

Traumatic stress: effects on the brain

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Traumatic stress has a broad range of effects on brain function and structure. Brain areas implicated in the stress response include the amygdala, hippocampus, and prefrontal cortex. Neurochemical systems, including cortisol and norepinephrine, play a critical role in the stress response. These brain areas play an important role in the stress response as well as memory, highlighting the important interplay between memory and the traumatic stress response. Antidepressants have effects on the hippocampus that counteract the effects of stress. Studies in patients with post-traumatic stress disorder (PTSD) show alterations in brain areas implicated in animal studies, including the amygdala, hippocampus, and prefrontal cortex, as well as in neurochemical stress response systems, including cortisol and norepinephrine. Treatments that are efficacious for PTSD show a promotion of neurogenesis in animal studies, as well as promotion of memory and increased hippocampal volume in PTSD. Future studies are needed to assess neural mechanisms in treatment response in PTSD.

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Effects of traumatic stress

Traumatic stressors such as early trauma can lead to post-traumatic stress disorder (PTSD), which affects about 8% of Americans at some time in their lives,¹ as well as depression,^{2,3} substance abuse,^{1,4} dissociation,⁵ personality disorders,^{6,7} and health problems.⁸ For many trauma victims, PTSD can be a lifelong problem.⁹ The President's New Freedom Commission Report highlights the importance of providing services for mental disorders related to early trauma.¹⁰⁻¹² However, the development of effective treatments is limited by gaps in knowledge about the underlying neurobiological mechanisms that mediate symptoms of trauma-related disorders like PTSD. This paper reviews preclinical and clinical studies on the effects of traumatic stress on the brain.

Normal development of the brain across the lifespan

To understand how traumatic stress occurring at different stages of the life cycle interacts with the developing brain, it is useful to review normal brain development. The normal human brain undergoes changes in structure and function across the lifespan from early childhood to late life. Understanding these normal developmental changes is critical for determining the difference between

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Selected abbreviations and acronyms

ACTH	<i>adrenocorticotrophic hormone</i>
BDNF	<i>brain-derived neurotropic factor</i>
BPD	<i>bipolar disorder</i>
CRF	<i>corticotropin-releasing factor</i>
CS	<i>conditioned stimulus</i>
FDG	<i>fluorodeoxyglucose</i>
HPA	<i>hypothalamic-pituitary-adrenal</i>
MRI	<i>magnetic resonance imaging</i>
mRNA	<i>messenger ribonucleic acid</i>
NAA	<i>N-acetyl aspartate</i>
PET	<i>positron emission tomography</i>
PTSD	<i>post-traumatic stress disorder</i>
US	<i>unconditioned stimulus</i>

normal development and pathology, and how normal development and pathology interact.

Although the bulk of brain development occurs in utero, the brain continues to develop after birth. In the first 5 years of life there is an overall expansion of brain volume related to development of both gray matter and white matter structures; however, from 7 to 17 years of age there is a progressive increase in white matter (felt to be related to ongoing myelination) and decrease in gray matter (felt to be related to neuronal pruning) while overall brain size stays the same.¹³⁻¹⁶ Gray matter areas that undergo the greatest increases throughout this latter developmental epoch include frontal cortex and parietal cortex.^{17,18} Basal ganglia decrease in size, while corpus callosum,^{19,20} hippocampus, and amygdala²¹⁻²³ appear to increase in size during childhood, although there may be developmental sex-laterality effects for some of these structures.²⁴ Overall brain size is 10% larger in boys than girls during childhood.²⁴

During the middle part of life (from age 20 to 70) there is a gradual decrease in caudate,²⁵ diencephalon,²⁵ and gray matter,^{25,26} which is most pronounced in the temporal²⁷ and frontal cortex,²⁶ with enlargement of the ventricles^{26,27} and no change in white matter.^{25,26} Studies have not been able to document changes in hippocampal volume in normal populations during this period.²⁷ After menopause in women at about the age of 50, however, there are changes in reproductive hormones, such as decreased levels of estrogen. Since estrogen promotes neuronal branching in brain areas such as the hippocampus,²⁸ a loss of estrogen may lead to changes in neuronal structure. Although the effects of menopause on the brain have not been well studied, it is known that

sex hormones also affect brain function and circuitry²⁹; therefore, the changes in sex hormones with menopause will presumably affect brain function as well as possibly structure. There is some evidence in super-elderly individuals (age >70) for modest reductions in hippocampal volume with late stages of aging.^{27,30} More robust findings have included increased ventricular volume and reduction in gray matter, temporal lobe, and cerebellum volumes with normal aging, that begins before the age of 70.^{25,27,31-33}

Therefore, trauma at different stages in life will presumably have different effects on brain development. The few studies that have looked at this issue do suggest that there are differences in the effects of trauma on neurobiology, depending on the stage of development at which the trauma occurs. Studies in this area, however, have been limited.

Neurobiology of PTSD

PTSD is characterized by specific symptoms, including intrusive thoughts, hyperarousal, flashbacks, nightmares, and sleep disturbances, changes in memory and concentration, and startle responses. Symptoms of PTSD are hypothesized to represent the behavioral manifestation of stress-induced changes in brain structure and function. Stress results in acute and chronic changes in neurochemical systems and specific brain regions, which result in long-term changes in brain “circuits,” involved in the stress response.³⁴⁻³⁷ Brain regions that are felt to play an important role in PTSD include hippocampus, amygdala, and medial prefrontal cortex. Cortisol and norepinephrine are two neurochemical systems that are critical in the stress response (*Figure 1*).

