According to the United States National Center for PTSD, post-traumatic stress disorder (PTSD) is a mental health disorder in which a person experiences severe anxiety after exposure to a traumatic event.\(^1\) In the United States, about 8 million adults receive a PTSD diagnosis each year. Trauma exposure is common, with about half of the public exposed to at least one traumatic event in their lifetime.\(^1,3,4\) Although many people who experience trauma exhibit some negative effects, these symptoms usually resolve in time. However, in some people, symptoms continue for an extended period of time, negatively affect daily life, or cause a large amount of distress.\(^1,6\)

PTSD is diagnosed in approximately 8% of men and 20% of women who experience trauma.\(^1\) Magnetic resonance (MR) imaging studies have shown several differences in the brains of patients with PTSD that might give some insight into their behaviors and feelings. Although the cause or causes of these differences are unclear, researchers have suggested they might be due to damage from abnormal cortisol levels, related to alcohol abuse and depression, or caused by a biological predisposition to develop PTSD when exposed to trauma.\(^7-15\)

PTSD-inducing events occur in a variety of circumstances, including abuse, war, natural disasters, and terrorist attacks (see Box 1).\(^1\) People in developing countries experience higher rates of PTSD because of the increased likelihood of urban violence, such as kidnapping, assault, and murder.\(^16\)

Although some traumatic events are more likely to result in PTSD, a person can develop this condition from any life event in which he or she feels traumatized or helpless.\(^1\)

People with PTSD experience a variety of symptoms (see Box 2). Re-experiencing a traumatic event is one of the most common symptoms associated with this disorder. This
Post-traumatic Stress Disorder (PTSD) occurs through remembering the event at unexpected times or as the result of triggers, nightmares, or flashbacks. Flashbacks occur when a person relives an event, feels as if the event is happening again, and experiences the same intense feelings that occurred during the traumatic event.1,5,17 Because of this, people with PTSD often avoid certain things that remind them of the event and that might trigger unpleasant memories. Nightmares, flashbacks, and triggers can result in a condition known as hyperarousal, which causes insomnia, difficulty concentrating, irritability, and the feeling of being constantly on alert.1,4,6,17 PTSD produces increased levels of fear, guilt, and anxiety. People with PTSD might think or feel differently about certain events or people and might not enjoy the same things they did before the trauma. As a result, changes in beliefs and feelings commonly are associated with PTSD. Some patients experience emotional numbing. They find it difficult to feel emotions, which can interfere with personal relationships and daily life. This might be one reason patients with PTSD have higher-than-average divorce rates.1 Depression and substance abuse occur in PTSD patients as well, and about half of men with PTSD struggle with alcohol dependence at some point in their life.1,18,19 Women with PTSD appear to have more problems with depression than with substance abuse.1

Along with these symptoms, patients with PTSD seem to suffer from memory problems.5,20 Deficits in verbal memory and attention are 2 of the most reported findings among PTSD memory studies.5,20-23 Memory issues vary greatly in these patients and can cause a lack of recall and intrusive memories. Some patients seem unable to recall certain aspects of the PTSD-inducing event.7,20 At the same time, these patients might also have recurring unwanted memories of events that are triggered at unexpected times.5,20 A meta-analysis of 28 PTSD studies reported that the amount of memory loss seemed to be related to the type of trauma experienced, with war veterans having the highest level of memory loss.20

Although these symptoms might appear to be psychosomatic, several brain areas differ structurally and functionally in patients with PTSD compared with control patients. This suggests an anatomical and physiological component to the disorder.24 Changes in the hippocampus, amygdala, anterior cingulate cortex (ACC), and prefrontal cortex (PFC) are reported frequently in PTSD studies using MR imaging. These areas
of the brain are important in the brain’s stress response, leading researchers to speculate that exposure to high levels of stress might cause changes in brain structure and function (see Figure 1). Research also suggests that PTSD might be biological, with some brain anatomy being more susceptible to PTSD than others after exposure to a traumatic event. However, studies on children and adolescents who experienced trauma show distinct changes from those who experienced trauma in adulthood. This supports the theory that exposure to trauma might be the cause of anatomical and physical changes in the brain that result in PTSD symptoms. Although the reason for these differences remains unclear, it is important for health care professionals to be aware of how the brain of a patient with PTSD might differ from the brain of a patient who does not have PTSD and to recognize how these differences in brain function might affect behavior.

**Brain Anatomy and PTSD-related Brain Changes**

The outer layer of the brain is referred to as the cortex. The cortex consists of gray matter and is made up of the cell bodies of neurons. Beneath the cortex lies white matter, which is composed of axons that connect the cell bodies in gray matter and allow signals to travel through the brain. Axons are covered in a myelin sheath made of a white fatty material that accelerates nerve impulses and gives white matter its color. Nerve fibers are grouped together into bundles that connect different parts of the nervous system. Projection fibers connect the brain to the spinal cord; association fibers connect different parts of the brain containing gray matter.

The corpus callosum contains bundles of white matter connecting the hemispheres of the brain. Some studies have shown a reduction in the corpus callosum in patients with PTSD. This part of the brain is crucial for communication between the right and left hemispheres. It has been suggested that degenerative changes in this area of the brain might be related to changes in the PFC that also have been observed in these patients. Two different theories have been suggested as to how these changes might be related. One theory states that because the corpus callosum allows communication between the 2 hemispheres, a decrease in myelination of this area might decrease communication and therefore impair development of the PFC. Another theory suggests that atrophy of the PFC might have caused damage to the axons connecting the PFC.

