Neuroimaging Studies Reveal Brain Changes in Posttraumatic Stress Disorder

Psychological trauma is highly prevalent — most people experience traumatic events in their lifetime. While most people recover from the experience of a trauma, some go on to develop posttraumatic stress disorder (PTSD) or other conditions. PTSD is characterized by three symptom clusters: re-experiencing of the event, avoidance or numbing, and hyperarousal symptoms.

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This type of study design cannot establish causality but has provided important information about the neurobiology of PTSD. Ingenious study designs are beginning to emerge, such as longitudinal studies (naturalistic and treatment-related) and twin studies. Structural neuroimaging studies are beginning to map out brain changes in PTSD, but many issues remain to be resolved.

This article will review structural and spectroscopy studies in PTSD and will discuss current theories of structural brain changes in this condition. The majority of structural imaging in PTSD has relied on magnetic resonance imaging (MRI) to examine gross anatomical abnormalities and volume changes of specific brain structures. Proton magnetic resonance spectroscopy (1H-MRS) also has been used to quantify certain neurometabolites in vivo.

THE HIPPOCAMPAL FORMATION

The hippocampus has received tremendous attention in PTSD research. The interest in this structure was sparked by vast preclinical literature of the effects of stress on the hippocampus. The hippocampus and adjacent entorhinal cortex have crucial functions in learning and memory, especially declarative or factual memory. The hippocampus is closely connected to the amygdala and also has a role in emotional regulation. Furthermore, it was recently discovered that neurogenesis occurs in the hippocampus of the adult brain.

The flip side of this high hippocampal plasticity is its increased vulnerability to a series of insults such as hypoxia, hypoglycemia, toxins, viruses, and even stress. Mounting preclinical evidence in different species has demonstrated that severe psychosocial stress causes neuronal shrinkage (atrophy) or even neuronal death in the hippocampus. Numerous studies in nonhuman species have demonstrated hippocampal atrophy in animal models of chronic stress, particularly in area CA3. This damage to hippocampal neurons is mediated by glucocorticoids and excitatory neurotransmitters via the N-methyl-D-aspartate (NMDA) receptor. For this reason, this type of damage is also known as excitotoxic or neurotoxic damage.

Hippocampal Volume in PTSD

Several studies have examined hippocampal volume in PTSD. These studies have used MRI and volumetric techniques to calculate hippocampal size. The type of trauma investigated, the methods to calculate and normalize volumes, and the control groups have varied among the studies.

Some studies have focused on com-
bat-related PTSD subjects. A summary of hippocampal findings in several studies focusing on combat-related PTSD is presented in Table 1 (see page 846). Bremner and colleagues investigated 26 patients with chronic, combat-related PTSD and 22 matched controls. PTSD subjects were found to have an 8% average decrease in right hippocampal volume compared with controls. Left hippocampal volume was decreased an average of 3.8% in PTSD subjects, but this was not statistically significant. Temporal and caudate volumes were measured as control regions and were not different between groups. Hippocampal volumes were not corrected for total brain size.

Similar findings have been replicated in several studies. Gurvists included seven veterans with combat-related PTSD, seven veterans without combat-related PTSD, and eight controls. Hippocampal volumes were 27% smaller in the PTSD subjects compared with both control groups. No differences were found between groups on volumes of the amygdala, temporal horn, whole brain, ventricles, or ventricular–brain ratios (indices of general atrophy). These results suggest hippocampal changes are related to PTSD symptoms but not to trauma alone, because trauma-exposed individuals without PTSD had no hippocampal volumetric changes.