The corticotropin-releasing factor (CRF)/hypothalamic-pituitary-adrenal (HPA) axis system plays an important role in the stress response. CRF is released from the hypothalamus, with stimulation of adrenocorticotrophic hormone (ACTH) release from the pituitary, resulting in glucocorticoid (cortisol in man) release from the adrenal, which in turn has a negative feedback effect on the axis at the level of the pituitary, as well as central brain sites including hypothalamus and hippocampus. Cortisol has a number of effects which facilitate survival. In addition to its role in triggering the HPA axis, CRF acts centrally to mediate fear-related behaviors,³⁸ and triggers other neurochemical responses to stress such as the noradrenergic system via the brain stem locus coeruleus.³⁹ Noradrenergic

neurons release transmitter throughout the brain, which is associated with an increase in alerting and vigilance behaviors, critical for coping with acute threat.⁴⁰⁻⁴² Studies in animals showed that early stress has lasting effects on the HPA axis and norepinephrine. A variety of early stressors resulted in increased glucocorticoid response to subsequent stressors.⁴³⁻⁴⁵ Maternally deprived rats had decreased numbers of glucocorticoid receptors in the hippocampus, hypothalamus, and frontal cortex.⁴⁶ Stressed animals demonstrated an inability to terminate the glucocorticoid response to stress,^{47,48} as well as deficits in fast-feedback of glucocorticoids on the HPA axis which could be related to decreased glucocorticoid receptor binding in the hippocampus.⁴⁹ Early postnatal adverse experiences increase hypothalamic CRF messenger ribonucleic acid (mRNA), median eminence CRF content, and stress-induced glucocorticoid⁵⁰ and ACTH release.⁴⁶ These effects could be mediated by an increase

in synthesis of CRH mRNA following stress.⁵¹ In nonhuman primates, adverse early experiences resulted in long-term effects on behaviors, as well as elevated levels of CRF in the cerebrospinal fluid.⁵² Exposure to chronic stress results in potentiation of noradrenergic responsiveness to subsequent stressors and increased release of norepinephrine in the hippocampus and other brain regions.⁴² Preclinical and clinical studies have shown alterations in memory function following traumatic stress,⁵³ as well as changes in a circuit of brain areas, including hippocampus, amygdala, and medial prefrontal cortex, that mediate alterations in memory.⁵⁴ The hippocampus, a brain area involved in verbal declarative memory, is very sensitive to the effects of stress. Stress in animals is associated with damage to neurons in the CA3 region of the hippocampus (which may be mediated by hypercortisolemia, decreased brain-derived neurotrophic factor (BDNF), and/or ele-