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**Figure 1.** Anatomical structures (A) and functional, motor, and sensory areas (B) of the brain. © 2016 ASRT.
to the corpus callosum. Although the mechanism of this damage has not been determined, it is evident that the corpus callosum is linked to the PFC, and damage to the 2 regions most likely is related. 17

Magnetic resonance imaging evaluations of white matter have shown an overall decrease in white matter in the brains of patients with PTSD and that this cortical thinning is correlated significantly with the severity of PTSD symptoms. 4,37,34-38 Although some general anatomical changes have been observed, notable differences between certain regions of these patient’s brains compared with brains of people who do not have PTSD are suggested. 3,17,24,39-47 The Table provides an overview of brain regions affected by PTSD, their functions, and key anatomical and functional findings on MR images of patients with PTSD.

Prefrontal Cortex
Located in the frontal lobe, the PFC contains the ACC, subcallosal cortex, and the medial frontal gyrus. 48 The PFC is one of the key elements of personality, social relationships, and impulse control. 39 Studies have found differences between the PFC of patients with PTSD and people who do not have PTSD that might help explain some PTSD symptoms.

A meta-analysis of 17 studies that used MR imaging to observe differences in gray matter in the brains of subjects with PTSD suggested that gray matter in the medial prefrontal cortex is reduced significantly compared with trauma-exposed individuals who have not developed PTSD or PTSD symptoms. 4 This area includes the ACC, which also shows a significant decrease in volume when observed separately from the rest of the medial PFC. 49 In studies that compared patients who had PTSD with people who had not experienced a trauma, gray matter reductions also were reported in the medial PFC of the patients with PTSD. 4 Although gray and white matter are important, studies on patients with multiple sclerosis, which results in gray and white matter atrophy, have reported that decreases in gray matter have the strongest correlation to the severity of clinical symptoms compared with white matter atrophy and lesions. Because the PFC controls several aspects of a person’s personality and fear responses, gray matter reduction in this area might explain some of the changes in behavior and attitudes of those suffering from PTSD. 72

### Table

| Principal Adult Brain Structures Affected by Post-traumatic Stress Disorder |
|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
| **Structure/Region** | **Function** | **Anatomical Magnetic Resonance Findings** | **Functional Magnetic Resonance Findings** |
| Prefrontal cortex | Center of personality, social relationships, impulse control | Reduced gray and white matter | Decreased activity |
| Anterior cingulate cortex | Regulates amygdala | Reduced gray and white matter; left anterior cingulate cortex smaller than right anterior cingulate cortex | Decreased activity |
| Rostral anterior cingulate cortex | Associated with emotion and fear responses | Decreased volume | — |
| Dorsal anterior cingulate cortex | Plays a role in decision-making; other cognitive tasks | Decreased volume | — |
| Corpus callosum | Facilitates communication between right and left hemispheres of the brain | Decreased size | — |
| Amygdala | Links memory to emotion; controls arousal | Increased volume | Increased activity |
| Hippocampus | Plays a role in short-term memory; helps encode emotional memory and process fear | Decreased volume | Decreased activity |
Although there are different ways to measure diffusion anisotropy, the most widely used is fractional anisotropy, which uses a mathematical formula to determine areas where diffusion is anisotropic or isotropic. From this information, a map can be made showing areas with these different characteristics (see Figure 3).

In one study, diffusion tensor imaging was used to create fractional anisotropy maps of the whole brain, which then were used to assess the differences in white matter volume between patients who developed PTSD from the same trauma and control patients. Significant decreases were noted in the fractional anisotropy values of patients with PTSD for the ACC, meaning that white matter was decreased significantly in these areas. The left ACC also was smaller than the right, suggesting that the effects of PTSD do not affect both sides of the brain equally.

This effect was reported in other studies in which the left hemisphere of the brain showed more atrophy than the right hemisphere (see Figure 4). White matter volume in the ACC also correlated to the severity of PTSD symptoms. Smaller ACC white matter volumes were seen in patients who experienced a greater degree of anxiety and confusion as a result of PTSD symptoms. Along with white matter changes, gray matter density

**Anterior Cingulate Cortex**

The ACC is located in the superoanterior portion of the corpus callosum (see Figure 2). The ACC is divided into 2 sections, the rostral and dorsal. The rostral ACC is related to emotion and fear responses whereas the dorsal ACC plays a role in decision-making and other cognitive tasks. The ACC is known to regulate the amygdala, which has been shown to be hyperactive in patients with PTSD. This led some researchers to investigate whether there are changes in the ACC of people with PTSD. As a result of these studies, differences in both volume and activation of the ACC have been noted in the brains of patients with PTSD compared with control patients.

Some studies have used diffusion tensor imaging with MR to examine white matter changes in the ACC of patients with PTSD. White matter is a type of fibrous tissue. In this type of tissue, water diffuses in the direction of the fibers and does not diffuse readily in directions perpendicular to the fibers. In this sense, the diffusion of water is characterized as anisotropic; it moves in only one direction. In other regions of the brain, such as gray matter and cerebrospinal fluid (CSF), water is isotropic; it travels in more than one direction. Diffusion tensor imaging is a type of MR imaging that uses these water characteristics to infer information about the types of tissues in certain areas.

