Stress-induced anatomical changes in white and gray matter: a review of literature

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Summary

Post traumatic stress disorder (PTSD) is a psychiatric abnormality caused by a drastic traumatic event or extreme stress, that exceeds the capability to adapt. There are many papers reporting anatomical brain changes induced by trauma and extreme stress, not only in white matter but in gray matter as well. Extreme stress and trauma are connected with elevation of cortisol level, which may cause damage to the hippocampus and may interfere with the anatomy of the hippocampus as well as its microstructure and cell number. Stress may inhibit the hippocampal neuroregeneration as well as hippocampal neurogenesis and even induce neuronal death within the hippocampus. Diffusion tensor imaging (DTI) is a powerful method enabling the visualization of the microstructure integrity of white matter, to evaluate the changes (rate and directionality) of water diffusion within myelin tracts and provide enhanced images of white matter tracts compared to traditional MRI morphometry images. One can evaluate the differences in white matter using fractional anisotropy (FA), which is a scalar metric of the degree of anisotropy and diffusion direction of water molecules, indicating fiber density, myelination and axon diameter. Many studies report reduced gray matter volume caused by extreme stress or trauma in people both with the diagnosis of PTSD as well as stress-exposed non PTSD in comparison to healthy controls. Studies have revealed reduced volume mostly in the hippocampus but also in regions such as anterior cingulate, corpus callosum, insula, septum pellucidum, subcallosal cortex, amygdala, prefrontal cortex and total brain volume. The right hippocampus may be prone to the effect of stress much more than the left hippocampus. Moreover, comparing trauma-exposed non-PTSD and PTSD participants, they have found volumetric abnormalities only within the right hippocampus among the PTSD group. They suggest an additional pathological process underlying PTSD, connected with the right hippocampus volume.

Keywords: stress, trauma, anatomy, brain anatomy

Post traumatic stress disorder (PTSD) is a psychiatric abnormality caused by a drastic traumatic event or extreme stress, that exceeds the capability to adapt. There are many papers reporting anatomical brain changes induced by trauma and extreme stress not only in white matter but in gray matter as well. Several animal studies revealed that chronic stress can affect the hippocampal volume f.e. because of extensive glucocorticosteroid release (46), corticotropine-releasing hormone (7), inhibition of neurogenesis (17), inhibition of brain-derived neurotrophic factor (12), altered serotonergic receptor function (25). Bremner revealed that extreme stress and trauma are connected with elevation of cortisol level (6), which may cause damage to the hippocampus (5) and may interfere with the anatomy of the hippocampus (46) as well as

its microstructure and cell number (2, 39, 58). Stress may inhibit the hippocampal neuroregeneration (16) as well as hippocampal neurogenesis (37), and even induce neuronal death within the hippocampus (58). White matter connects cortical and sub-cortical structures and occupies 440% of total brain volume (38). Diffusion tensor imaging (DTI) is a powerful method allowing the visualization of microstructure integrity of white matter, to evaluate the changes (rate and directionality) of water diffusion within myelin tracts (9), and provides enhanced images of white matter tracts compared to traditional MRI morphometry images (38). One can evaluate the differences in white matter using fractional anisotropy (FA), which is a scalar metric of the degree of anisotropy and diffusion direction of water molecules (15), indicating fiber density,

myelination and axon diameter (3). Reduced FA in DTI imaging is usually a sign of reduced integrity of white matter fibers. More specific information can be obtained using axial diffusivity (AD, along the axon) and radial diffusivity (RD, perpendicular to the main axonal axis).

Gray matter

Many studies report reduced gray matter volume caused by extreme stress or trauma in people both with the diagnosis of PTSD as well as stress-exposed non PTSD in comparison to healthy controls. Studies have revealed reduced volume mostly in hippocampus (14) but also in regions such as anterior cingulate (57), corpus callosum, insula, septum pellucidum (27), subcallosal cortex, amygdala, prefrontal cortex (42, 48, 55) and total brain volume (26). The cause of hippocampal volume reduction is still unknown but it was proven by McEwen that it was capable of reorganization (30). Processes that lead to oxidative stress may be the cause of damage to this structure and its reduction (23, 24).

