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Structural Brain Changes in PTSD

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<http://dx.doi.org/10.5772/64080>

Abstract

Chronic stress induces structural and hormonal changes in the various brain structures: caudate nucleus, putamen, hippocampus, amygdala, prefrontal cortex in participants with post-traumatic stress disorder. Based on the results of recent neuroimaging studies on post-traumatic stress disorder, hippocampus, amygdala, and prefrontal cortex play a key role in triggering the typical symptoms of PTSD. Cortisol, as the primary stress hormone, together with dehydroepiandrosterone, tries to return the body to its original state of homeostasis, but its disturbed concentration levels can modify brain structures volumes. The scanning was performed using a 3.0 T whole-body scanner (Philips Medical Systems, Best, The Netherlands). Saliva was taken from all examined participants, for the determination of cortisol concentration and its effect on volume changes of the examined brain structures. The strongest headache that might occur during the day was marked on the pain rating scale (0–10). Hamilton depression rating scale was used for rating the depression level. Studies are moving toward the recognition of different biomarkers that would indicate the presence of clinically significant symptoms and a predisposition or increased risk of developing post-traumatic stress disorder, which can be made by increasing the number of studies, number of participants, and number of different methodologies.

Keywords: Brain, chronic stress, posttraumatic stress disorder, rats, psychosocial stress

1. Introduction

One in two people will be exposed to a life-threatening trauma event in their life [1]. Prolonged stress results in neuroendocrine deficiency axis and defensive mechanisms are weakened, and stress hormones are activated. Definition of neuroanatomical or morphological substrate is crucial in defining any condition, illness or disorder in medicine and

psychiatry. There is almost no area of the brain that is not directly or indirectly affected by the stress or trauma impact [2–5]. The field of neuroimaging has made tremendous advances in the past decade and has contributed greatly to our understanding of post-traumatic stress disorder (PTSD). Recent neuroimaging investigations have shown significant neurobiological changes in PTSD. The areas of the brain that are different in patients with PTSD compared to those in control subjects appear to be: hippocampus, amygdala, and prefrontal cortex. The amygdala appears to be hyperreactive to trauma-related stimuli. The hallmark symptoms of PTSD may be related to a failure of higher brain regions to dampen the exaggerated symptoms of arousal and distress that are mediated through the amygdala in response to reminders of the traumatic event [6–8]. The findings of structural and functional neuroimaging studies of post-traumatic stress disorder are reviewed as they relate to our current understanding of this disorder. Some volumetric investigations show that some other subcortical brain structures are also involved in trauma impact such as caudate nucleus, putamen [9–11].

2. Methods of investigation

2.1. Magnetic resonance imaging

Magnetic resonance imaging generally presents the most important volumetric and structural assessment tool in general evaluation and determination of morphological substrate in post-traumatic stress disorder. The MRI scanner detects the radiofrequency energy emitted and energy level changes represent different brain structures. T1- and T2-weighted images are used for differentiating the white and grey matter and for delineating hyperintensities, respectively. The advantage of this procedure is its safety in the first place, since it does not involve ionizing radiation. Neuroimaging investigations mostly involve a magnetic field varying from 1 to 3 Tesla (T). Various MRI techniques are available for clinical use such as fast spin echo, high-performance gradients, echo planar, and diffusion weighted imaging. In a study of male therapy-naïve participants with PTSD, Starcevic et al. [12] performed the scanning using a 3.0 T whole-body scanner (Philips Medical Systems, Best, The Netherlands). After the scanning, all the participants were coded in order to blind the volumetric evaluation team, and sent for the subsequent volumetric analysis. MIPAV software with three integrated software tools (brain extraction, Talairach alignment, tissue segmentation) was used for brain volume estimation. Volume measurements of the cerebral structures examined in the study were performed on 3D T1-weighted MR images (acquisition parameters were as follows: TR = 9.8 ms; TE = 4.6 ms; flip angle = 8; section thickness = 1.2 mm; number of sections = 120; no section gap; whole-brain coverage; FOV = 224 mm; matrix = 192; reconstruction matrix = 256). Routine T2-weighted MRI and FLAIR were performed to rule out a mass lesion as a contributory factor to memory loss or cognitive decline. After the data had been collected, the input data (3D T1 images) were transformed to 152 common spaces, using transformations based on 12 deg of freedom (i.e., three translations, three rotations, three scalings, and three skews). After subcortical and cortical registration, we applied the sub-