The Beck Depression Inventory is a clinical test used to assess the severity of symptoms in patients with depression. It is a 21-item questionnaire in which the patient self-reports and ranks the severity of symptoms on a scale of 0 to 3. Although not intended for diagnosis, this assessment assists clinicians in determining the severity of symptoms, the potential need for hospitalization, and relative changes in symptoms during treatment. Using controls for Beck Depression Inventory scores, the authors compared MR images of those who developed PTSD symptoms with images from similarly depressed patients without PTSD. The images showed a decrease in the rostral ACC volume in the subjects with PTSD. Additional results were seen seemed to decrease in the ACC of patients with PTSD. The right ACC was not decreased significantly in these patients, the size of the right ACC showed strong correlation to the severity of PTSD symptoms.

One study looked at post-trauma survivors of urban violence and tried to compare those who developed PTSD with those who seemed resistant to PTSD. The goal of that study was to determine whether certain people are predisposed to developing PTSD following a traumatic incident. The authors acknowledged that the subjects who developed PTSD symptoms also had higher rates of depressive disorders; therefore, scores from the Beck Depression Inventory were used as a covariate. The Beck Depression Inventory is a clinical test used to assess the severity of symptoms in patients with depression. It is a 21-item questionnaire in which the patient self-reports and ranks the severity of symptoms on a scale of 0 to 3. Although not intended for diagnosis, this assessment assists clinicians in determining the severity of symptoms, the potential need for hospitalization, and relative changes in symptoms during treatment. Using controls for Beck Depression Inventory scores, the authors compared MR images of those who developed PTSD symptoms with images from similarly depressed patients without PTSD. The images showed a decrease in the rostral ACC volume in the subjects with PTSD. Additional results were seen

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**Figure 3.** Two types of diffusion tensor imaging. A. The trace image reflects the total amount of diffusion occurring in each region and highlights the ventricles, with little difference between white and gray matter. B. The fractional anisotropy image highlights regions where diffusion is oriented in a single direction. The ventricles and gray matter are dark, whereas the white matter tracts are bright. Reprinted with permission from Rosenbloom M, Sullivan EV, Pfefferbaum A. Using magnetic resonance imaging and diffusion tensor imaging to assess brain damage in alcoholics. Alcohol Res Health. 2003;27(2):146-152.

**Figure 4.** The significant reduction regions in trauma survivors with recent-onset post-traumatic stress disorder (PTSD) (n = 10) compared with normal controls (n = 20) are rendered onto the standard T1 template of the Montreal Neurological Institute. The trauma survivors with recent-onset PTSD had a significantly decreased gray matter volume in the left ACC (P < .05, family-wise error corrected, with k > 50 voxels). Reprinted from Chen Y, Fu K, Feng C, et al. Different regional gray matter loss in recent onset PTSD and non PTSD after a single prolonged trauma exposure. PloS One. 2012;7(11):e48298. Licensed under the Creative Commons Attribution license.
When controlled for the number of days since trauma exposure, subjects who developed PTSD showed a significant decrease in the volume of the right rostral ACC and left dorsal ACC. When controlling for depression, childhood trauma exposure, and number of days from trauma, there was a reduction in the right rostral ACC of patients with PTSD.\(^{16}\)

Despite variation between studies as to which part of the ACC differs, the average size of the ACC of patients with PTSD appears decreased.\(^{16,34,39,41}\) A few studies have reported that there might be a difference in the shape of the ACC rather than the actual volume; however, this finding is less common.\(^{36,73}\) Traditional MR imaging can be used to show the size of the ACC and the amount of white matter present, and some fMR imaging studies have observed the level of activation in this area. Some have reported that the ACC in patients with PTSD is hyperactive.\(^{38,40,49}\) A decrease in activity in this area can result in difficultly or inability to extinguish a fear.\(^{39,76,77}\)

**Amygdala**

Considering that the ACC plays a role in the activity of the amygdala, it is not surprising that the amygdala also can have irregular activity in patients with PTSD.\(^{34}\) The amygdala is located in the temporal lobe, anterior to the hippocampus (see Figure 1). One of its main roles is to link memory to emotion by creating emotional responses to certain stimuli.\(^{48,55,56}\) Emotion has been linked to memory performance, and some studies have shown subjects to have enhanced memories when they are linked with emotion.\(^{56,78-80}\)

Some have reported that the amygdala can be anatomically different in patients with PTSD compared with control patients. One study used MR imaging to compare the brain anatomy of subjects who developed PTSD with those who did not develop PTSD after experiencing urban violence. After controlling for depression symptoms, childhood trauma, and number of days since the trauma, PTSD subjects showed an increase in the volume of the right amygdala.\(^{16}\) This is a common finding in PTSD research, and several other studies have found concordant results.\(^{48,57}\)

Along with increased size, increased amygdala activation can be demonstrated on fMR scans when patients with PTSD are exposed to frightening images or situations. Several studies performed fMR imaging on patients with PTSD while presenting the patient with trauma-related stimuli. These cues ranged from visual stimuli, such as photographs, to auditory stimuli, such as trauma-related narratives or sounds.\(^{50,46,49,51,58}\)