Trauma itself may cause the reduction of the hippocampal volume as meta-analysis performed by Karl et al. and Woon et al. report (26, 55). Karl et al. analyzed several studies and revealed that stress-exposed non-PTSD group of patients and PTSD patients in comparison to healthy controls turned out to have significantly smaller hippocampal volume bilaterally (26), which was confirmed by several meta-analyses made by Smith et al., Kitayama et al., Woon et al. (9, 47, 55). Differences in hippocampal volume between non-PTSD and PTSD patients were seen only in samples with severe PTSD patients (2). Left hippocampus was significantly smaller in the PTSD group. On the contrary meta-analysis performed by Woon proved that right hippocampal volume was smaller in the PTSD group (55). Winter et al. found reduced hippocampal volumes among burn-survivors with no diagnosis of PTSD (53), which is consistent with Woon et al. results presenting that left, right and total hippocampal volume reduction was found among stress-exposed non-PTSD group in comparison to healthy controls. Karl et al. suggests that trauma exposure is connected with smaller hippocampal volumes and volumetric alterations may appear in different localizations (26). Pedraza et al. in their paper reported smaller left hippocampus volume in comparison to right hippocampus in healthy participants (38), which was not seen in a study by Woon et al. analyzing hippocampal volume in trauma-exposed non-PTSD patients (55). They made a suggestion that the right hippocampus may be prone to the effect of stress to a greater degree than left hippocampus. Moreover, comparing trauma-exposed non-PTSD and PTSD participants, they found volumetric abnormalities within only the right hippocampus among the PTSD group. They suggest an additional pathological process underlying PTSD, connected with the right hippocampus volume.

Vascular, environmental factors (8, 17, 19-21), as well as oxidative stress (18, 19, 22) may impact the severity of changes within the hippocampus. Among PTSD patients and trauma-exposed healthy participants, abnormalities in cerebral blood flow were noted. Bonne et al. report increased, bilateral cerebellar perfusion in patients with PTSD in comparison to trauma-exposed healthy patients and higher cerebral blood flow within the right precentral gyrus, post central gyrus and superior temporal gyri in trauma-exposed healthy patients compared to healthy participants (4). Moreover, healthy controls had higher cerebral blood flow in left medial temporal region, including hippocampus, prehippocampal and fusiform gyri. Perfusion abnormalities may be an important factor determining symptom severity in patients with PTSD, which was confirmed by Bonne et al., where a positive correlation between extrastriate perfusion and PTSD was shown (4).

White matter

White matter fibers ensure both anatomical and functional connectivity linking distinct regions of the brain and can be analyzed using diffusor tensor imaging and fiber tractography. There are only several studies describing the influence of stress on white matter. Decreased fractional anisotropy (FA) was found in patients with PTSD within the corpus callosum (30, 52), prefrontal cortex (47), anterior cingulum (29, 47, 56) and posterior cingulum (46). Fewer studies reported increased FA within anterior cingulum (1) and superior frontal gyrus (58).

Kitayama et al. presented a study describing two groups of patients exposed to traumatic events, who developed PTSD and did not suffer from PTSD (29). In both groups white matter abnormalities were found within left forceps major, middle frontal gyri and dorsolateral prefrontal cortex. They linked increased FA in the prefrontal cortex with severity of PTSD symptoms. Reuveni et al. revealed that in their study that severity of PTSD symptoms was connected with increased FA along the cingulum and suggested that quality of fiber integrity was positively correlated with the severity of PTSD symptoms (40). Paul et al. made a statement based on their study that early life stress had influenced the microstructural integrity of the white matter, mostly in the genu of the corpus callosum, where the FA was significantly reduced (37). They connect those abnormalities with degenerative effect of stress hormones on still maturing white matter, which is also suggested by Teicher et al. (49). De Bellis et al. and Jackowski et al. reported lower corpus callosum volumes among maltreated children as well (11, 25).

There are critical windows during white matter development when axons are particularly vulnerable and can be damaged by focal stress or trauma as several animal studies have shown. Pruning and myelination process in corpus callosum can be altered by the

Tab. 1. Anatomical alterations within white and gray matter in people exposed to PTSD and traumatic events