![Figure 1. Scatter plot of PTSD severity versus left hippocampal volume in 12 PTSD subjects.](image)

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Findings</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>17 CSA/PTSD, 17 controls</td>
<td>12% decrease in left hippocampal volume</td>
<td>Bremner13</td>
</tr>
<tr>
<td>21 CSA (15 with PTSD), 21 controls,</td>
<td>4.9% decrease in left hippocampal volume, 2.9% decrease in right hippocampal volume (n.s.)</td>
<td>Stein14</td>
</tr>
<tr>
<td>12 PTSD (6 with CSA), 10 controls</td>
<td>12% decrease in bilateral hippocampal volume</td>
<td>Villarreal15</td>
</tr>
<tr>
<td>10 CSA/PTSD, 12 with CSA/no PTSD, 11 controls</td>
<td>16% decrease in hippocampal volume in PTSD compared with trauma controls</td>
<td>Bremner16</td>
</tr>
<tr>
<td>10 subjects with PTSD, 27 trauma survivors</td>
<td>No differences in hippocampal volume at baseline or 6 months posttrauma</td>
<td>Bonne18</td>
</tr>
<tr>
<td>11 battered women with PTSD, 11 battered women without PTSD</td>
<td>No difference in hippocampal volume</td>
<td>Fennema-Noestestine24 (a)</td>
</tr>
<tr>
<td>25 survivors of the sarin attack in Tokyo</td>
<td>Automated method, 8 subjects past PTSD, 1 current PTSD, 16 never had PTSD, No hippocampal changes</td>
<td>Yamasue25</td>
</tr>
</tbody>
</table>

(a) = Negative study conducted in adults with chronic, severe PTSD

PTSD = posttraumatic stress disorder; CSA = childhood sexual abuse, n.s. = not statistically significant.
Figure 2. Hippocampal volumes in PTSD subjects before and after 9 to 12 months of treatment with paroxetine.

Gilbertson et al.\textsuperscript{10} studied monozygotic twin pairs discordant for combat exposure. One brother in each pair had served in Vietnam and the other brother had not. Twelve subjects with severe PTSD and their identical twins were compared with 23 non-PTSD twin pairs. Both subjects with severe PTSD and their unexposed twins had a total hippocampal volume that was 10% smaller than that of the non-PTSD pairs. PTSD symptom severity correlated negatively with hippocampal volumes both in the affected twin and the nontraumatized, non-PTSD brother. The results were interpreted as indicative of genetic factors determining hippocampal volumes.

In a small study, Hedges et al.\textsuperscript{11} compared four subjects with combat-related PTSD and no histories of substance abuse with four normal controls. Bilateral hippocampal volumes were smaller in PTSD subjects. Both groups were similar on volumes of total brain, ventricles, and gray and white matter. These findings are important because alcohol dependence is associated with hippocampal atrophy\textsuperscript{12} and therefore has been a confounding factor in PTSD volumetric studies.

Other reports have focused on adult survivors of childhood abuse. A summary of hippocampal findings in civilian PTSD is presented in Table 2 (see page 847). Bremner et al.\textsuperscript{13} studied 17 adults with PTSD from childhood physical abuse, sexual abuse, or both, as well as 17 nonabused controls. PTSD subjects had a 12% mean decrease in left hippocampal volume compared with controls; this change was not accounted for by use of alcohol. A nonsignificant mean decrease of 5% was noted in right hippocampal volume. No differences in temporal or caudate volumes were found. Stein et al.\textsuperscript{14} studied 21 women with a history of severe sexual abuse, 15 of whom had PTSD, and 21 controls who were nonabused

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Results</th>
<th>Author</th>
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<tbody>
<tr>
<td>21 combat veterans, 8 controls</td>
<td>10% decrease in NAA/Cre in right MTL</td>
<td>Freeman\textsuperscript{29}</td>
</tr>
<tr>
<td>18 combat veterans, 19 controls</td>
<td>23% decrease in bilateral hippocampal NAA</td>
<td>Schuff\textsuperscript{31}</td>
</tr>
<tr>
<td>11 abused children, 11 controls</td>
<td>Decreased NAA/Cre ratio anterior cingulate</td>
<td>De Bellis\textsuperscript{34}</td>
</tr>
<tr>
<td>8 PTSD, 5 controls</td>
<td>Decreased NAA (trend) in left hippocampus.</td>
<td>Villarreal\textsuperscript{32}</td>
</tr>
<tr>
<td>14 veterans with PTSD, 7 veterans without PTSD</td>
<td>11% decrease in left hippocampal NAA/Cre</td>
<td>Mohanakrishnan-Menon\textsuperscript{30}</td>
</tr>
<tr>
<td>9 POWs with PTSD, 12 POW without PTSD</td>
<td>Decreased NAA/Cre in left MTL (trend)</td>
<td>Brown\textsuperscript{31}</td>
</tr>
</tbody>
</table>

PTSD = posttraumatic stress disorder; POW = prisoner of war; NAA = N-acetyl aspartate, Cho = Choline, Cre = Creatine, MTL = medial temporal lobe; = decreased
women. Left hippocampal volume was 5% smaller in the abused women (those both with and without PTSD), while right hippocampal volume had a non-significant decrease.