Shin et al reported that the amygdala in patients with PTSD was hyperresponsive to fear-inducing stimuli unrelated to the patient’s trauma.\(^{48}\) This most likely is due to a lack of regulation from the PFC, which controls the amount of activity in the amygdala. As a result of the decrease in PFC activity seen in PTSD, the amygdala lacks restraints.\(^{59}\) An increase in the size and activity of the amygdala could explain why patients with PTSD experience intense details of the emotional memories of the traumatic event they experienced. The amygdala also controls arousal, so an increase in amygdala activity could lead to the hyperarousal and increased fear observed in patients with PTSD.\(^{57}\)

Some studies did not find changes in amygdala volume and activation between patients with PTSD and control patients. Shin et al proposed possible reasons for this lack of amygdala response, including insufficient triggering of PTSD symptoms and poor image resolution.\(^{48}\)

**Hippocampus**

The hippocampus is located in the medial temporal lobe, posterior to the amygdala (see Figure 1). It appears to play a direct role in short-term memory and also has been shown to work with the amygdala to encode emotional memory and process fear.\(^{48}\) Episodic memory is used to recall events. These types of events, such as recalling a vacation or other memorable experience, are relived as they are remembered. The recollection of facts without remembering how they were learned is called semantic memory. For example, if a person is asked when the Declaration of Independence was signed, he or she might use semantic memory to answer 1776 but not be able to recall the event that led him or her to retain the information. In general, patients with damage to the hippocampus seem to have trouble with short-term, episodic memory; however, they do not have impairment with vocabulary or semantic memories. There have been some cases in which patients
maintained their distant episodic memories after hippocampal damage, making it unclear how the hippocampus is involved in memory. Two main theories suggest why this occurs: the declarative theory and the multiple trace theory.\(^81\)

The declarative theory of memory suggests that old episodic memories are transferred to areas outside the medial temporal lobe, which is where the hippocampus is located. In this case, if damage to the hippocampus occurs, semantic memories and episodic memories that occurred in the past will not be affected. However, because new memories are stored in the hippocampus, damage to that area can result in deficits in creating new episodic memories.\(^81\)

The multiple trace theory suggests that recent and older episodic memories are stored in the hippocampal, perihinal, and parahippocampal regions. According to this theory, memory traces are created when a new memory is formed. These traces represent a memory and are stored in the hippocampal region but sorted in the neocortex where the actual memory is stored. When a memory is accessed, a new trace is made by the hippocampus, resulting in more traces for older and more frequently accessed memories. The more traces a certain memory has, the less likely it will be lost if damage occurs. Damage might result in some traces being lost, which would cause difficulty in accessing the memory and theoretically would lead to a loss of memory quality as well. Over time, semanticization occurs in situations in which the old episodic memories are interwoven into the person’s general knowledge. At this time, the memory is transformed from an episodic memory into a semantic memory that no longer depends on the hippocampus to be recalled and thus would not be affected by damage to the hippocampus.\(^81\)

Regardless of how the hippocampus works, it does seem to play a role in memory recall.\(^7\) Patients with damage to the hippocampus caused by surgery and epileptic seizures show subsequent reductions in memory. A positive relationship has been observed between hippocampal size and the ability to remember lists of words. In these cases, lower verbal memory performance is correlated with smaller hippocampal size.\(^7, 64-65\) It is believed that the left hippocampus is related to verbal memory and the right controls visual memory, which is the ability to remember pictures, objects, and people.\(^64\)

Patients with combat-related PTSD have reported the most severe memory-related issues.\(^7, 61-63\) These memory lapses occur in various levels of severity ranging from forgetting events that happened right after a traumatic experience to forgetting one’s own identity. In addition to short-term issues, memory lapses in distant memories seem to occur for years after the traumatic event.\(^21, 23, 27, 53\) Along with episodic memory deficits, patients with PTSD have trouble with declarative memory, such as remembering facts and lists; however, these patients have shown no deficits in IQ.\(^1, 12, 27\) Veterans have been reported to have more problems with memory, specifically verbal memory, compared with nonveterans, and even more severe verbal memory impairments are seen in military personnel who were prisoners of war compared with military personnel who were not prisoners of war.\(^7, 20, 32, 37\)

Deficits in memory appear to increase with the amount of time a patient has experienced PTSD symptoms.\(^20, 27, 65\) Sekiguchi et al used MR to demonstrate this phenomenon in survivors of the Great East Japan Earthquake. Researchers measured hippocampal volumes before trauma exposure and then at 2 different times after trauma exposure.\(^64\) The researchers found that the volume of the hippocampus decreased soon after trauma exposure and was further decreased 1 year after the trauma, as seen in Figure 5.\(^65\) Control subjects of the same age who had not experienced a trauma showed no decrease in hippocampal volumes, suggesting that trauma exposure had an increasing effect on hippocampal volume as time-since-trauma increased.\(^64\) This finding might offer some explanation as to why veterans have been shown to have increased issues with recall compared with subjects who have experienced other traumas. The majority of studies on veterans were with subjects who served in the Vietnam War and had PTSD for many years. Some researchers suggest that the duration of their trauma might be a cause of the increased intensity of their symptoms rather than the type of trauma they endured.\(^10, 37\)

Because of the important role the hippocampus plays in memory, researchers have wondered about the effect trauma has on the hippocampus.\(^15, 48, 62, 66, 82-84\) Some studies have shown decreased hippocampal volume in the right and left hippocampus as well as smaller ratios of
During this test, the patient is interviewed by a trained professional and answers a series of questions about his or her PTSD symptoms. Each symptom is graded for severity on a scale of 0 to 5, with 0 signifying the symptom is not present and 5 indicating that the symptom is extreme or incapacitating. Because PTSD symptoms vary among patients, these scores allow clinicians to note the severity of certain symptoms, make a diagnosis, and determine how to best treat the patient.