cortical mask to locate the cortical and subcortical structures of interest, followed by segmentation. The total, absolute volumes of structures of interest were calculated, taking into account the transformations made in the first stage. As for the certainty of precision of segmentation, boundary correction was used to determine whether or not the boundary voxels belonged to the structure examined. That was one of the most important steps through which the accuracy of the delineated measured cerebral structures were determined using the Z-value of 3, corresponding to a 99.998% certainty that the observed voxels belonged to the particular structure. After all MR scans were registered and segmented, all segmented regions of interest were visually checked for errors during registration and segmentation.

2.2. Determination of cortisol levels

Secretion of cortisol shows the circadian rhythm characterized by a sudden increase in concentration early in the morning and a gradual decrease until the end of the day. Since stress induces higher levels of cortisol, the concentrations remain elevated until the cause of the stress is eliminated. The main role of cortisol is to help the body under stress to adapt to the changing conditions. Steroids can be determined in a sample of blood, urine, and saliva. Salivary cortisol is a measurement of active free-cortisol concentration which follows a diurnal rhythm of serum or plasma cortisol. Saliva sampling protocols are simple and noninvasive. Proper sample preparation is important for the accurate determination of cortisol in saliva. There are various commercially available saliva sets: simple sterile containers, containers with cotton pellet (Salivette), or specialized systems for collecting saliva. Salivettes are mostly used for saliva sampling. This system includes cotton rolls to be placed in the mouth and the patient chews on them for about 30 s to 30 min followed by transferring the sample to the test tube. With regard to the stability of cortisol, patients can store the samples in their home refrigerators at a temperature between 4° and 8° for up to seven days before taking them to the laboratory for testing. Before psychological testing and magnetic resonance imaging, all patients underwent a structural psychiatric interview and ventilation psychotherapy without taking any medications. The disorder was diagnosed according to the guidelines of the 10th revision of the International Classification of Diseases (ICD 10). Saliva was taken from all participants for the determination of cortisol concentration. The concentration was determined by the available commercial kit (Salivette) twice a day in the morning (7 h) and the evening (21 h).

3. Neuroanatomical substrates and structural, volumetric changes

3.1. Hippocampus

The animal stress model investigations showed that stress produced damage to the hippocampus, a brain area involved in learning and memory, situated in the medial temporal lobe just under the cortical surface, with associated memory deficits. The hippocampus contains high levels of glucocorticoid receptors which make it more vulnerable to chronic stress than most other brain areas [13]. The mechanism involves glucocorticoids and possibly serotonin acting through excitatory amino acids to mediate hippocampal atrophy. Under normal