Another study investigated 12 patients with PTSD from mostly civilian trauma (with the exception of 1 combat veteran) and 10 controls without PTSD. Six of those with PTSD had histories of childhood abuse. The patients with PTSD had hippocampal volumes that were, on average, 12% smaller bilaterally. This difference was significant after correcting for lifetime weeks of alcohol intoxication. Left hippocampal volumes correlated negatively with PTSD severity (Figure 1, see page 847). PTSD and depression scores correlated negatively with left hippocampal volume, but PTSD scores were a better predictor of hippocampal volumes.

In another study, Bremner et al. compared 10 women with histories of childhood abuse and PTSD and 12 women with childhood abuse but no PTSD with 11 nontraumatized controls. Bilateral hippocampal volumes were 16% smaller in the PTSD group compared with the traumatized controls and 19% smaller compared with the non-traumatized controls.

Vermoten and colleagues conducted brain MRIs in PTSD patients before and after 9 to 12 months of treatment with paroxetine. Twenty out of 28 participants completed all procedures. PTSD symptoms improved significantly with paroxetine; additionally, a 4.6% mean increase in hippocampal volume was observed after treatment (Figure 2, see page 848).

Some reports have failed to replicate changes in hippocampal volume in PTSD. Bonne et al. conducted brain MRIs in 37 people about 1 week after trauma and again 6 months later. No differences were found in hippocampal volumes between the 10 who developed PTSD and the 27 who did not, either at baseline or at the 6-month follow-up. These findings are inconclusive because they do not support the notion of pre-existing hippocampal changes or hippocampal damage resulting from the trauma. However, the participants had a more recent onset of symptoms compared with those in studies that showed smaller hippocampi, in which the patients typically had PTSD present for decades at the time they were studied. It is hoped that the authors will report subsequent brain measures in the patients from this study.

Studies in children with PTSD have failed to replicate hippocampal volume changes but report differences in other brain structures. These studies will be reviewed later in this article. The lack of hippocampal changes in children with PTSD is intriguing because adult survivors of childhood abuse have been found to have smaller hippocampi, suggesting smaller hippocampi may only be evident once the brain reaches maturation.

Of the studies that failed to replicate hippocampal findings in PTSD, only two were conducted in adult subjects with chronic and severe PTSD. Schuff et al. found no differences in hippocampal volume between 18 people with combat-related PTSD and 18 controls. Participants with PTSD were found to have lower hippocampal N-acetylasparte (NAA), a neuronal marker. Implications of this finding will be discussed later in this article. The other study was conducted by Fennema-Notestine and colleagues, who compared 22 battered women, 11 with and 11 without PTSD, with 17 controls and found no differences in hippocampal or parahippocampal gyrus volumes.

Yamasue et al. investigated 25 survivors of the Tokyo sarin attack, nine with lifetime PTSD and 16 that never had PTSD. Of the nine with lifetime PTSD, only one had active symptoms at the time of the evaluation. This group did not focus on the hippocampus and instead used a fully automated method to compare all brain regions. Compared with trauma survivors, those with lifetime PTSD were found to have decreased left anterior cingulate gray
matter volume and no difference in hippocampal volume. This patient sample did not have the severity and chronicity present in other study samples with demonstrated hippocampal changes.

In conclusion, the majority of reports in adults patients with chronic and severe PTSD related to combat exposure or childhood abuse report reductions in hippocampal size. Two studies failed to replicate these findings; one of combat veterans and another of battered women. Additionally, patients with PTSD in remission and those investigated 6 months after trauma did not demonstrate hippocampal changes. Finally, no changes in hippocampal size have been found in abused children with PTSD.