Analysis has shown a significant negative correlation between a CAPS score and left hippocampal volume (ie, patients with smaller hippocampal volumes had higher CAPS scores). These results suggest that hippocampal volume is related to the number and intensity of symptoms experienced by patients with PTSD, although some studies have not shown this relationship.

Results have varied for studies on hippocampal volume of patients with PTSD; however, a decrease in the volume of the hippocampus of these patients has been suggested. Two meta-analyses of PTSD studies found an overall reduction in the volume of the hippocampus in patients with PTSD compared with control subjects who did not have PTSD. In subjects who were exposed to trauma but did not develop PTSD, decreases in hippocampal volume were present but less severe or unilateral. The results of these studies suggest a decrease in hippocampal volume in those exposed to trauma and an exaggerated decrease in subjects who developed PTSD.
Fear Conditioning and PTSD

The PFC, ACC, amygdala, and hippocampus play primary roles in fear conditioning. In fear conditioning, a subject associates a certain stimulus with a fear-inducing stimulus. This is done by exposing the subject to the neutral conditioned stimulus and the fear-inducing unconditioned stimulus repeatedly. After conditioning, when the subject is exposed to the neutral conditioned stimulus, a fear response is evoked unconsciously. If the subject then is exposed repeatedly to the neutral conditioned stimulus without the negative stimulus, the fear response is extinguished. The subject then forms a conditioning memory of the neutral and negative stimuli pair invoking a fear response and an extinction memory of the neutral stimulus alone without the fear response. If the fear conditioning and extinction conditioning took place in different contexts, whether a person feels fear when exposed to the neutral stimulus now depends on the context of the situation he or she is in when exposed to the neutral stimulus.

For example, imagine a person is placed in a white room and conditioned to feel fear when exposed to a red ball. The next day, the person enters a room with tan walls and is exposed repeatedly to the red ball without a negative stimulus; the fear is extinguished. In the future, if the person sits in a tan room and sees a red ball, no fear response is evoked because the context of the situation was similar to when the fear was extinguished. In another context, the red ball might evoke a fear response. This is known as extinction recall, in which the extinction environment becomes a safe context. Fear recall, on the other hand, occurs when the environment in which the fear was acquired becomes a dangerous context and exposure to this context along with the neutral conditioned stimulus invokes a fear response.

Hyperarousal is one of the main symptoms of PTSD. Patients with hyperarousal symptoms experience a constant state of fear, might feel panicked or agitated, and have a feeling of impending danger even in nondangerous situations. Some researchers have suggested that this hyperactive response to fear is a result of differences in brain function and the effect of these differences on fear conditioning. One possibility is that patients with PTSD have an increased susceptibility to fear conditioning, thereby causing them to relate neutral objects to fearful feelings more easily and more often than do people without PTSD. Another possibility is that once fear is conditioned, patients with PTSD have a decreased ability to extinguish acquired fears or an inability to recognize safe contexts, thus giving those patients an inappropriate fear response even when in a safe environment. This is particularly evident in patients with PTSD who might become conditioned to feel fear when exposed to certain noises. For example, an airplane crash survivor might feel fear if he or she hears the sound of an airplane. While watching a movie, the person hears the sound of an airplane and feels afraid even though he or she is in the safe context of a movie theater. MR studies have shown differences in the brains of patients with PTSD that might offer some insight into why these PTSD symptoms occur.

Studies have shown apparent changes in the volume and activity of several brain regions in PTSD subjects but a potential difference in the way the brains of patients with PTSD respond to fear-conditioned stimuli. Several fMR studies have looked at the way the brains of these patients react when exposed to a neutral conditioned stimulus in a safe context vs a dangerous context. The brains of patients with PTSD seem unable to use contextual information to differentiate between a safe vs a dangerous environment. While the fear is being extinguished in PTSD subjects, there seems to be decreased activation of the ventromedial PFC and increased activation of the amygdala compared with control subjects. After extinction, when exposed to the neutral stimulus in a safe context, patients with PTSD have an abnormally high level of fear and the ventromedial PFC and hippocampus activity is decreased. At the same time, amygdala and ACC activity increase, most likely due to a lack of regulation by the less active PFC. In control subjects, during extinction, the PFC shows higher levels of activity than the amygdala, which represents fear levels, is decreased. This suggests that in a healthy brain, during extinction, the PFC regulates the amount of amygdala activity that is appropriate for the safe context. This forms an extinction memory so that the amygdala will have a similar level of activity when in the safe context in the future, which seems to be the case. In patients with
PTSD, decreased activity in the PFC during extinction causes a lack of regulation of the amygdala and therefore an increase in activity in the amygdala. This might cause problems in forming an extinction memory and difficulty in recognizing the context as safe. Because the hippocampus plays such a large role in memory, a decrease in activation of the PFC and hippocampus while in the safe situation might cause further difficulty with recall of the extinction memory. This leads to an inability to recognize the safe situation, resulting in an abnormally high level of fear.  

Interestingly, people with PTSD also showed an inappropriate neurological response to the neutral stimulus in a dangerous context. Although these people showed an increase in amygdala activation when exposed to the conditioned stimulus in the safe environment, they showed a lower-than-normal level of amygdala and PFC activation when in the dangerous context compared with control subjects. Differing amygdala activity levels lead patients with PTSD to experience higher-than-normal levels of fear in safe contexts and lower-than-normal levels of fear in dangerous contexts.  

