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Abstract

Post-traumatic stress disorder (PTSD) is a psychiatric condition in which an individual presents with intrusion, lability of mood, emotional numbness and avoidance after exposure to severe traumatic events. Neuropsychological studies have shown that PTSD patients have impaired attention, working memory, and new learning; electroencephalography reveals that affected persons have heightened processing of trauma-related information, but weaker processing of neutral information. These findings suggest possible structural and functional abnormalities in memory-related brain areas. The hippocampal formation, which plays an important role in memory processes, probably exerts significant effects in the pathogenesis of PTSD.

The hippocampus, an important component of the brain limbic system, is the area that controls learning and memory. While playing a significant role in spatial learning and memory, it is also implicated in anxiety behaviours. Moreover, functional and structural abnormalities of the hippocampus are believed to be associated with a number of psychiatric disorders. The hippocampus is also one of the brain structures that regulates stress responses. Studies with animals demonstrated that chronic stress may lead to changes in hippocampal structure in rats, including suppression of neurogenesis, neural dendritic atrophy and neuron loss. Changes in hippocampal structure and function are therefore considered to be causally inter-related to the development of many psychiatric diseases. Researchers studying the brain structure of patients with PTSD have focused mainly on the hippocampal region. This paper aimed to present an organised and selected review / analysis of relevant published Chinese and English literature on this topic.

Alterations in Hippocampal Formation of Adult Patients with Post-traumatic Stress Disorder

Since the first report by Bremner et al in 1995 describing magnetic resonance imaging (MRI) which showed a reduction in right hippocampus volume in PTSD patients compared with the controls, a variety of different reports have been published on this subject. Most of these found that the hippocampal volume of PTSD patients was relatively...
smaller than that in healthy controls or persons exposed to traumatic events but not suffering from PTSD.

In the study by Brenner et al., the hippocampal volume of the right side in veterans with PTSD was about 8% smaller than that in healthy controls, and this reduction in size correlated with defects in declarative memory function. However, the research group also conducted a study on childhood sexual abuse–related PTSD patients, and found that the left hippocampal volume was 12% smaller than that in healthy controls. Despite controlling for different confounders, this difference was still significant, whereas there was no significant difference between right hippocampal volumes. Subsequently, a number of studies compared hippocampal volumes of PTSD patients with healthy controls, and reported that patients had smaller volumes (unilaterally or bilaterally), whereas another study reported no significant difference. Post-traumatic stress disorder is often associated with different psychiatric co-morbidities, such as substance dependence, which in turn may exert detrimental effects on the brain structure. Many researchers choosing to study PTSD patients opted to exclude patients with associated substance dependence and other mental disorders, in order to exclude the influence of such confounders. Although the methods of measurement vary, the results suggested that, compared with healthy controls, patients with PTSD displayed a decrease in bilateral, left, or right hippocampal volume (ranged from 5 to 11%). Another study stated that the reduction in hippocampal volume was negatively correlated with dissociation symptoms and/or duration of the disease.

The control groups chosen by the abovementioned studies were all healthy persons. Based on the fact that PTSD patients had been exposed to severe trauma scenarios, researchers proposed that the decrease in hippocampal volume might not be caused by that disorder, but by the traumatic experience itself. To further clarify the relationship between changes in hippocampal volume to trauma exposure per se and/or PTSD, many researchers chose controls with the same or similar traumatic experiences but did not suffer PTSD. In literature reviews, it was reported that the total or unilateral size of the hippocampus was smaller or that the density of hippocampal gray matter decreased in PTSD patients in comparison with controls without PTSD. However, some studies did not find any significant change, and some reported that the hippocampal volume was related to intrusion symptoms of PTSD. The findings of 2 meta-analyses showed that the hippocampal volume of PTSD patients reduced. In addition, many studies have reported that N-acetyl aspartate (an indirect means of inferring tissue damage) in the hippocampal region of PTSD patients was decreased.

In an MRI study by Felmingham et al. on 21 PTSD patients and 17 patients exposed to trauma but without PTSD, the findings suggested that even after controlling for age, depressive symptoms and total brain size, hippocampal volumes of the PTSD patients were smaller than those of the controls. Besides, right hippocampal volume correlated negatively with the duration of PTSD. Based on this result, it could be suggested that PTSD leads to a decrease in the hippocampal volume, and longer duration may exert an accumulative effect. On the other hand, in an MRI study by Gilbertson et al. on 12 veterans with PTSD and 23 veterans without PTSD involving comparison with their twin brothers who had not exposed to trauma, it revealed that hippocampal volume of PTSD patients correlated negatively with the severity of PTSD (Clinician-Administered PTSD Scale [CAPS] scores). Interestingly, the hippocampal volumes of the untraumatised twins of the PTSD patients were also negatively correlated with the CAPS scores of PTSD patients. Also, on comparing the twins of PTSD patients with that of non-PTSD patients, the hippocampal volumes in the former group were significantly smaller. These results indicated that a small hippocampus may confer a risk factor for the development of PTSD, but not the PTSD caused the hippocampal volume loss. The follow-up data analysis of the study group reported similar findings.