PROTON MAGNETIC RESONANCE SPECTROSCOPY

Proton magnetic resonance spectroscopy (1H-MRS) is conducted in standard MRI scanners and is able to provide a "chemical picture" of the intact brain. 1H-MRS allows the measurement of neurometabolites such as NAA, choline-containing compounds (Cho), and creatine (Cre), among others. NAA is located only in neurons and therefore is considered an indicator of neuronal integrity. Reduced NAA has been associated with neuronal injury or death. NAA provides additional information (besides volume changes) about neuronal integrity and therefore is an important and complementary technique to volumetric studies.

Single-voxel 1H-MRS has been used to investigate markers of neuronal integrity in the medial temporal lobe of PTSD subjects. In this type of study, one brain region, where the voxel is placed, is analyzed at a time. In one study using this technique, Freeman et al. found that 21 patients with combat-related PTSD had a 10% mean reduction in right medial temporal lobe NAA/Cre ratio compared with eight combat-veteran controls without PTSD. Within the PTSD group, the right medial temporal lobe NAA/Cre values were 6% lower than the left. Table 3 summarizes spectroscopy studies in PTSD (see page 848).

Schuff et al. found that 18 veterans with combat-related PTSD had a 23% bilateral decrease in hippocampal NAA (without hippocampal volume changes) compared with 19 controls. Mohanakrishnan Menon et al. found that left hippocampal NAA/Cre was about 11% lower in 14 veterans with mostly combat-related PTSD, compared with seven veterans without PTSD. Brown et al. investigated nine former prisoners of war (POWs) with PTSD and 12 POWs without PTSD. Those with PTSD had a trend toward lower left medial temporal lobe NAA/Cre.

A preliminary report of eight PTSD patients with civilian trauma and five healthy controls revealed a trend toward lower absolute NAA and Cre in the left hippocampus. Analysis of the complete subject sample indicated that left hippocampal NAA was only lower in younger PTSD patients compared with younger controls (unpublished data, 2004).

<table>
<thead>
<tr>
<th>TABLE 4. Other Brain Changes in Adults with PTSD</th>
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<tbody>
<tr>
<td>Subjects</td>
</tr>
<tr>
<td>Former POWs</td>
</tr>
<tr>
<td>41 combat veterans, 21 controls</td>
</tr>
<tr>
<td>12 PTSD, 10 controls</td>
</tr>
<tr>
<td>11 battered women with PTSD, 11 without PTSD</td>
</tr>
<tr>
<td>25 survivors of the sarin attack in Tokyo</td>
</tr>
<tr>
<td>18 Vietnam veteran nurses, 9 with and 9 without PTSD</td>
</tr>
<tr>
<td>10 combat veterans with PTSD, 21 controls</td>
</tr>
<tr>
<td>48 MZ twin pairs discordant for combat exposure</td>
</tr>
<tr>
<td>12 PTSD, 10 controls</td>
</tr>
</tbody>
</table>

PTSD = posttraumatic stress disorder, POWs = prisoners of war, CSF = cerebrospinal fluid, MZ = monozygotic.
In summary, 1H-MRS studies mostly have been conducted in combat veterans with PTSD and have found decreased hippocampal or medial temporal lobe NAA concentrations, usually expressed as ratios to Cho or Cre. These findings are consistent with decreased hippocampal neuronal integrity or density. Studies report deceased NAA in the right medial temporal lobe, 29,33 the left medial temporal lobe, 30,31 and bilaterally. 23 Reduced left hippocampal NAA concentrations were reported in one civilian sample. 32

While reduced hippocampal NAA has been reported consistently, lateralization findings are inconsistent. It is possible that NAA changes are bilateral but studies have not had enough power to detect differences. So far, most studies have focused on the medial temporal lobe, with the exception of the occipital white matter, 32 the anterior cingulate, 34 and basal ganglia. 35 For this reason, it is not known how specific hippocampal changes are. Future studies should use spectroscopic imaging, a technique that allows the simultaneous investigation of multiple areas of the brain and therefore could provide important information about neurotransmitter changes in multiple brain regions of patients with PTSD.