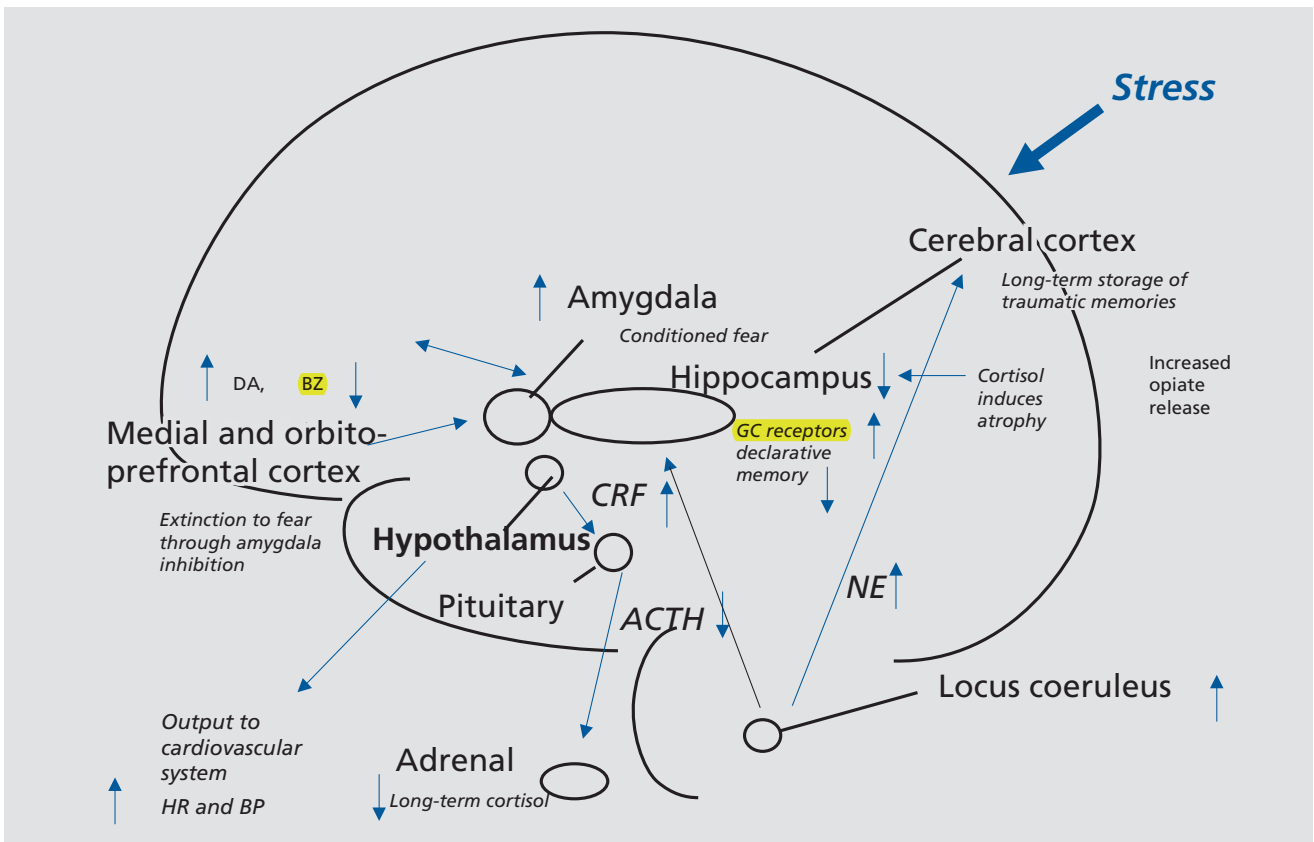


Figure 1. Lasting effects of trauma on the brain, showing long-term dysregulation of norepinephrine and cortisol systems, and vulnerable areas of hippocampus, amygdala, and medial prefrontal cortex that are affected by trauma. GC, ?????; CRF, corticotropin-releasing factor; ACTH, adrenocorticotropin hormone; NE, norepinephrine; HR, heart rate; BP, blood pressure; DA, dopamine; BZ, ?????

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vated glutamate levels) and inhibition of neurogenesis.⁵⁵⁻⁶⁰ High levels of glucocorticoids seen with stress were also associated with deficits in new learning.^{61,62}

Antidepressant treatments have been shown to block the effects of stress and/or promote neurogenesis.^{58,63-66}

Animal studies have demonstrated several agents with potentially beneficial effects on stress-induced hippocampal damage. It has been found that phenytoin blocks the effects of stress on the hippocampus, probably through modulation of excitatory amino acid-induced neurotoxicity.⁶⁷ Other agents, including tianeptine, dihydroepiandrosterone (DHEA), and fluoxetine have similar effects.^{63,64,66,68-73} These medications may share a common mechanism of action through upregulation of cyclic adenosine monophosphate (cAMP) response element binding protein (CREB) that may lead to regulation of expression of specific target genes involved in structural modeling of the hippocampus. Such treatment effects on BDNF and *trkB* messenger ribonucleic acid (mRNA), can have long-term effects on brain structure and function. There is new evidence that neurogenesis is necessary for the behavioral effects of antidepressants,^{74,75} although this continues to be a source of debate.^{72,76}

The hippocampus demonstrates an unusual capacity for neuronal plasticity and regeneration. In addition to findings noted above related to the negative effects of stress on neurogenesis, it has recently been demonstrated that changes in the environment, eg, social enrichment or learning, can modulate neurogenesis in the dentate gyrus of the hippocampus, and slow the normal age-related decline in neurogenesis.^{77,78} Rat pups that are handled frequently within the first few weeks of life (picking up rat pups and then returning them to their mother) had increased type II glucocorticoid receptor binding which persisted throughout life, with increased feedback sensitivity to glucocorticoids, and reduced glucocorticoid-mediated hippocampal damage in later life.⁷⁹ These effects appear to be due to a type of “stress inoculation” from the mothers’ repeated licking of the handled pups.⁸⁰ Considered together, these findings suggest that early in the postnatal period there is a naturally occurring brain plasticity in key neural systems that may “program” an organism’s biological response to stressful stimuli. These findings may have implications for victims of childhood abuse.

Long-term dysregulation of the HPA axis is associated with PTSD, with low levels of cortisol found in chronic PTSD in many studies⁸¹⁻⁸⁶ and elevations in CRF.^{82,87} Not all studies, however, have found lower cortisol levels in

PTSD.^{88,91} Exposure to a traumatic reminder appears to be associated with a potentiated release of cortisol in PTSD.⁹² The few studies of the effects of early stress on neurobiology conducted in clinical populations of traumatized children have generally been consistent with findings from animal studies. Research in traumatized children has been complicated by issues related to psychiatric diagnosis and assessment of trauma.⁹³ Some studies have not specifically examined psychiatric diagnosis, while others have focused on children with trauma and depression, and others on children with trauma and PTSD. Sexually abused girls (in which effects of specific psychiatric diagnosis was not examined) had normal baseline cortisol and blunted ACTH response to CRF,⁹⁴ while women with childhood abuse-related PTSD had hypercortisolemia.⁹⁵ Another study of traumatized children in which the diagnosis of PTSD was established showed increased levels of cortisol measured in 24-hour urines.⁹⁶ Emotionally neglected children from a Romanian orphanage had elevated cortisol levels over a diurnal period compared with controls.⁹⁷ Maltreated school-aged children with clinical-level internalizing problems had elevated cortisol compared with controls.⁹⁸ Depressed preschool children showed increased cortisol response to separation stress.⁹⁹ Adult women with a history of childhood abuse showed increased suppression of cortisol with low-dose (0.5 mg) dexamethasone.¹⁰⁰ Women with PTSD related to early childhood sexual abuse showed decreased baseline cortisol based on 24-hour diurnal assessments of plasma, and exaggerated cortisol response to stressors (traumatic stressors¹⁰¹ more than neutral cognitive stressors).¹⁰² We also found that patients with PTSD had less of an inhibition of memory function with synthetic cortisol (dexamethasone) than normal subjects.¹⁰³ Adult women with depression and a history of early childhood abuse had an increased cortisol response to a stressful cognitive challenge relative to controls,¹⁰⁴ and a blunted ACTH response to CRF challenge.¹⁰⁵ These studies suggest that early abuse is associated with long-term changes in the HPA axis.