This supports the theory that patients with PTSD might have deficits in processing contextual information that would allow them to feel safe in a safe situation, thereby causing them to feel fear at inappropriate times. It appears that patients with PTSD might not only feel fear at inappropriate times, but also do not feel the expected levels of fear when in dangerous contexts.

Causes of PTSD-related Brain and Memory Changes

The cause of brain and memory changes remains unclear, but several theories have been suggested. One theory suggests that exposure to stress causes anatomical changes in the brain and defects in the stress response. When a person is exposed to stress, the hypothalamus releases corticotrophin-releasing factor. This release causes the pituitary gland to produce adrenocorticotropic hormone (ACTH), which triggers the adrenal cortex to produce cortisol. The release of cortisol, a type of glucocorticoid hormone, then acts on the pituitary gland, hippocampus, and hypothalamus to halt the stress response and prevent further cortisol release. This is referred to as the hypothalamic-pituitary-adrenal axis.  

Although the initial traumatic event causes high levels of cortisol to be released, studies have shown that people with PTSD exhibit chronically high levels of corticotrophin-releasing factor in their CSF and lower-than-normal blood cortisol levels throughout their lives, suggesting that chronic stress, and PTSD in particular, might cause changes to the hypothalamic-pituitary-adrenal axis.  

Glucocorticoids, such as cortisol, cause an increase in cells’ vulnerability to metabolic changes and allow tissues to become damaged more easily. High levels of cortisol have negative effects on the hippocampus in particular, which seems to be very vulnerable to stress. It appears that glucocorticoid release results in a decrease in hippocampal dendrites and neurons, changes in synapse structure, and a lack of neuronal regeneration. Studies have shown a decrease in hippocampal volume after long-term glucocorticoid administration and as a result of prolonged stress. Patients with PTSD have a large amount of stress during the initial trauma and continue to live in a similar high-stress environment after the trauma because of nightmares, flashbacks, trauma triggers, and hyperactive fear responses. Because hippocampal size has been shown to have an inverse relationship to the duration of PTSD symptoms, chronic stress conditions might continue to damage the hippocampus even after the initial trauma. In addition, defects in the hypothalamic-pituitary-adrenal axis can interfere with the negative feedback loop, causing abnormal levels of cortisol to be present throughout the course of the disorder. Aside from increased stress caused by PTSD symptoms, a lack of control of cortisol levels might cause further damage to the brain, resulting in increased brain changes in patients who have protracted PTSD symptoms.  

Because the hippocampus plays such a large role in memory, some have suggested that hippocampal damage due to glucocorticoid release might result in the memory issues experienced by patients with PTSD. In addition to overall volume decreases, differences have been noted in a certain subfield of the hippocampus, the dentate gyrus, which contains neural adult stem cells important for neurogenesis and critical for memory formation. Glucocorticoid and cortisol administration in healthy subjects has resulted in impairments in verbal declarative memory, one of the
key deficits in patients with PTSD, further supporting this hypothesis. Increases in cortisol due to stress also have been shown to decrease memory temporarily.\textsuperscript{99,101} In these cases, memory function returned to normal after cortisol levels decreased, showing a relationship between cortisol and memory function.\textsuperscript{99,101}

In further support of this theory, Cushing disease is characterized by high levels of cortisol, and patients with the disease have shown decreased hippocampal volume and deficits in memory.\textsuperscript{17} In theory, if glucocorticoids are the problem, they could have a large effect on the hippocampus because of the high number of glucocorticoid receptors in this part of the brain.\textsuperscript{8,27,66}

The corpus callosum also seems to be vulnerable to the negative effects of cortisol. Because it is composed of white matter, myelination is critical, and stress hormones inhibit the production of glial cells that are responsible for myelination.\textsuperscript{17} This might explain why some report the size of the corpus callosum to be smaller in patients with PTSD, with an increased effect on the corpus callosum of patients exposed to trauma at a young age, before the corpus callosum is developed fully.\textsuperscript{17,99,101,103}

One of the problems with this theory is that glucocorticoids affect both sides of the brain equally, which does not explain why some studies report that in patients with PTSD, only one side of the hippocampus is smaller.\textsuperscript{4,7,66,69} Serotonin, on the other hand, plays a role in the stress response and does not have a symmetric effect on the brain.\textsuperscript{7,104} Studies of serotonin have shown that tianeptine, a drug that decreases serotonin levels, also decreases the memory deficits from stress, suggesting that serotonin might play a role in hippocampal damage from stress.\textsuperscript{27,105-107} In addition, selective serotonin reuptake inhibitor drugs often are used as an effective treatment for PTSD.\textsuperscript{1,5}

It also is possible that altered volume in the hippocampus and ACC is not trauma induced but rather present at birth, acting as a risk factor for development of PTSD when a person is exposed to trauma.\textsuperscript{4,7,25-28,108} Sekiguchi et al found that earthquake survivors who experienced PTSD symptoms had smaller ACC volumes than survivors who did not develop PTSD. However, when comparing MR images acquired before trauma exposure with post-trauma images, researchers found that smaller ACC volumes already were present in the group that later developed PTSD symptoms. Because the ACC plays a role in processing fear, it is possible that smaller ACC volumes before the trauma resulted in deficits in fear processing when exposed to the earthquake, which led to a predisposition to develop PTSD symptoms.\textsuperscript{55,107} In addition, some twin studies have shown smaller hippocampus volumes in patients with PTSD and their identical twins who were not exposed to trauma. In these studies, patients with smaller hippocampal size also were experiencing more severe PTSD symptoms.\textsuperscript{4,13,25,26,66} These results support the theory that smaller hippocampal volume is a risk factor for development of PTSD rather than a result of trauma exposure.\textsuperscript{4,25,26}