![Figure 4. Scatter plot of cerebrospinal fluid as a fraction of intracranial volume versus age in people with PTSD and normal controls. The slope is significantly different between groups.](image)

**THEORIES OF HIPPOCAMPAL CHANGES IN PTSD**

Alcohol dependence, a frequent comorbid condition in people with PTSD, is associated with lower hippocampal volume. 12 Therefore, it can be argued that hippocampal changes are related to alcohol intake and not PTSD. However, volumetric and spectroscopy studies typically have controlled for alcohol intake by including it in the analysis models 15 or by including a control group matched for alcohol use. 8,29 Furthermore, a recent study in PTSD

**TABLE 5. Volumetric and Spectroscopy Studies in Children with PTSD**

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Findings</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>44 abused children with PTSD, 61 controls</td>
<td>No hippocampal changes, decreased intracranial volume, decreased corpus callosum, increased lateral ventricles</td>
<td>De Bellis19</td>
</tr>
<tr>
<td>24 abused children with PTSD, matched controls</td>
<td>No hippocampal changes, decreased cerebral volumes, decreased frontal lobe asymmetry</td>
<td>Carrion21</td>
</tr>
<tr>
<td>9 abused children with PTSD, 9 controls</td>
<td>No changes in hippocampus, temporal lobe volumes at baseline or at 2 years follow up</td>
<td>De Bellis20</td>
</tr>
<tr>
<td>61 abused children with PTSD, 122 controls</td>
<td>Decreased brain volumes, increased frontal lobe CSF, decreased corpus callosum</td>
<td>De Bellis22</td>
</tr>
<tr>
<td>11 abused children with PTSD, 11 controls</td>
<td>1H-MRS, decreased NAA/Cre ratio in anterior cingulate</td>
<td>De Bellis34</td>
</tr>
</tbody>
</table>

PTSD = posttraumatic stress disorder; 1H-MRS = proton magnetic resonance spectroscopy, NAA = N-acetyl aspartate, Cre = creatine
subjects without histories of alcohol abuse found smaller hippocampi. Therefore, it is unlikely that alcohol comorbidity accounts for smaller hippocampi in PTSD.

Different hypotheses have been put forth to explain hippocampal changes in PTSD, but the more accepted are the neurotoxic and the genetic. The neurotoxic hypothesis proposes that traumatic events and subsequent PTSD cause hippocampal damage through an interaction of elevated glucocorticoids and excitatory neurotransmitters. The genetic hypothesis is based on the results of a twin study and proposes that smaller hippocampal volumes are genetically determined and are a risk factor for developing PTSD after exposure to trauma. The etiology of brain volume changes in PTSD cannot be determined with the studies conducted so far. Because the majority of volumetric and $^1$H-MRS studies have been cross-sectional, they cannot establish causality.

There is increasing evidence of normal hippocampal volumes in trauma survivors without PTSD, thus indicating that trauma alone is not sufficient to cause hippocampal changes and that these are only associated with PTSD. Findings from a longitudinal study are inconclusive. They do not support genetic theory because hippocampal volumes were not different at baseline in subjects that developed PTSD and do not support a neurotoxic theory because hippocampal volumes did not differ at 6 months. More longitudinal studies are needed to investigate volume and neurotransmitter changes before trauma and at different points in time.

The only neuroimaging treatment study of PTSD found increased hippocampal volume after treatment with paroxetine. The selective serotonin reuptake inhibitors (SSRIs) are considered the first line of treatment in PTSD, and there is mounting evidence that antidepressants induce hippocampal cellular changes that in turn include increased neurogenesis. The findings of Vermetten et al. are interesting and consistent with this line of basic neuroscience research, but do not necessarily support either theory. Hippocampal neuronal integrity potentially could improve both in damaged and in genetically smaller hippocampi.