Yehuda et al. compared the hippocampal volume of those suffering PTSD immediately after their trauma with that of persons suffering PTSD after repeated exposure to trauma. This showed that hippocampal volumes of the former were smaller and proposed that a small hippocampal volume might be predisposing for PTSD. It is therefore necessary to conduct prospective studies to have a better understanding of the cause-and-effect relationship between PTSD and the alteration in hippocampal volume.

Studies with animals indicated that the alterations in the hippocampal neurons caused by stress are reversible. Some researchers studied the reversibility of the human brain structure. The study of Vermetten et al. showed that treatment with selective serotonin reuptake inhibitors may reverse the decrease in hippocampal volume encountered in PTSD patients through stimulating the growth of hippocampal neurons (paroxetine therapy for 1 year that increased hippocampal volume by 5%), and helped improve deficits in their declarative memory. Bossini et al. used sertraline of 100 mg/day to treat PTSD patients for 6 months and observed an increase in hippocampal volume (9.9% on the left side, 8.4% on the right side). These suggested that the change in the hippocampal formation of human brain has a certain degree of reversibility, and that small volumes were not due to the risk factor of PTSD, but were probably prompted by excitability. Notably, psychological treatment (such as cognitive behavioural therapy) was also effective in improving clinical symptoms of PTSD, but whether it can also cause alterations in hippocampal volume still lacks proof.

The above studies suggest that decrease in hippocampal volume and function are closely related to PTSD. Such abnormalities may lead to clinical symptoms associated with memory disorders. It is however not certain whether these alterations in the hippocampal formation occur in PTSD exclusively, or are common changes in the brain structure of all the individuals subjected to excitability or who experience mental disorders. It is therefore
necessary to compare the hippocampal formation of PTSD patients with that of patients with other mental disorders or experiencing stress.

**Alterations in Hippocampal Formation of Children Suffering from Post-traumatic Stress Disorder**

Many studies have shown that early experiences of stress or trauma can affect the development of brain structure and cause changes in response towards excitability. However, compared with research on adult patients with PTSD, there are relatively few MRI studies on children, and most studies have found no alteration in hippocampal volume.

De Bellis et al conducted a test on 44 abused children (aged 7-17 years) and 44 healthy children matched for sex, age, and body weight who had not experienced trauma. The findings revealed no significant difference in the hippocampal size between the groups. In this study another sample (28 PTSD patients, aged 4.9-16.5 years) was compared with 66 healthy controls matched for gender and age, which did not yield any difference in hippocampal volume. A subsequent meta-analysis also found that hippocampal volume in childhood PTSD patients was not smaller than that in controls.

Tupler et al conducted MRI scans (GE, 1.5T) on 61 children with PTSD due to childhood abuse (aged 4-17 years), and compared them with a healthy control group matched for gender and age. After controlling for the brain size, the hippocampal volume of PTSD patients was significantly greater than that of the controls. This size difference was due to a larger volume of hippocampal white matter, whereas the size in hippocampal gray matter did not differ between the groups. This study also suggested that the total volume of the hippocampus was positively correlated with age and the severity of psychological symptoms of trauma.

The reason for the difference in findings for hippocampal size of PTSD patients in childhood-adolescence and the adults is still unknown, but could be linked to neural development. Children's brains are still in the process of development, therefore their brain structure at different ages may differ. Gogtay et al carried out an imaging study on 31 children and adolescents to assess normal hippocampal development. Throughout the follow-up (4-10 years), MRI scans of the hippocampus were conducted every 2 years, which showed imbalanced development in different parts of hippocampus. In the process of development from childhood to teenage / adulthood (4-25 years), the total size of the hippocampus did not change significantly, but a decrease in size of the front part of hippocampus and increase in the rear part were found. This type of alteration in size adds many confounding factors to studies in childhood. Furthermore, the traumatic stress of childhood may change the neuronal development, synaptogenesis, dendritic growth and pruning, though these effects may not be immediately apparent in childhood and become significant only in the late stages of development. It is also possible that the early traumatic stress only causes short-term changes in neural development. Moreover, changes in hippocampal volume become covered up as the nervous system gradually develops.