Cognitive function and brain structure in PTSD

Studies in PTSD are consistent with changes in cognition and brain structure. Multiple studies have demonstrated verbal declarative memory deficits in PTSD.^{53,106-108} Patients with PTSD secondary to combat¹⁰⁹⁻¹¹³ and childhood abuse^{114,115} were found to have deficits in verbal

declarative memory function based on neuropsychological testing. Studies, using a variety of measures (including the Wechsler Memory Scale, the visual and verbal components of the Selective Reminding Test, the Auditory Verbal Learning Test, Paired Associate Recall, the California Verbal New Learning Test, and the Rivermead Behavioral Memory Test), found specific deficits in verbal declarative memory function, with a relative sparing of visual memory and IQ.^{109-113,115-124} These studies have been conducted in both patients with PTSD related to Vietnam combat,^{109-113,116,119-121,123} rape,¹¹⁷ the Holocaust,¹²⁴⁻¹²⁶ adults with early childhood abuse,¹¹⁵ and traumatized children.¹¹⁸ One study in adult rape survivors showed that verbal declarative memory deficits are specifically associated with PTSD, and are not a nonspecific effect of trauma exposure.¹¹⁷ Another study of women with early childhood sexual abuse in which some, but not all, of the patients had PTSD, showed no difference between abused and nonabused women,¹²⁷ while another study was not able to show a difference between Vietnam veterans with and without PTSD.¹²⁸ Other types of memory disturbances studies in PTSD include gaps in memory for everyday events (dissociative amnesia),¹²⁹ deficits in autobiographical memory,¹³⁰ an attentional bias for trauma-related material,¹³¹⁻¹⁴⁰ and frontal lobe-related impairments.¹⁴¹ These studies suggest that traumas such as early abuse with associated PTSD result in deficits in verbal declarative memory. It is not clear if cognitive deficits in early abuse survivors are specific to PTSD and are not related to the nonspecific effects of abuse. These effects were specific to verbal (not visual) memory, and were significant after controlling for IQ. Some of these studies used neuropsychological tests of declarative memory, such as the Wechsler Memory Scale (WMS) and Selective Reminding Test (SRT), that have been validated as sensitive to loss of neurons in the CA3 region of the hippocampus in epileptics who underwent hippocampal resection.^{142,143} Vietnam veterans with PTSD were originally shown by us to have 8% smaller right hippocampal volume based on magnetic resonance imaging (MRI) relative to controls matched for a variety of factors such as alcohol abuse and education ($P < 0.05$); smaller volume was correlated with deficits in verbal declarative memory function as measured with the Wechsler Memory Scale.¹⁴⁴ A second study from our group showed a 12% reduction in left hippocampal volume in 17 patients with childhood abuse-related PTSD compared with 17 case-matched controls, that was sig-

nificant after controlling for confounding factors.¹⁴⁵ Smaller hippocampal volume was shown to be specific to PTSD within the anxiety disorders, and was not seen in panic disorder.¹⁴⁶ Gurvits et al¹⁴⁷ showed bilateral hippocampal volume reductions in combat-related PTSD compared with combat veterans without PTSD and normal controls. Combat severity was correlated with volume reduction. Stein et al¹⁴⁸ found a 5% reduction in left hippocampal volume. Other studies in PTSD have found smaller hippocampal volume and/or reductions in *N*-acetyl aspartate (NAA), a marker of neuronal integrity.¹⁴⁹⁻¹⁵³ Studies in childhood¹⁵⁴⁻¹⁵⁶ and new onset^{157,158} PTSD did not find hippocampal volume reduction, although reduced NAA (indicating loss of neuronal integrity) was found in medial prefrontal cortex in childhood PTSD.¹⁵⁹ In a recent meta-analysis we pooled data from all of the published studies and found smaller hippocampal volume for both the left and the right sides, equally in adult men and women with chronic PTSD, and no change in children.¹⁶⁰ More recent studies of holocaust survivors with PTSD did not find a reduction in hippocampal volume, although PTSD patients who developed PTSD in response to an initial trauma had smaller hippocampal volume compared with those who developed PTSD after repeated trauma, suggesting a possible vulnerability of smaller hippocampal volume.¹⁶¹ Two independent studies have shown that PTSD patients have deficits in hippocampal activation while performing a verbal declarative memory task,^{149,162} although it is unclear if this is a deficit in activation or higher hippocampal blood flow at baseline. Both hippocampal atrophy and hippocampal-based memory deficits reversed with treatment with the selective serotonin reuptake inhibitor (SSRI) paroxetine, which has been shown to promote neurogenesis (the growth of neurons) in the hippocampus in preclinical studies.¹⁶³ In addition, treatment with the anticonvulsant phenytoin led to an improvement in PTSD symptoms¹⁶⁴ and an increase in right hippocampal and right cerebral volume.¹⁶⁵ We hypothesize that stress-induced hippocampal dysfunction may mediate many of the symptoms of PTSD which are related to memory dysregulation, including both explicit memory deficits as well as fragmentation of memory in abuse survivors. It is unclear at the current time whether these changes are specific to PTSD, whether certain common environmental events (eg, stress) in different disorders lead to similar brain changes, or whether common genetic traits lead to similar outcomes.