conditions, hippocampus blends together all the elements of a memory from all the sensory areas. Short-term memories are stored in the hippocampus, but when they are no longer required as conscious memories, the hippocampus processes these into other parts of the brain to create longer term memories. Patients with post-traumatic stress disorder from Vietnam combat and childhood abuse showed deficits on neuropsychological measures that have been validated as probes of hippocampal function [14, 15]. In addition, magnetic resonance imaging (MRI) showed a reduction in volume of the hippocampus in both combat veterans and victims of childhood abuse [5, 14, 15]. In combat veterans, the hippocampal volume reduction was correlated with deficits in verbal memory on neuropsychological testing. These studies introduce the possibility that experiences in the form of traumatic stressors can have long-term effects on the structure and function of the brain [4, 16, 17]. Stress related steroids like cortisol, as a primary stress hormone, affect the hippocampus by reducing the excitability of some hippocampal neurons, thus inhibiting the genesis of new neurons in the dentate gyrus and causing atrophy of dendrites in pyramidal cells of the specific CA3 region, which leads us the conclusion that humans who experienced chronic traumatic stress had atrophy of the hippocampus more often than of other parts of the brain. All above mentioned brain changes effects are present in post-traumatic stress disorder [18]. Hippocampal damage interferes with the proper processing of information coming from the amygdala making an individual very vulnerable to new disturbing stimuli. This has been confirmed by experiments on animals, where damage to hippocampal functions results directly in behavioral disinhibition [19–21]. The volume reduction of the hippocampal formation may be explained by a negative impact of cortisol at the level of the hippocampal cells. General reduction of any structure of the brain may be caused by the negative effect of cortisol to a cell of such structure [22, 23]. Intense stress is associated with the release of endogenous stress hormones and transmitters of cortisol, epinephrine, and norepinephrine, vasopressin, oxytocin, and endogenous opiates, and their role is reflected in the launch of altered metabolism and release of energy necessary to respond to stress. Then glucose is released and changes occur in the immune system. In a healthy organism, these changes are of short duration, and the baseline cortisol level of functioning is established as soon as the danger has passed, while in the case of prolonged stress, if it is very intense, there is a dysfunction of the system response to stress and to its desensitization [24]. Studies that have investigated the functions of neurohormones in post-traumatic stress disorder show reactions that are opposite of the normal response to stress. The sudden cortisol concentration increase is one of the standard elements of the response to stress and, as a result, can damage the hippocampal formation, which leads to cognitive deficits in the form of memory impairment. Glucocorticoids and catecholamines modulate the reciprocal effects in the manner that in acute stress the response regulates cortisol stress hormones via negative feedback through the hippocampus, hypothalamus, and pituitary gland. Based on the results of their study, researchers suggest that cortisol is a potent hormone that can even interfere with other processes in the body after the exposure to acute stress [22, 23, 25]. Alternately, released catecholamines and corticosteroids stimulate active behaviors necessary to overcome stress, whereas in the case of low levels of corticosteroids, the increased irritability is caused by inadequate and uncontrolled reactions of fight or flight. Chronic stress induces decreased basal cortisol levels. On the other hand, acute stress can be seen as a leading factor of decreased

activation of pulsatile stress hormone release, and increased number of glucocorticoid receptors in the hippocampus structure [25]. Kuljić and colleagues showed in their study that chronic stress caused a reduction in corticosterone concentration indicating the exhaustion of the hypothalamic-pituitary-adrenal axis, as was shown in an experimental study in rats [26]. A study conducted by Resnick et al. [27] showed that reduced cortisol made people more susceptible to post-traumatic stress disorder, for example, those with a personal history of sexual abuse [27]. The occurrence of post-traumatic stress disorder was manifested after 3 months in individuals who suffered from reduced levels of cortisol immediately after the car accident [28, 29].