Considering the large amount of support for both theories, it might be that patients with PTSD have altered brain function from birth that leads to further damage from glucocorticoids.\textsuperscript{8} A third explanation is that decreased hippocampal volume is unrelated to PTSD and is instead a result of comorbidities, such as alcohol abuse and depression.\textsuperscript{6,8}

Effects of Trauma Exposure

Children and adolescents might respond to trauma in different ways. At young ages (<7 years), children might have trouble with toilet training and being separated from their parents. From ages 7 to 11 years, children might have nightmares, experience aggressive behavior, have trouble in school, or have difficulty making friends. They also might attempt to process trauma by drawing pictures of the event, telling stories, or creating trauma-related play scenarios. As children get older, their symptoms begin to mirror adult PTSD symptoms.\textsuperscript{1} Children often seem resilient after experiencing trauma and might develop subclinical post-traumatic stress without severe symptoms. In time, however, symptoms might emerge and post-traumatic stress and depression might develop into chronic conditions in adulthood.\textsuperscript{7} These differences might be related to maturity of the brain anatomy at the time of trauma exposure.

Before birth and into early childhood, new neurons are formed at rates of up to 40 000 new synapses per second.\textsuperscript{110} At age 6 months, myelination begins in the
At this time, the volume of gray matter and white matter increase, thus increasing overall brain volume. By age 2 years, the increase in neurons is complete and children are left with an overabundance of neurons, most of which are unnecessary. Synaptic pruning then begins, during which time approximately 50% of these neurons are eliminated. Until age 17 years, gray matter decreases because of synaptic pruning while myelination of axons continues, causing an increase in white matter. Because a decrease in gray matter occurs during the time that white matter increases, overall brain size stays the same. Several areas of the brain, including the hippocampus, amygdala, and PFC, continue to develop and increase in size into adulthood. Because these areas undergo development at a young age and are more vulnerable to damage, research has been conducted on how child maltreatment and other types of trauma exposure affect these brain regions.

**Intracranial Volume**

Child abuse is one factor leading to the development of PTSD symptoms and includes direct emotional, physical, and sexual abuses; neglect; and witnessing domestic abuse. Pediatric patients with PTSD who were victims of abuse but are otherwise medically healthy have shown several differences in brain anatomy. The intracranial and cerebral volumes of these patients were decreased significantly compared with those of control subjects. In addition, the lateral ventricles and the cortical and prefrontal cortical areas contained significantly more CSF. The size of the lateral ventricles also increased with the duration of maltreatment. Figure 6 shows an MR image of a child suffering from abuse-related PTSD compared with a control subject who did not have PTSD. In this case, the lateral ventricles were significantly larger in the brain of the patient with PTSD.

In addition, intracranial volume was correlated with the age at which the patient experienced the trauma. Patients who experienced trauma at a younger age had smaller intracranial volumes and decreased intracranial volume as the duration of the maltreatment increased. Subjects who experienced more than one traumatic event in childhood were more likely to develop PTSD as an adult; however, this effect seems to be dependent on the patient’s age at the time of the trauma. One study found that subjects who experienced sexual abuse in adolescence after age 12 years were 10 times more likely to develop PTSD as an adult compared with those who experienced sexual abuse before age 12 years. These findings suggest that childhood trauma, specifically abuse, might interfere with brain development, and trauma might have a different effect on development when experienced at a younger age or for an extended period of time.

**Corpus Callosum**

In childhood, the corpus callosum is not fully developed. The posterior region becomes myelinated at a much younger age than does the anterior region, which is one of the last areas of the brain to develop. Because the anterior and posterior areas of the corpus callosum develop at different times, they are more susceptible to damage and are vulnerable to stress at different times. As a result, stress at an early age might affect the entire undeveloped corpus callosum, and stress at a later age might affect the undeveloped anterior region while the posterior corpus callosum remains intact. In child maltreatment studies, the corpus callosum appears to decrease significantly in size as the duration of abuse increases. However, patients who were exposed to trauma at a young age have been reported to have deficits in other parts of the corpus callosum. This suggests that the effect of abuse on the brain is related to the age at which the abuse occurs.
Post-traumatic Stress Disorder and Magnetic Resonance Imaging

More severe volume effects were seen with longer duration of abuse, and these effects also seemed to be amplified in younger patients. Although these trends were seen in children who had PTSD as a result of child abuse, another explanation can be offered. A massive amount of brain growth occurs in the first 2 years of life, with intracranial volume nearing its full size by age 5 years. Although trauma and stress most likely play a role in brain development, many children living in abusive situations also experience environments that might lead to underdevelopment of brain tissue. Stimulating environments and proper nutrition also are important to brain development, as is proper nutrition while in utero. In this study, however, it was determined that malnutrition was unlikely to be the cause of decreased brain volume because the participants were of normal weight during the time of the study and at birth.