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The meaning of findings related to deficits in memory and the hippocampus in PTSD, and questions related to the relative contribution of genetic and environmental factors, has become an important topic in the field of PTSD and stress research. There are three possible models, taking into account genetic or environmental factors, which have been proposed to explain smaller hippocampal volume in PTSD, which include Model A (Environment), Model B (Environment and Genetics) and Model C (Genetic).¹⁶⁶⁻¹⁶⁹ In Model C (Genetic), smaller hippocampal volume represents a premorbid risk factor for PTSD. In support of this model Pitman and colleagues¹⁷⁰ have demonstrated that lower premilitary IQ is associated with combat-related PTSD, as well as finding a correlation between PTSD symptoms and hippocampal volume in twin brothers.¹⁵¹ Model A (Environment) states that stress leads to damage or inhibition of neurogenesis via hypercortisolemia, decreased BDNF, or increased glutamate. Model B (Environment/Genetics) states that a combination of environmental and genetic factors leads to deficits in hippocampal function and structure. Showing that an intervention like medication changes hippocampal volume and cognition would provide support for at least a partial contribution of the environment to the outcomes of interest. In addition to the hippocampus, other brain structures have been implicated in a neural circuitry of stress, including the amygdala and prefrontal cortex. The amygdala is involved in memory for the emotional valence of events, and plays a critical role in the acquisition of fear responses. The medial prefrontal cortex includes the anterior cingulate gyrus (Brodmann's area [BA] 32) and subcallosal gyrus (area 25) as well as orbitofrontal cortex. Lesion studies demonstrated that the medial prefrontal cortex modulates emotional responsiveness through inhibition of amygdala function. Conditioned fear responses are extinguished following repeated exposure to the conditioned stimulus in the absence of the unconditioned (aversive, eg, electric shock) stimulus. This inhibition appears to be mediated by medial prefrontal cortical inhibition of amygdala responsiveness. Animal studies also show that early stress is associated with a decrease in branching of neurons in the medial prefrontal cortex.¹⁷¹ Rauch and colleagues found smaller volume of the anterior cingulate based on MRI measurements in PTSD¹⁷²; we have replicated these findings in women with abuse and PTSD.¹⁶⁰ An important question is whether these effects are reversible with treatment.

Neural circuits in PTSD

Brain imaging studies have shown alterations in a circuit including medial prefrontal cortex (including anterior cingulate), hippocampus, and amygdala in PTSD. Many of these studies have used different methods to trigger PTSD symptoms (eg, using traumatic cues) and then look at brain function. Stimulation of the noradrenergic system with yohimbine resulted in a failure of activation in dorsolateral prefrontal, temporal, parietal, and orbitofrontal cortex, and decreased function in the hippocampus.¹⁷³ Exposure to traumatic reminders in the form of traumatic slides and/or sounds or traumatic scripts was associated with an increase in PTSD symptoms, decreased blood flow, and/or failure of activation in the medial prefrontal cortex/anterior cingulate, including Brodmann's area 25, or subcallosal gyrus, area 32 and 24, as measured with positron emission tomography (PET) or functional MRI (fMRI).¹⁷⁴⁻¹⁸³ Other findings in studies of traumatic reminder exposure include decreased function in hippocampus,¹⁷⁶ visual association cortex,^{176,180} parietal cortex,^{176,179,180,184} and inferior frontal gyrus,^{176,179,180,184} and increased function in amygdala,^{181,184} posterior cingulate,^{174,176,177,180} and parahippocampal gyrus.^{174,176,178} Shin and colleagues found a correlation between increased amygdala function and decreased medial prefrontal function with traumatic reminders,¹⁸¹ indicating a failure of inhibition of the amygdala by the medial prefrontal cortex that could account for increased PTSD symptoms with traumatic reminders. Other studies found increased amygdala and parahippocampal function and decreased medial prefrontal function during performance of an attention task,¹⁸² increased posterior cingulate and parahippocampal gyrus and decreased medial prefrontal and dorsolateral prefrontal function during an emotional Stroop paradigm,¹⁸⁵ and increased amygdala function with exposure to masked fearful faces.¹⁸⁶ Retrieval of emotionally valenced words¹⁸⁷ (eg "rape-mutilate") in women with PTSD from early abuse resulted in decreases in blood flow in an extensive area which included orbitofrontal cortex, anterior cingulate, and medial prefrontal cortex (BA 25, 32, and 9), left hippocampus, and fusiform gyrus/inferior temporal gyrus, with increased activation in posterior cingulate, left inferior parietal cortex, left middle frontal gyrus, and visual association and motor cortex.¹⁸⁸ Another study found a failure of medial prefrontal cortical/anterior cingulate activation, and decreased visual association and parietal

cortex function, in women with abuse and PTSD relative to women with abuse without PTSD, during performance of the emotional Stroop task (ie, naming the color of a word such as “rape”).¹⁸⁹ We recently found increased amygdala activation with classical fear conditioning (pairing a shock and a visual stimulus), and decreased medial prefrontal cortex function with extinction, in abuse-related PTSD.¹⁹⁰ The findings described above point to a network of related regions mediating symptoms of PTSD, including medial prefrontal cortex, anterior cingulate, hippocampus, amygdala, posterior cingulate, parietal, visual association, and dorsolateral prefrontal cortex.¹⁹¹

Fewer brain imaging studies have been performed in children with PTSD. Several studies have shown alterations in electroencephalogram (EEG) measures of brain activity in children with a variety of traumas who were not selected for diagnosis compared with healthy children. About half of the children in these studies had a psychiatric diagnosis. Abnormalities were located in the anterior frontal cortex and temporal lobe and were localized to the left hemisphere.^{192,193} Two studies have found reductions in brain volume in children with trauma and PTSD symptoms.^{154,155} One group did not find reductions in hippocampal volume, either at baseline or over a longitudinal period,^{154,156} while another group found an 8.5% reduction in hippocampal volume that was not significant after controlling for smaller brain volumes in the PTSD group.¹⁵⁵ One study used single-voxel proton magnetic resonance spectroscopy (proton MRS) to measure relative concentration of NAA and creatinine (a marker of neuronal viability) in the anterior cingulate of 11 children with maltreatment-related PTSD and 11 controls. The authors found a reduction in the ratio of NAA to creatinine in PTSD relative to controls.¹⁵⁹ Studies have also found smaller size of the corpus callosum in children with abuse and PTSD relative to controls,¹⁵⁴ as well as larger volume of the superior temporal gyrus.¹⁹⁴ In a study of abused children in whom diagnosis was not specified, there was an increase in T2 relaxation time in the cerebellar vermis, suggesting dysfunction in this brain region.¹⁹⁵ The reason for differences in findings between adults and children are not clear; however, factors such as chronicity of illness or interaction between trauma and development may explain findings to date.