3.2. Amygdala

The amygdala is a structure described as a center of normal expression of emotions to external stimuli and realistic perception and response to stress and fear. Located deep and medially inside the temporal lobes, it is involved in processing memory, emotional reactions, and decision making [30]. There was a weak activation within the paradigm of experimental functional MRI imaging (fMRI) for war veterans. The occurrence of different blood flow consistent with the level of an emotional reaction is a common finding during the experimental paradigm performance in psychiatry; however, this was not the case for former warriors in whom it was shown in reduced amygdala complex and the lack of displaying the symptoms of PTSD [31, 32]. The exposure to a traumatic event results in autonomic activation, after which the amygdala evaluates information and, depending on that assessment, determines the emotional significance of the entrance and triggers a structure such as hypothalamus, hippocampus, and basal prosencephalon, which then determines the behavioral, autonomic and neurohormonal function and its manifestation. In a study conducted on forty-nine male patients, Starcevic et al. [12], found that both left and right amygdala volumes were statistically significantly different between individuals with PTSD and individuals without PTSD, with the emphasis on the volume of the left amygdala as more significant. LeDoux [21] discovered the crucial role of the amygdala in the emotional brain, which he called neural alarm, which can take control over behavior even when the prefrontal cortex is still at the stage of selecting an equal reaction to external stimulation. Rogers et al. [33] show that the left amygdala volume has a significant negative correlation with the severity of PTSD symptomatology as well as with the reduced gray matter density in the left anterior cingulate cortex. A smaller amygdala volume was associated with the presence of cancer-related intrusive recollections in a sample of 76 breast cancer survivors [34]. Normal amygdala volumes do not necessarily preclude functional abnormalities in the amygdala in participants with PTSD. As a case in point, the results of a functional neuroimaging meta-analysis in participants with PTSD found evidence of amygdala abnormalities, particularly in the left amygdala, where two distinct clusters of abnormal function were identified: a ventral anterior hyperactivation cluster and a dorsal posterior hypoactivation cluster [35, 36]. The amygdala has a great potential and therefore research should go in the direction of a more detailed examination of this structure.

3.3. Prefrontal cortex

With its executive function, the prefrontal cortex, a cerebral cortex that covers the front part of the frontal lobe, has been indicated by many authors and researchers as an integral link between an individual's personality and basic psychological functions of the frontal cortex [37]. Brain imaging studies have shown that the reduced volume and interconnections of the frontal lobes with other cerebral regions can be found in individuals with different mental disorders such as post-traumatic stress disorder [38, 39]. A structural neuroimaging research study indicates that marked improvements in prefrontal and hippocampal grey matter volume occur in individuals who have physical exercise [40]. Researchers, who have studied the prefrontal cortex as a part of the brain that suppresses memories, showed that it could not function at lower levels in people with stress related disorders like in healthy subjects. When individuals with stress-related disorders were asked to suppress their memory of certain words, their brains showed activation in the hippocampus, which was higher than normal [41].

The reduction of brain structure volume may occur as a result of molecular alterations in those specific brain areas. Researchers [41, 42] showed increased blood flow in the upper prefrontal region of the brain in a study conducted on both men and women who suffered from post-traumatic stress disorder. This is to be expected because different structures of cerebrum are triggered in the same task paradigm in men and women. Cortisol, the main stress hormone, which is involved in the apoptotic actions in the brain and consequently reduction of solitary brain structure, has a great influence in bilateral and general reduction of brain volume at the expense of increasing the ventricles of the brain [43].

3.4. Caudate nucleus, putamen, and globus pallidus

Subcortical structures such as caudate nucleus and putamen have been described as structures involved not only in motor function, but in cognitive processes and that their volume decrease was associated with major depression and Alzheimer's disease. Chronic stress induces neuroendocrine deficiency and weakened defensive mechanisms which lead to post-traumatic stress disorder. Cortisol, as the primary stress hormone, together with dehydroepiandrosterone, tries to return the body to its original state of homeostasis, but its disturbed concentration levels can modify brain structures volumes. Negative effects of cortisol result in volume decrease of subcortical structures [44].

Globus pallidus, as a major subcortical grey structure, participates in the regulation of sleep via the nigrostriatal dopamine and through its connections with subthalamic nucleus [45]. Studies carried out on an experimental model of the rat have shown that damage to the globus pallidus leads to disruption of sleep. Sleep disorders, which are considered among the most severe symptoms of post-traumatic stress disorder, are leading to hypoxic changes and changes in metabolism in the brain, which alters, to a high degree, dopamine levels, and the degree of blood flow through the brain, which, in turn, leads to brain atrophy [46]. Sleep deprivation, one of the most annoying symptoms in PTSD suffering subjects, could not be neglected. Higher values of the Hamilton depression rate score in patients with more frequent headaches, who, in addition, have a greater decrease in volume, could be explained with the

theory of sleep deprivation influence, and long-term cortisol effects after the stressing event, although insomnia and headaches are reported to be more frequent in women [47, 48] .