Although studies on children and adolescents have not found consistent changes in hippocampal volume of PTSD patients, neural biochemical studies indicated an increase in urine cortisol and salivary cortisol levels in children with PTSD or abused children with PTSD symptoms. An increase in cortisol may be an important cause leading to damage of hippocampal neurons, dendritic atrophy, and subsequent change in hippocampal volume. The increased cortisol levels detected in the test of children and adolescents with PTSD indirectly suggest a possible mechanism for changes of hippocampal formation.

Studies on the changes in hippocampal formation of children and adolescents with PTSD are still very limited. Results thus far are not sufficient to infer significant differences between children and adults for the impact of PTSD on the hippocampus. Moreover, the current studies on children entail a relatively large age range. Researches of future studies need to improve the homogeneity of their samples to reduce the influence of confounding factors, such as age, experience of trauma, and duration of PTSD.

**Studies on Hippocampal Formation**

The hippocampus is not a homogeneous single brain structure with different localisations subserving different functions. It has been proposed that PTSD may only affect some areas, for which studies have targeted alterations in the size of certain parts of hippocampus only. Vythilingam et al carried out a hippocampal MRI scan (GE, 1.5T) on 14 soldiers who suffered from PTSD after warfare, 23 soldiers who did not suffer from PTSD after warfare, 22 reservists and 29 healthy civilians. They separately assessed the 3 divided regions of the hippocampus: the head, the body, and the tail. Total hippocampal size of these 3 soldier groups was significantly smaller than that in the healthy civilian group. Notably, only the hippocampal head of PTSD patients was smaller than those of the healthy civilians. It has therefore been suggested that only the hippocampal head may be affected by PTSD. Bonne et al carried out an MRI study (GE, 3T) on 22 PTSD patients and 22 healthy controls (matched for gender and age) by dividing the hippocampus into 3 subregions of subiculum, anterior and posterior. Only the size of posterior part of PTSD patients was smaller than that of the healthy controls. In the study by Golier et al and Yehuda et al on slaughter survivors and PTSD soldier patients, the longitudinal axis of the hippocampus was equally divided into 4 parts, but no significant difference in size of any subregions was found.

One of the reasons for inconsistent results was the unclear or inconsistent division of the hippocampus into substructures / subregions. Different parts of the hippocampus have distinct histological and other specific features,
Many studies with animals have found that stress suggests that PTSD may only have specific effects on the traumatic events, but no significant changes ensued. This was further analysed by excluding controls not exposed to whereas age had no effect on this difference. The study patients was significantly smaller than that of the controls, that the size of CA3 / dentate gyrus sub-structure of PTSD cortex was also included in the analysis. The results showed that the size of CA3 / dentate gyrus sub-structure of PTSD patients was significantly smaller than that of the controls, whereas age had no effect on this difference. The study was further analysed by excluding controls not exposed to traumatic events, but no significant changes ensued. This suggests that PTSD may only have specific effects on the hippocampal CA3 / dentate gyrus region of human brains. Many studies with animals have found that stress can cause structural remodelling in hippocampal CA3 and dentate gyrus regions, which provides supporting evidence for changes in the specific sub-structure of the hippocampus in human brains. Stress-related neural structural remodelling mainly includes the inhibition of neurogenesis, dendritic branching and synaptic genesis, as well as the change in neuronal plasticity. The dentate gyrus is one of the rare regions in adult brains where neurogenesis takes place. A large number of small granule cells can be produced from dentate gyrus neurons. Memory has an important role in the pathogenesis of PTSD, and the production of such small granule cells is considered to be related to memory formation. Persistent stress may lead to the inhibition of neurogenesis in rats, and cause a significant decline in the number of small granule cells and a significant decrease in size of the dentate granule cell layer. Chronic stress can also lead to a decrease in the dentate gyrus region of brain-derived neurotrophic factor (BDNF) expression. Since the growth and differentiation of BDNF and stem cells are closely inter-related, decreased expression may inhibit neurogenesis. Chronic stress can lead to the damage of the hippocampal CA3 pyramidal dendritic skeleton of rats, especially to its microtubule, and directly lead to a shortening and thickening in primary dendrites. Similarly, psychosocial stress may also cause a decrease in the length and number of branches of the CA3 region taper neuronal dendrites in the tree shrew. These changes are considered related to the increase in PTSD glucocorticoid production. CA3 is the main region of the hippocampus affected by glucocorticoids. In addition, the decline in neuronal synaptic plasticity and the reduction in the number of neurons caused by the stress are also considered to be related to the decreased volume of the dentate gyrus and CA3 region. Although these animal experiments support the possibility that PTSD may have specific effects on the CA3 / dentate gyrus region in hippocampus, direct evidence that stress causes the change in the brain hippocampal dentate gyrus and CA3 neurons is still lacking.