In summary, dysfunction of a circuit involving the medial prefrontal cortex, dorsolateral prefrontal cortex, and possibly hippocampus and amygdala during exposure to

traumatic reminders may underlie symptoms of PTSD. These studies have primarily assessed neural correlates of traumatic remembrance, while little has been done in the way of utilizing cognitive tasks as probes of specific regions, such as memory tasks as probes of hippocampal function.

MRI assessment of brain abnormalities in PTSD and trauma spectrum disorders

Findings of smaller hippocampal volume appear to be associated with a range of trauma related psychiatric disorders, as long as there is the presence of psychological trauma. We have used MRI to show smaller hippocampal volume in PTSD,^{144,145,149,196} depression,¹⁹⁷ depression with early abuse,¹⁹⁸ borderline personality disorder (BPD) with early abuse,¹⁹⁹ and Dissociative Identity Disorder (DID) with early abuse.²⁰⁰ The greatest magnitude of difference was seen in the DID patients, who had unusually severe early childhood sexual abuse histories. We did not find changes in hippocampal volume in patients with panic disorder without a history of abuse (suggesting that findings are not generalized to other anxiety disorders).²⁰¹ We found smaller amygdala volume in BPD with early abuse¹⁹⁹ and increased amygdala volume in depression.^{197,202} Patients with depression had smaller orbitofrontal cortex volume with no changes in anterior cingulate (BA 32) or medial prefrontal cortex (BA 25).²⁰³ More recently, we found smaller anterior cingulate volume in women with abuse and PTSD relative to controls.²⁰⁴

Neural circuits in women with abuse and PTSD

We have used PET to study neural circuits of trauma-related disorders in women with early abuse and a variety of trauma spectrum mental disorders. Initially we studied women with abuse and PTSD.^{54,205-208} We initially measured brain activation with a paragraph-encoding task in conjunction with PET O-15 water measurement of brain blood flow. Women with abuse and PTSD showed a failure of hippocampal activation during the memory task relative to controls.¹⁴⁹ Women with abuse and PTSD in this study also had smaller hippocampal volume measured with MRI relative to both women with abuse without PTSD and nonabused non-PTSD women. The failure of hippocampal activation was significant after controlling differences in hippocampal volume as

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well as accuracy of encoding. In another study we measured neural correlates of exposure to a personalized script of childhood sexual abuse. Women with abuse and PTSD showed a failure of medial prefrontal and hippocampal activation relative to abused women without PTSD.¹⁷⁶ Women with abuse and PTSD also showed a failure of medial prefrontal and hippocampal function during recall of paired word associates with traumatic-emotional content (eg, “rape-mutilate”),¹⁸⁸ and decreased medial prefrontal function during an emotional Stroop task with trauma-content words.²⁰⁹ Other studies showed a failure of medial prefrontal activation in women with BPD and early abuse during an abandonment script.²¹⁰ Women with BPD and abuse had increased psychophysiological responses to abandonment scripts relative to trauma scripts, while women with PTSD and abuse had the opposite pattern,²¹¹ indicating differential responding in those two disorders in spite of the common exposure to early abuse.

In another project we studied 19 physically healthy women including women with a history of severe childhood sexual abuse and the diagnosis of current PTSD (N=8) and women without childhood abuse or PTSD (N=11).²¹² All subjects underwent PET measurement of cerebral blood flow and psychophysiology measurement of heart rate and skin conductance during habituation, acquisition and extinction conditions, on a single day, with scanning during a control condition on another day separated by 1 week from the active condition. Subjects were randomly assigned to undergo either the active condition or the control condition first (ie, active-control or control-active). Subjects were told at the beginning of the study that they would be exposed to electric shocks and viewing images on a screen during collection of PET and psychophysiology data. During habituation subjects were exposed to a blue square on a screen (conditioned stimulus [CS]), 4 seconds in duration, followed by 6 seconds of a blank screen. CS exposure was repeated eight times at regular intervals over 80 seconds in two separate blocks separated by 8 minutes. One PET image of brain blood flow was obtained starting from the beginning of each of the blocks. During active fear acquisition exposure to the blue square (CS) was paired with an electric shock to the forearm (unconditioned stimulus [UCS]). Subjects had 8 paired CS-UCS presentations at 10-second intervals for each of two blocks. With extinction subjects were again exposed to the blue squares (CS) without shock (“active” extinction). On a second day subjects

went through the same procedure with electric shocks delivered randomly when the blue square was not present (unpaired CS-UCS) (an equal number as on day 1) during scans 3 and 4, which served as a control for active fear acquisition.

PTSD subjects had increased symptoms of anxiety, fear, dissociation, distress substance use disorders (SUDs) and PTSD at all time points during both study days relative to non-PTSD. Acquisition of fear was associated with increased skin conductance (SC) responses to CS exposure during the active versus the control conditions in all subjects. There was increased SC for PTSD during the first CS-UCS presentation. Extinction of fear was associated with increased skin conductance (SC) responses to CS exposure during the active versus the control conditions in all subjects. When PTSD and non-PTSD subjects were examined separately, SC levels were significantly elevated in non-PTSD subjects undergoing extinction following the active compared with the control condition during session one.