3.5. The link between stress, post-traumatic stress disorder, and cortisol

Cortisol is the primary stress hormone, a steroid hormone of the adrenal cortex, which participates in the regulation of metabolism of carbohydrates, fats, and proteins. It has a role in stress and a variety of inflammatory processes in the body [49]. Dysregulation of the secretion of this hormone triggers severe dysregulation mechanisms in the body during stress with far-reaching consequences. Hypothalamic-pituitary-adrenal axis activates during the stress. If the acute stress is not removed and is prolonged to chronic stress, such deregulated secretion of cortisol can lead to outbreaks of a disease caused by suppressive effects of cortisol on the immune system. Frequent infections and neoplasms can also occur [50]. The stimulative effect of cortisol on proinflammatory cytokines leads to autoimmune diseases and malignancies [51].

Endocrine imbalance is reflected in altered cortisol concentrations and increased sensitivity of the liver, which produces insulin in the case of increased cortisol secretion leading to the clinical manifestation of increased blood glucose levels [52, 53]. Hypercortisolism and cognitive deficits that can also occur are associated with obsessive compulsive disorder, panic disorder, or melancholic depression [54]. The ability to bind cortisol receptors in the hippocampus affects memory and consciousness. Excessive production of cortisol can lead to hippocampal atrophy that can be clinically seen in different dissociative disorders [55]. Yehuda et al. [56] showed the correlation of chronic stress and post-traumatic stress disorder with lower cortisol levels. They explained it as the huge influence of chronic stress on the hypothalamic-pituitary-adrenal axis, which is exhausted. Other research has shown that there is increased secretion of cortisol in those with PTSD. Such research has been conducted on veterans from Vietnam who had been diagnosed with PTSD. There is documented data from studies that have monitored the course and development of PTSD in abused children showing also increased secretion of cortisol due to the experienced and re-experienced trauma. This suggests that the levels of circulating basal cortisol may occur until a person develops a mechanism leading either to healing, in the sense that they will not develop PTSD, or to triggering the effects of increased cortisol concentrations in response to stress and consequently to the development of some psychiatric disorder like post-traumatic stress disorder or some other manifestation, for example, a somatic one. Despite previous studies, some researchers have documented normal levels of cortisol during stress [23, 25, 56]. Female population is still more affected by the post-traumatic stress disorder, but recent studies pinpoint the effects of the global situation that affects to a great extent the trauma level in male population. In a study of 49 male therapy naïve patients with PTSD, Starcevic et al. [12] documented decreased levels of cortisol, which induced decreased volumes of, especially, left amygdala, right putamen, total hippocampal volume, and prefrontal cortex.

Headaches, as primary manifestations of hyperarousal, are among the major occurrences in patients with post-traumatic stress disorder. They appear to be associated with decreased volumes of subcortical cerebral structures as well as with co-occurrence of anxiety and depression in male therapy naïve patients with PTSD [12, 44].

4. Future prospective

Researchers have made a significant progress in identifying neuroanatomical structures that could be defined as substrates or predictors of post-traumatic stress disorders. Given the complexity of the genesis of post-traumatic stress disorder, it is unlikely that it will be defined by only one biomarker. Neuroimaging investigation defined decreased volumes of most cerebral structures as neuroanatomical substrates in PTSD, and some of them, such as left amygdala, can be used as possible predictive structures for this psychiatric disorder [12].

Studies are moving toward the recognition of different biomarkers that would indicate the presence of clinically significant symptoms and a predisposition or increased risk for developing the post-traumatic stress disorder. Such recognition can be achieved by increasing the number of studies, participants and of different methodology like diffusion tensor imaging (DTI) or functional magnetic resonance imaging (fMRI) and then correlated with the results obtained from animal model studies.

Particular attention should be focused to further assessment of morphological predictive factors in establishing a definitive diagnosis of post-traumatic stress disorder.

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