**OTHER BRAIN CHANGES IN PTSD**

There is evidence of other structural brain changes in PTSD, including cerebral atrophy, white matter changes, corpus callosum, and cavum septum pellucidum. Table 4 (see page 850) provides a summary of several studies of these changes. Peters et al. used computer tomography (CT) to investigate former POWs and found increased ventricular–brain ratio, an indicator of brain atrophy. Canive et al. investigated 41 veterans with combat-related PTSD and 21 controls using MRI and a fluid-attenuated inversion recovery. Two PTSD patients had increased atrophy and 8 had focal white matter abnormalities in the periventricular regions or regions near the white/gray cortical junction. Confounding factors included previous alcohol dependence, depression, and medical comorbidity.

Another study found increased cerebrospinal fluid volume and decreased white matter volume in patients with PTSD. These results were consistent with generalized white matter atrophy. The PTSD group also showed a larger cerebrospinal fluid increase with advancing age, indicating more accelerated atrophy (Figure 4, see page 851).

A study in female victims of partner abuse with and without PTSD compared with nonabused controls revealed no hippocampal changes. Trauma survivors, however, had smaller supratentorial cranial vaults and smaller frontal and occipital gray matter volumes compared to nonabused controls. Other studies have not found evidence of cerebral atrophy in adults with PTSD.9,11,43
As discussed in the hippocampal section, confounding variables could explain the changes, and therefore more research is needed in this area.

Volumetric studies in children with PTSD have indicated generalized brain changes but no hippocampal findings. Table 5 (see page 851) summarizes neuroimaging research in children. De Bellis et al. investigated 44 abused children with PTSD and 61 controls. Children with PTSD had smaller intracranial volumes, decreased total mid sagittal area of corpus callosum, and enlarged lateral ventricles. No differences were found on hippocampal volumes. A positive correlation of brain volume with age of onset of PTSD (with earlier onset, smaller volumes) and a negative correlation with duration of abuse (with longer duration, smaller volumes) were found. PTSD severity also correlated negatively with brain volume and corpus callosum area.

Similar findings were replicated in a subsequent study of abused children with PTSD. Carrion et al. studied 24 abused children with PTSD compared with controls and found an attenuation of frontal lobe asymmetry, smaller total brain and cerebral volumes, and no differences in hippocampal volumes. A study of 61 abused children and 122 controls reported similar findings of smaller brain volumes, increased frontal lobe cerebrospinal fluid, and smaller corpus callosum. PTSD subjects did not show the normal age increase in corpus callosum volume: this was more evident in males. A longitudinal study found no differences in hippocampal or temporal lobe volumes in nine children with PTSD and nine controls studied at baseline or 2 years later.

In summary, volumetric studies in children indicate generalized impairment in brain development or generalized atrophy and specific involvement of the corpus callosum, a white matter structure that connects the brain hemispheres, but no hippocampal changes. Findings of decreased midsagittal area of the corpus callosum have been replicated in adult subjects with civilian PTSD (unpublished data, 2004).

Myslobodsky et al. studied 10 subjects with combat-related PTSD and 21 controls using MRI. The PTSD group had an increased frequency of cavum septum pellucidum (50%) compared with controls (14%). The cavum septum pellucidum is a neurodevelopmental variant that consists of a small cleft in the callosal-septal interface. This finding was thought to be a developmental abnormality that perhaps made subjects more vulnerable to develop PTSD.

May et al. investigated 48 monozygotic twin pairs discordant for combat exposure in which 24 subjects had a diagnosis of PTSD. The authors found an interaction between the proportion of abnormal cavum septum pellucidum and diagnosis of PTSD, as well as a correlation of abnormal cavum septum pellucidum between exposed and unexposed twins. The investigators concluded both that there are genetic and environmental factors determining abnormal cavum septum pellucidum and that abnormal cavum septum pellucidum is a familiar vulnerability factor for PTSD.

Lim et al. investigated 16 subjects with PTSD from a fire and eight controls using 1H-MRS and found lower NAA/Cre ratios in the basal ganglia of those with PTSD but no changes in frontal periventricular white matter or parietal periventricular white matter. The findings of no NAA changes in white matter are consistent with a previous study.