PTSD subjects showed activation of the bilateral amygdala during fear acquisition compared to the control condition. Non-PTSD subjects showed an area of activation in the region of the left amygdala. When PTSD subjects and control subjects were directly compared, PTSD subjects showed greater activation of the left amygdala during the fear conditioning condition (pairing of US and CS) relative to the random shock control than healthy women. Other areas that showed increased activation with fear acquisition in PTSD included bilateral superior temporal gyrus (BA 22), cerebellum, bilateral inferior frontal gyrus (BA 44, 45) and posterior cingulate (BA 24). Fear acquisition was associated with decreased function in medial prefrontal cortex, visual association cortex, and medial temporal cortex, inferior parietal lobule function, and other areas. Extinction of fear responses was associated with decreased function in the orbitofrontal and medial prefrontal cortex (including subcallosal gyrus, BA 25, and anterior cingulate BA 32), visual association cortex, and other areas, in the PTSD subjects, but not in the controls. Amygdala blood flow with fear acquisition was negatively correlated with medial prefrontal blood flow with fear extinction (increased blood flow in amygdala correlated with decreased blood flow in medial prefrontal cortex) in all subjects ($r=-0.48$; $P<0.05$). Increased amygdala blood flow with fear acquisition was positively correlated with PTSD ($r=0.45$), anxiety ($r=0.44$) and dissociative ($r=0.80$) symptom levels in PTSD (but not non-PTSD) subjects.

There was a negative correlation between medial prefrontal blood flow during extinction and anxiety as measured with the **???? (PASS)** during extinction in the PTSD group only which was significant after correction for multiple comparisons ($r=-0.90$; $P=0.006$).¹⁹⁰ This study was consistent with increased amygdala function with fear acquisition, and decreased medial prefrontal (anterior cingulate) function during extinction in PTSD. This is consistent with the model of an overactive amygdala and a failure of medial prefrontal cortex to extinguish, or shut off, the amygdala, when the acute threat is no longer present.

Treatment of PTSD

Intervening soon after the trauma is critical for long-term outcomes, since with time traumatic memories become indelible and resistant to treatment.²¹³ Early treatments are not necessarily effective. For instance studies have shown that Critical Incident Stress Debriefing (CISD) can be associated with a worsening of outcome relative to no treatment at all.²¹⁴ Pharmacological treatment of chronic PTSD has shown efficacy originally for imipramine,²¹⁵ amitriptyline,²¹⁶ and phenazine,²¹⁵ and later for brofaramine,²¹⁷ paroxetine,^{218,219} and sertraline.²²⁰ Selective serotonin reuptake inhibitors (SSRIs) are now recommended as first-line treatment for PTSD.²²¹⁻²²⁶ The utility of early treatment is also demonstrated by animal studies showing that pretreatment before stress with antidepressants reduces chronic behavioral deficits related to stress.^{227,228} Antidepressants, including both norepinephrine and **serotonin reuptake inhibitors, as well** as gabapentine and phenytoin, promote nerve growth (neurogenesis) in the hippocampus, while stress inhibits neurogenesis.^{63,64,66,69,71,75,229} This is important because hippocampal neurogenesis has been shown to be required for antidepressant response.⁷⁴ Few studies have examined the effects of pharmacological treatment on brain structure and function in patients with trauma related mental disorders. We studied a group of patients with depression and found no effect of fluoxetine on hippocampal volume, although there were increases in memory function²³⁰ and hippocampal activation measured with PET during a memory encoding task. Depressed patients with a history of childhood trauma were excluded, and we subsequently have found hippocampal volume reductions at baseline in women with early abuse and depression but not in women with depression without

early abuse;¹⁹⁸ this suggests that the study design of excluding patients with early trauma may account for the negative result. Other studies in depression showed that smaller hippocampal volume was a predictor of resistance to antidepressant treatment.²³¹ Smaller orbitofrontal cortex volume is associated with depression; one study in geriatric depression found smaller orbitofrontal cortex volume, while length of antidepressant exposure was correlated with larger orbitofrontal volume.²³²

Several studies have looked at functional brain imaging response to antidepressants in depression. Single photon-emission computed tomography (SPECT) blood flow studies in depression showed antidepressants increased anterior cingulate, right putamen, and right thalamus function.²³³ SPECT Xenon-133 studies showed reduced prefrontal function at baseline in depression, with treatment responders showing reduced perfusion in prefrontal cortex compared to nonresponders after treatment.²³⁴ In a fluorodeoxyglucose (FDG) PET study of brain function patients with depression treated with fluoxetine who had a positive response to treatment had limbic and striatal decreases (subgenual cingulate, hippocampus, insula, and pallidum) and brain stem and dorsal cortical increases (prefrontal, parietal, anterior, and posterior cingulate) in function. Failed response was associated with a persistent 1-week pattern and absence of either subgenual cingulate or prefrontal changes.²³⁵ Sertraline resulted in an increase in middle frontal gyrus activity in depression measured with PET FDG, as well as increased function in right parietal lobe and visual association cortex.²³⁶ Successful paroxetine therapy of depression was associated with increased glucose metabolism measured with PET in dorsolateral, ventrolateral, and medial aspects of the prefrontal cortex, parietal cortex, and dorsal anterior cingulate. Areas of decreased metabolism were noted in both anterior and posterior insular regions (left) as well as right hippocampal and parahippocampal regions.²³⁷ In another PET FDG study, at baseline, subjects with depression had higher normalized metabolism than controls in the prefrontal cortex (and caudate and thalamus), and lower metabolism in the temporal lobe. With treatment with paroxetine, subjects with depression had metabolic changes in the direction of normalization in these regions.²³⁸ A PET FDG study of patients with depression and controls showed that at baseline, the mean metabolism was increased in the left and right lateral orbital cortex/ventrolateral prefrontal cortex (PFC), left amygdala, and posterior cingulate cortex, and decreased in the subgenual anterior cin-

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gulated cortex (ACC) and dorsal medial/dorsal anterolateral PFC in depressives relative to controls. Following treatment with antidepressants, metabolism significantly decreased in the left amygdala and left subgenual ACC. The metabolic reduction in the amygdala and right subgenual ACC appeared largely limited to those subjects who both responded to treatment and remained well at 6 months' follow-up.²³⁹ Another study showed that antidepressant treatment of depression resulted in a decrease in amygdala activation with emotional faces as measured with fMRI.²⁴⁰ In summary, studies show changes in limbic and prefrontal cortical regions with successful antidepressant treatment of depression.