In the past, MRI studies on depression, schizophrenia, dementia, dissociative identity disorder and other diseases have reported decreases in hippocampal size. These results seem to suggest that changes in hippocampal volume may not have specificity, but is a common feature of many mental disorders. However, Wang et al also found that the CA1 sub-structure size of PTSD patients is significantly correlated with age, which is consistent with the result described by Mueller et al on the normal elderly and dementia patients. This suggests that different mental disorders may affect different aspects of the hippocampal formation, and PTSD is only associated with the changes in the CA3 / dentate gyrus region. Owing to the dearth of studies on these aspects, research directed at understanding the relationship between PTSD and other mental disorders on hippocampal development may be helpful.

**Longitudinal Studies on the Changes in Hippocampal Formation**

Although a number of studies have shown smaller hippocampal sizes in PTSD patients, the cause-effect relationship still remains unclear. Proneness to PTSD may predate experience of the traumatic event, and could be regarded as a risk factor. It is also possible that a reduction in hippocampal volume is caused after experiencing traumatic event and after the manifestation of PTSD. Due to the unpredictability of the occurrence of trauma and the difficulties involved with follow-up, most imaging studies of PTSD have been cross-sectional. Thus, it is difficult to clarify this cause-effect relationship, as till now only a small number of researchers have conducted longitudinal studies.

Magnetic resonance imaging scans (GE, 1.5T) were carried out by De Bellis et al on 9 PTSD patients in early puberty due to abuse in childhood and 9 age- and gender-matched healthy children. Follow-up MRI scans conducted after 2 to 3 years (late puberty) showed no significant difference in baselines and follow-up hippocampal volumes between the 2 groups. Yet the left hippocampal volumes in both groups showed a tendency to decrease with time (p < 0.06), whilst the decrease in the PTSD group was greater (p < 0.1). Bonne et al conducted a baseline MRI scan (Elsin GYREX, 2T) on 37 trauma survivors seeking diagnosis at the emergency room 1 week after a trauma incident, followed by follow-up scans during the next 6 months. Six months later, 10 subjects were diagnosed with PTSD. The scans did not show any significant difference in hippocampal volume between the PTSD and non-PTSD patients. There are several possible reasons for these negative results. First, sufficient change of hippocampus may require long-term exposure to trauma, not merely a single incident. Second, PTSD patients may undergo functional change within a short period of experiencing the traumatic events, but it takes a longer time to detect measurable declines in hippocampal volume, whereas the study only entailed follow-up for 6 months; also, a small hippocampal volume may be a predisposing factor for chronic rather than acute PTSD. A
12-to-18-month follow-up was carried out by Carrion et al on 15 children experiencing traumatic stress. The results yielded a significant decrease in hippocampal volume and a significant correlation of baseline plasma cortisol level, with both the severity of PTSD symptoms and the decline in size of the right hippocampus. However, this study did not include any control group, so it was difficult to control for confounding factors. Despite this, the study provided preliminary evidence of damage to the hippocampus of human brains caused by stress.

Longitudinal studies provide comprehensive observations on important changes in the development of PTSD, which may clarify cause-effect relationships and understand its pathogenesis and association with changes in brain structure. Future studies need to expand sample sizes, control for confounding factors, undertake longer periods of follow-up, and carry out a more detailed analysis on hippocampal formation.

**Conclusion**

Over the past decade, the MRI studies have shown the abnormalities in PTSD patients after trauma, but the results have been inconsistent, or even contradictory. The reasons for such anomalies may entail difference in the MRI testing techniques per se and the design of different studies, quite apart from the heterogeneity of PTSD itself. Several future research directions are worth developing: (1) Long-term longitudinal study on hippocampal formation to analyse the cause-effect relationship between the abnormality of hippocampal formation and PTSD; (2) Adopting subtype classification according to the specific neurophysiological or neural biochemical markers of PTSD to improve the homogeneity of study samples, with reference to the concept of genetic endophenotypes; (3) Including patients with other mental disorders as in control groups in order to clarify whether abnormal hippocampal formation is specific to PTSD; and (4) In-depth study on the effects of drug treatment and psychotherapy on the hippocampal structure of PTSD, so as to explore the significance of hippocampal measurement as a clinical outcome indicator.

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**References**


