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The impact of post-traumatic stress disorder on hippocampal volume

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ABSTRACT

Essentially, it is believed that stress leads to changes in neuronal morphology, suppression of neuronal development, and a reduction in hippocampal volume in both humans and animals. Stress is any condition that can negatively affect the psychological and, consequently, physiological well-being of an organism. When this condition becomes excessive or chronic, it can lead to anxiety, as well as psychiatric disorders such as depression and schizophrenia, alongside behavioral disturbances and the use of harmful substances. Studies conducted on both animals and humans have reported that the hippocampus, a region of the medial temporal brain involved in the formation of short-term memory, is highly sensitive to stress and presents pathological findings. In this review, we aim to examine in detail the effects of stress disorders, resulting from trauma, on hippocampal volume.

Keywords: Gray matter, hippocampal volume, post-traumatic stress disorder, treatment response.

Post-traumatic stress disorder (PTSD) is a psychiatric condition that can occur in individuals who have experienced or witnessed a traumatic event such as a natural disaster, serious accident, terrorist attack, war/conflict, or rape, or those who have been under the threat of death, sexual violence, or severe injury.[1-3] In situations where stress is present, depending on its severity, it can negatively affect many cognitive activities, such as learning and memory, significantly reducing quality of life.

The hippocampus, located in the medial temporal lobe of the brain, is a part of the limbic system that plays a role in memory, the neuroendocrine regulation of stress hormones, and spatial orientation.[2,4] The hippocampus consists of the dentate gyrus (DG), CA1, CA2, and CA3 regions, along with the Ammon's horn and subiculum. Additionally, it contains a principal layer composed of glutamatergic granule cells, pyramidal neurons, and neuropil. This region hosts numerous gamma-aminobutyric acid-ergic (GABAergic) interneurons, which are irregularly distributed. Neuropil is a structure made up of unmyelinated axons, dendrites, and glial cells, and it contains a high density of synapses. Information flow to the hippocampus occurs through the nearby entorhinal cortex, a part of the brain located in the temporal lobe that plays a crucial role in memory formation.[4]

The hippocampus, due to its high density of glucocorticoid receptors, is particularly sensitive to the toxic effects of glucocorticoid levels released in response to stress. It plays a primary role in regulating stress hormones and their responses via the hypothalamic-pituitary-adrenal (HPA) axis, making it a focal point of PTSD research.[5-7]

Glucocorticoids are steroid hormones secreted by the adrenal glands in response to daily activities and stress. These hormones have various effects on the body, including cardiovascular, metabolic, immunological, and homeostatic functions. The most important glucocorticoid hormone, cortisol, exerts its effects by binding to glucocorticoid receptors. Learning and memory formation can be disrupted when the activation of glucocorticoid receptors in the hippocampus by stress hormones impairs its normal physiology. In cases of PTSD, the glucocorticoid receptors in the hippocampus show increased sensitivity to

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cortisol compared to normal conditions, despite unchanged or even reduced cortisol levels in some cases. This heightened sensitivity leads to an amplified cortisol effect in brain regions comprising the HPA axis, a neuroendocrine system that regulates various physiological and behavioral activities.[8,9]