Late Adolescent Trauma

Natural disasters are among the greatest causes of PTSD. The 2008 Great Sichuan earthquake in China affected more than 46 million people and killed almost 70,000. Many studies have been performed on how this disaster affected the brains of adults who experienced the earthquake, and some researchers wondered if traumatic events affect a developing brain in a different way. Du et al were the first to study subconscious neural responses to stimuli in adults who experienced late adolescent (age 17-19 years) trauma. Although the goal of many studies is to determine changes in patients who have already received a clinical diagnosis of PTSD, this study chose to image the brains of patients with subclinical PTSD who were known to have experienced the earthquake. The subjects were shown 4 minutes of 6 alternating images. Within these images were neutral and earthquake-related images. The subjects were unaware of the presence of the earthquake-related images and the purpose of the study. The goal was to determine how the subconscious brain responded to trauma-related imagery.

The results of the study on the earthquake survivors contrasted with the results of other adult studies in several areas. No difference was seen in amygdala activation between earthquake and nonearthquake images. However, in adult patients with PTSD, increased amygdala activation and decreased PFC function in attention and concentration areas have been noted. In addition, a decrease in ACC and medial PFC activation was expected; however, the subjects actually showed an increase in activation of these areas. This might have been because of the age at which the subjects were exposed to trauma.

In adolescents, brain development occurs at varying rates at different times. If an adolescent is exposed to a traumatic experience during a period of rapid development in a certain part of the brain, there is a greater chance that this area of the brain will be affected. Even at age 19 years, the ACC and PFC are not developed fully and require greater activation for processing of emotions. Developmental disruption of these areas because of trauma might have caused the adult brain to require higher levels of ACC and PFC activation to process emotions. This speculation is further supported because as ACC activation increased, PTSD symptoms decreased. This result has been found in previous studies, and it has been suggested that the ACC plays some role in regulating the amygdala. In the Du et al study, increased ACC activation might have regulated the amygdala and caused the lack of amygdala response. Researchers suggested that this control system could be the reason these subjects did not develop clinical PTSD when exposed to a severe trauma.

Conclusion

Extensive research has been conducted on the brains of patients with PTSD to determine whether they might differ from people who do not have PTSD. Diffuse decreases in white and gray matter have been reported in patients who develop PTSD after various traumas. The areas in which these types of white and gray matter changes occur might provide some insight into the anatomical and physiological reasons for PTSD symptoms.

Despite some inconsistencies between studies, strong trends in PTSD research have emerged. For health care professionals, it is important to be aware of the potential differences in the brain of a patient with PTSD and the effects that these differences might have on behavior.
References


Post-traumatic Stress Disorder and Magnetic Resonance Imaging


Post-traumatic Stress Disorder and Magnetic Resonance Imaging

1. In patients with post-traumatic stress disorder (PTSD), symptoms such as insomnia, difficulty concentrating, irritability, and the feeling of being constantly on alert is a condition known as:
   a. numbing.
   b. hyperarousal.
   c. avoidance.
   d. anxiety.

2. Which of the following areas of the brain are important in the brain’s stress response and frequently show changes on magnetic resonance imaging studies of patients with PTSD?
   1. amygdala
   2. anterior cingulate cortex (ACC)
   3. hippocampus
   a. 1 and 2
   b. 1 and 3
   c. 2 and 3
   d. 1, 2, and 3

3. Which physical property does diffusion tensor imaging use to analyze brain composition?
   a. water diffusion
   b. hydrogen atom concentration
   c. blood flow
   d. tissue density

4. Fractional anisotropy maps have shown that the ACC of patients with PTSD:
   a. is hypoactive.
   b. has reductions in gray matter density.
   c. shows decreased white matter.
   d. is enlarged.

5. Hyperarousal symptoms experienced by many patients with PTSD are most likely caused by an increase in activity in which part of the brain?
   a. hippocampus
   b. amygdala
   c. ACC
   d. prefrontal cortex (PFC)
6. The memory deficits seen in patients with PTSD are significantly correlated with IQ deficits also seen in these patients.
   a. true
   b. false

7. While a fear is being extinguished in a patient with PTSD, the amygdala shows increased activation. What is the most likely cause of this increased activity?
   a. Memory deficits cause a faulty memory of the initial fear conditioning.
   b. Increased hippocampal activation is overstimulating the hypothalamic-pituitary-adrenal axis.
   c. The PFC is not regulating the amygdala properly.
   d. High levels of cortisol are activating receptors in the amygdala.

8. Glucocorticoid release results in:
   a. an increase in neuronal activity.
   b. a decrease in blood sugar.
   c. a decrease in hippocampal dendrites.
   d. hypoactivity of the PFC.

9. The corpus callosum is particularly vulnerable to the negative effects of cortisol because:
   a. the corpus callosum continues to develop into late adulthood.
   b. cortisol inhibits the production of glial cells important for myelination.
   c. the corpus callosum has a high number of glucocorticoid receptors.
   d. damaged white matter of the corpus callosum can affect surrounding neurons.

10. In what way does the corpus callosum of patients with PTSD who experienced trauma in adulthood differ from that of people who experienced trauma in childhood?
    a. The posterior corpus callosum in those who experience trauma as adults remains intact.
    b. The entire corpus callosum of those who experience trauma as adults shows deficits.
    c. The ACC is enlarged in those who experience trauma as adults.
    d. No deficits are seen in the corpus callosum of patients who experience trauma as adults.

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