogan MA, Bozkurt MF, Erbas O. Effects of prenatal testosterone exposure on the development of autism-like behaviours in offspring of Wistar rats. Int J Dev Neurosci. 2023 Apr;83:201-15.
63. Rogers MA, Yamasue H, Abe O, Yamada H, Ohtani T, Iwanami A, et al. Smaller amygdala volume and reduced anterior cingulate gray matter density associated with history of post-traumatic stress disorder. Psychiatry Res. 2009 Dec 30;174:210-6.
64. Fani N, King TZ, Shin J, Srivastava A, Brewster RC, Jovanovic T, et al. STRUCTURAL AND FUNCTIONAL CONNECTIVITY IN POSTTRAUMATIC STRESS DISORDER: ASSOCIATIONS WITH FKBP5. Depress Anxiety. 2016 Apr;33:300-7.
65. Erdogan MA, Kirazlar M, Yigitturk G, Erbas O. Digoxin Exhibits Neuroprotective Properties in a Rat Model of Dementia. Neurochem Res. 2022 May;47:1290-8.
66. Fani N, King TZ, Brewster R, Srivastava A, Stevens JS, Glover EM, et al. Fear-potentiated startle during extinction is associated with white matter microstructure and functional connectivity. Cortex. 2015 Mar;64:249-59.
67. Herringa RJ. Trauma, PTSD, and the Developing Brain. Curr Psychiatry Rep. 2017 Aug 19;19:69.
68. Weiss SJ. Neurobiological alterations associated with traumatic stress. Perspect Psychiatr Care. 2007 Jul;43:114-22.
69. Savolainen KM, Loikkanen J, Naarala J. Amplification of glutamate-induced oxidative stress. Toxicol Lett. 1995 Dec;82-83:399-405.
70. Barmanbay BN, Altuntaş İ, Erbaş O. The Role of Serotonin in Breast Cancer. JEB Med Sci 2022;3:221-6.
71. Vermetten E, Bremner JD. Circuits and systems in stress. I. Preclinical studies. Depress Anxiety. 2002;15:126-47.
72. Steardo L Jr, Carbone EA, Menculini G, Moretti P, Steardo L, Tortorella A. Endocannabinoid System as Therapeutic

Target of PTSD: A Systematic Review. Life (Basel). 2021 Mar 9;11:214.

73. Budney AJ, Hughes JR, Moore BA, Vandrey R. Review of the validity and significance of cannabis withdrawal syndrome. Am J Psychiatry. 2004 Nov;161:1967-77.
74. Kayalı A, Arda DB, Bora ES, Uyanikgil Y, Atasoy Ö, Erbaş O. Oxytocin: A Shield against Radiation-Induced Lung Injury in Rats. Tomography. 2024 Aug 29;10:1342-53.
75. Cameron C, Watson D, Robinson J. Use of a synthetic cannabinoid in a correctional population for posttraumatic stress disorder-related insomnia and nightmares, chronic pain, harm reduction, and other indications: a retrospective evaluation. J Clin Psychopharmacol. 2014 Oct;34:559-64.
76. Ragen BJ, Seidel J, Chollak C, Pietrzak RH, Neumeister A. Investigational drugs under development for the treatment of PTSD. Expert Opin Investig Drugs. 2015 May;24:659-72.
77. Erbaş O, Altuntaş İ. Oxytocin and Neuroprotective Effects [Internet]. Oxytocin and Health. IntechOpen; 2021. Available from: http://dx.doi.org/10.5772/intechopen.96527
78. Peters J, Dieppa-Perea LM, Melendez LM, Quirk GJ. Induction of fear extinction with hippocampal-infralimbic BDNF. Science. 2010 Jun 4;328:1288-90.
79. Green CR, Corsi-Travali S, Neumeister A. The Role of BDNF-TrkB Signaling in the Pathogenesis of PTSD. J Depress Anxiety. 2013 Oct 4;2013:006.
80. Old Protein, New Medicine - Brain-Derived Neurotrophic Factor [Working Title] [Internet]. Biochemistry. IntechOpen; 2024. Available from: http://dx.doi.org/10.5772/intechopen.111201.
81. Pala HG, Erbas O, Pala EE, Artunc Ulkumen B, Akman L, Akman T, et al. The effects of sunitinib on endometriosis. J Obstet Gynaecol. 2015 Feb;35:183-7.