In PTSD patients, morphological changes in CA1, a subregion of the hippocampus with neurons projecting to the medial prefrontal cortex, are caused by elevated glucocorticoid levels.[10] Glucocorticoids bind to two types of intracellular receptors in the brain: glucocorticoid receptors, which are found in cerebral neurons and glial cells, and mineralocorticoid receptors, which are located in structures within limbic regions such as the hippocampus.[11] The intracellular metabolism of glucocorticoids is carried out by 11β-hydroxysteroid dehydrogenase (11β-HSD) enzymes, which have two distinct subtypes: type 1 and type 2. Type 1 increases intracellular cortisol levels, whereas type 2 inactivates glucocorticoids by converting cortisol into its inactive form, cortisone.[12] Since only 11β-HSD type 1 is present in hippocampal and other limbic system cells, the effect of glucocorticoids in these regions results in an increase in intracellular cortisol levels.[13] The affinity of mineralocorticoid receptors for glucocorticoids is 10 times higher than that of glucocorticoid receptors.[11] Therefore, glucocorticoids primarily stimulate mineralocorticoid receptors in the hippocampal region, increasing intracellular cortisol levels. Elevated glucocorticoid levels lead to oxidative stress damage in mitochondria within the cells, resulting in a decrease in the transport of neurotransmitters to synaptic regions.[14] At the same time, the stimulation of glucocorticoid metabolism reduces the expression of brain-derived neurotrophic factor, which is involved in neuronal growth and survival, synaptic plasticity, and learning functions.[15] Therefore, chronic exposure to glucocorticoids leads to a decrease in the number of neurons by inhibiting the regeneration of axons after the differentiation of hippocampal neurons.[16]

Following the morphological changes in CA1, disruptions in the hypothalamo-pituitary-adrenocortical (HPA) axis and prefrontal-limbic system have been observed.[17] Moreover, morphological alterations in other hippocampal subregions such as CA2-3, DG, and the (pre) subiculum are due to the highest activity of glucocorticoid receptors. Therefore, CA2-3 and the subiculum are the most sensitive subregions to the negative effects of stress.[18]

Following PTSD, glucocorticoids have been observed to alter hippocampal dendritic morphology, inhibit neurogenesis in the brain, negatively affect short-term memory, reduce hippocampal volume, and impair synaptic plasticity.[2,19] For example, magnetic resonance imaging (MRI) studies conducted on PTSD patients have shown a reduction in hippocampal volume in trauma-exposed subjects compared to those who were not exposed, supporting this observation.[20-22] Additionally, in a study that followed the analysis of PTSD severity, it was observed that the severity of PTSD was significantly associated with hippocampal volume ($d=-0.15$, $p=0.013$).[20]

Pediatric cross-sectional studies have shown that children with PTSD have abnormal development in fronto-limbic regions compared to other children of the same age group. As the fronto-limbic regions of children with PTSD develop, their hippocampal volume is smaller compared to normal, while increased amygdala reactivity and a reduction in amygdala-prefrontal connectivity over time have also been observed.[23] Additionally, in another study conducted on adults of the same age, weight, and height, structural brain imaging of individuals with various childhood trauma histories was analyzed. The results reported that their hippocampal volumes were much smaller compared to those of adults with no trauma history.[24] In another study on PTSD, it was reported that individuals with dissociative identity disorder (DID), a condition characterized by memory, identity, and consciousness fragmentation without any medical illness, had smaller hippocampal volumes compared to healthy individuals. Furthermore, a reverse relationship between the traumatic events they experienced and their personality disorders was observed.[25] In addition, a study conducted on patients with PTSD and DID observed that the hippocampal

volumes of the patients were smaller compared to healthy individuals.[24]

Our literature review revealed that some studies support the hypothesis that a low hippocampal volume is a hereditary risk factor for the development of PTSD.[26-28] However, in contrast to this finding, another study on the genetic predisposition to hippocampal shrinkage compared monozygotic and dizygotic twins, and reported that the volumetric reduction was not associated with any genetic condition.[29]

In a study conducted with 40 PTSD patients and 36 trauma-resistant healthy control subjects, observed over a period of 10 weeks, the clinical evaluations and MRI results indicated that, following treatment, the hippocampal volume of the patients who responded to treatment had increased.[30,31]

In conclusion, it is quite clear that the effects of stress play a significant role in the course of our lives. The physiology of living organisms is highly susceptible to disruption following stressful situations. Numerous studies have shown that hippocampal volume decreases after PTSD, thereby providing evidence of the biological and physiological effects of stress. Another finding of our study is that these effects result not so much from an increase in the hormones released after stress, but from the structural damage caused by chronic exposure of receptors to these hormones, which leads to increased sensitivity of the receptors. Additionally, another report from studies indicates that hippocampal volume reduction is not related to genetic predisposition.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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