In summary, an emerging literature mostly about children with PTSD is documenting generalized brain changes. Some studies in adults have also reported changes consistent with atrophy, including increased ventricular–brain ratio, increased white matter lesions, increased white matter atrophy, smaller frontal and occipital gray matter volumes, and reduced area in the corpus callosum (unpublished data, 2004). Other studies in adult populations have not replicated findings of generalized brain atrophy. However-
er, these measures have not been explored consistently in all volumetric studies in PTSD, particularly the early ones. Future studies should continue to investigate measures of whole brain volume, and in particular, white matter and gray matter volumes of different cortical and subcortical structures.

THE ANTERIOR CINGULATE

The cingulate gyrus is a paralimbic structure thought to play a role in emotion regulation. The anterior portion of this region, or anterior cingulate (AC), has been found to have abnormal activation in subjects with PTSD. The AC has an important role in the extinction of fear conditioning. The AC had been further subdivided into a dorsal or cognitive division, pregenual or affective division, and subcallosal or visceral division (Figure 5, see page 852).

Some evidence from volumetric and spectroscopy studies has implicated the anterior cingulate in PTSD. A study in survivors of the sarin attack in Tokyo found decreased gray matter volume in the AC. As discussed, most of the subjects did not meet criteria for current PTSD. Rauch et al. investigated 18 female nurses exposed to trauma in the Vietnam war, nine with current PTSD and nine without current or past PTSD. The nurses with PTSD were found to have decreased volumes in pregenual and subcallosal AC.

DeBellis et al. used $^1$H-MRS in 11 abused children with PTSD and 11 controls. Those with PTSD had smaller NAA/Cr ratios in the AC. The results from these volumetric and spectroscopy studies are consistent with atrophy or reduced neuronal density of the AC in PTSD subjects. These findings are intriguing because some functional neuroimaging studies have reported decreased activation of this area in PTSD. The cause of these structural and functional changes of the AC is not known; it is possible that pre-existing abnormalities make people vulnerable to develop PTSD or that these changes result from excitotoxic damage.

SUMMARY

Volumetric brain imaging studies conducted in adults with chronic, severe PTSD consistently report smaller hippocampal volumes when compared either to trauma-exposed individuals without PTSD or to non-traumatized controls. $^1$H-MRS studies have been conducted mostly in combat veterans and report lower concentrations of hippocampal NAA, a putative neuronal marker. All of these findings are consistent with decreased hippocampal neuronal density in adults with chronic, severe PTSD.

The inclusion of trauma controls has provided information that trauma alone is not associated with hippocampal changes. Both neurotoxic and genetic theories have been proposed to explain hippocampal changes in PTSD. The neurotoxic theory is based in extensive animal literature and proposes that the hippocampus is actually damaged or atrophied by neurotoxic effects of trauma and PTSD. A significant body of animal literature has documented hippocampal neuronal atrophy in models of chronic stress.

The genetic theory proposes that hippocampal size is genetically determined and that smaller volumes predispose individuals to develop PTSD when they encounter trauma. The main support for the genetic theory is a study in monozygotic twins that found smaller hippocampal volumes in veterans with PTSD but also in their non-traumatized twins. The only naturalistic longitudinal study did not find hippocampal changes at baseline or at 6 month post-trauma points in people that developed PTSD and therefore did not support either theory. Another treatment study reported that hippocampal volume actually increased after treatment with paroxetine. This finding does not necessarily
support either theory. As a result, more longitudinal studies are needed.

Several studies have failed to replicate hippocampal changes in PTSD; most of these have been conducted in children. Some studies in adults with PTSD have also failed to replicate hippocampal changes but they have typically been conducted in cases that are less chronic and severe.

An emerging literature is documenting other structural brain changes in PTSD. Studies in children report decreased brain volumes, increased ventricle volumes and decreased area of the corpus callosum, raising the possibility of more generalized brain atrophy or developmental abnormalities in PTSD. Some studies in adults with PTSD have found white matter changes, increased brain atrophy, smaller volume of the anterior cingulate, increased incidence of cavum septum pellucidum and smaller area of the corpus callosum. As is the case with other brain changes, developmental and environmental factors could be the determinants of these changes. More research is needed in this area.

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