	Study	White matter		Study	Grey matter
PTSD	Kitayama et al. (28) Villareal et al. (51)	decreased FA in corpus callosum	PTSD	Fennema-Notestine et al. (14) Woon et al. (55) Smith (47) Kitayama et al. (29)	reduced volume of hippocampus
	Schuff et al. (45)	decreased FA in prefrontal cortex		Woodward et al. (54)	reduced volume of anterior cingulate
	Schuff et al. (45) Zhang et al (57) Kim et al. (27)	decreased FA in anterior cingulum		Hedges et al. (23)	reduced volume of corpus callosum, insula, septum pellucidum
	Fani et al. (13)	decreased FA in posterior cingulum		Rauch et al. (39) Schuff et al. (46) Weniger et al. (52)	reduced volume of subcallosal cortex, amygdala, prefrontal cortex
	Abe et al. (1) Reuveni et al. (40)	increased FA in anterior cingulum		Hedges and Woon (24)	reduced total brain volume
	Zhang et al. (57)	increased FA in superior frontal gyrus		Bonne et al. (4)	increased bilateral cerebral blood flow
	Rinne-Albers et al. (41)	demyelination and dysmyelination process in corpus callosum, uncinate fasciculus, cingulum	Traumatic event	Karl et al. (26) Woon et al. (55) Smith (47) Kitayama et al. (29) Winter and Irlle (53) Pedraza et al. (38)	reduced volume of hippocampus
Prenatal stress event	Sarkar et al. (44)	reduced FA increased PD in right uncinate fasciculus		Bonne et al. (4)	higher cerebral blood flow in the roght precentral gyrus, postcentral gyrus superior temporal gyri
Traumatic event	De Bellis et al. (11) Jackowski et al. (25)	lower corpus callosum volumes			

influence of stress hormones as studies have revealed. During the development of corpus callosum several changes can be detected, such as axonal myelination, redirection and pruning. Axon structural density, organization, myelination can be determined using diffused tensor imaging (DTI). It is a diagnostic tool used to measure the level of water diffusion and water diffusion direction by the use of DTI parameters such as fractional anisotropy (FA). FA is a collective parameter of white matter integrity, informing of diffusion along the axon, and thus cell parameters such as fiber coherence, axonal density, intracellular and extracellular volume and myelination degree. Decreased FA can be an indicator of white matter integrity and in order to attain precise assessment of the white matter, additional parameters are used such as mean diffusivity (MD), radial diffusivity, which is a myelin marker (RD), and axial diffusivity, an axonal marker (AD) (49).

A study performed by Rinne-Alberts revealed decreased FA in the corpus callosum, and using additional DTI parameters, they found demyelination and dysmyelination process in corpus callosum, uncinate fasciculus and cingulum (41). They found increased RD and MD parameters in corpus callosum, which reflects demyelination (less development of the myelin sheet) and dysmyelination (aberrant development of the myelin sheet). A study has shown increased FA in the middle frontal gyri and left superior frontal gyri in patients with PTSD, however with decreased RD

and AD, which they connected with microstructural redevelopment within axon and myelin (28). They also suggest that alterations of white matter in patients with PTSD are probably caused by decreased axonal density or abnormalities within intracellular structure, which is indicated by AD parameter and increased glial cell density or higher myelination indicated by RD parameter.

One can find in the literature that chronic stress can interfere in the morphology of the Ranvier nodes, altering the protein distribution in the corpus callosum and causing longer, thicker and more numerous oligodendrocytic processes (32, 51). Studies on mice performed by Miyata et al. (32) did not find any changes in axon diameter in the corpus callosum but ultrastructural analysis of the Ranvier nodes revealed a reduced length of axon nodes probably caused by chronic stress exposure. The same study claims that chronic stress affects only the structure of mature oligodendrocytes. Moreover, they studied patients with major depressive disorder and found that chronic stress caused rather axonal structure changes than demyelination. DTI study revealed AD reduction, which suggests axonal damage and no deviation in RD, which is the marker of demyelination (33).

There are reports in the literature that decreased FA in white matter tracts adjacent to the hippocampus can be related to stress and focal trauma itself, independently of PTSD (10). Sarkar et al. studied 22 children,

aged 6-9, with prenatal stress events experienced by their mothers and found reduced FA and increased perpendicular diffusivity of the right uncinate fasciculus among those children (44). They concluded that prenatal stress might interfere with neurodevelopment of tracts connecting amygdala and prefrontal cortex, altering the structures itself and, moreover, changes in white matter were “tract specific.” Those changes are linked with increased myelination (44).

Extreme stress and trauma causes anatomical alterations not only within gray matter but white matter as well. The pathological changes were reported not only among patients with diagnosed PTSD but also among trauma-exposed non-PTSD participants. Early life stress that affects maturing white matter can cause permanent damage to the white matter in adults. DTI is a reliable method of visualizing white matter enabling assessment of structural connectivity and the evaluation of subtle changes within white matter.

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