Fewer studies have looked at the effects of pharmacological treatment on the brain in anxiety disorders. One PET FDG study showed that caudate function decreased with treatment of obsessive compulsive disorder with antidepressants.²⁴¹ Paroxetine resulted in a decrease in glutamate/glutamine measured with magnetic resonance spectroscopy (MRS) in children with obsessive-compulsive disorder (OCD).²⁴² Patients with PTSD were shown to have an increase in hippocampal volume and memory function with paroxetine,¹⁶³ and increased right hippocampal and right cerebral volume with phenytoin.¹⁶⁵ No published studies have looked at the effects of pharmacological treatment on brain function in PTSD, or on

sensitive markers of brain chemistry like NAA.

Brain biomarkers like NAA represent an objective marker of neural plasticity. To date psychiatry has relied on subjective reports as the gold standard. However, this is limited by self-reporting and the subjective interpretations of symptoms and response to treatment. Brain markers of antidepressant response may provide a complementary approach to assessing response to treatment, as well as providing insight into the mechanisms of treatment response. Our group is trying to look at mechanisms in the brain underlying treatment response in PTSD.

Effects of pharmacotherapy on brain function and structure in PTSD

We have begun to assess the effects of pharmacotherapy on brain structure and function in PTSD.²⁴³ We recently assessed the effects of phenytoin on brain structure and function. Studies in animals show that phenytoin, which is used in the treatment of epilepsy and is known to modulate glutamatergic function, blocks the effects of stress on the hippocampus.⁶⁷ We studied nine patients with PTSD in an open-label function before and after treatment with phenytoin. Phenytoin resulted in a significant improvement in PTSD symptoms.¹⁶⁴ Phenytoin also resulted in increases in both right hippocampal volume and right hemisphere volume.¹⁶⁵ These findings indicate that phenytoin has an effects on PTSD symptoms as well as brain structure in PTSD patients.

We have assessed the effects of open-label paroxetine on memory and the hippocampus in PTSD. Male and female patients with symptoms of PTSD were medication-free for at least 4 weeks before participation in the study. Twenty-eight patients were found to be eligible and started the medication phase. Of the total patient sample five patients did not finish due to noncompliance; 23 patients completed the study.

Before patients started the medication phase, neuropsychological tests were administered, including the *Wechsler Adult Intelligence Scale – Revised*, WAIS-R (arithmetic, vocabulary, picture arrangement, and block design test), two subtests of the *Wechsler Memory Scale-Revised*, WMS-R, including logical memory (free recall of two story narratives, which represents verbal memory) and figural memory (which represents visual memory and involved reproduction of designs after a 6-second presentation); and the verbal and visual components of the *Selective Reminding Test*, SRT.

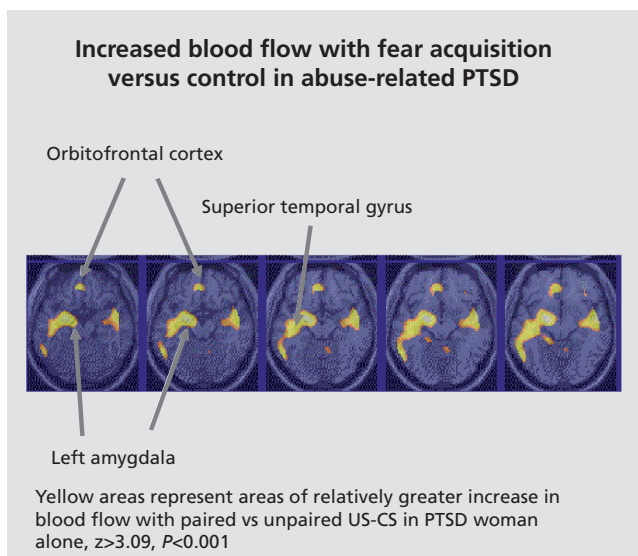


Figure 2. Neural correlates of fear conditioning in women with abuse and PTSD. There was increased amygdala activation with fear acquisition using a classical conditioning paradigm relative to non-PTSD abused women. PTSD, post-traumatic stress disorder

Paroxetine was prescribed in the first visit after the pre-treatment assessments. All patients started open-label with a dose of 10 mg daily and were titrated up to 20 mg in 4 days.

Paroxetine treatment resulted in a mean 54% reduction in PTSD symptoms as measured with mean changes from baseline on the CAPS total score ($P < 0.005$) among study completers. Improvement was equally strong on all symptom cluster scores (Re-experiencing, Avoidance/Numbing, Hyperarousal). Treatment also resulted in significant improvements in verbal declarative memory as measured with the WMS-R paragraph recall for delayed recall ($P < 0.005$) and percent retention (80.2 to 91.1; $P = 0.003$), but not immediate recall. Improvements were significant on all subscales of the Verbal Component of the SRT; including long-term recall and delayed recall.

Repeated measures ANOVA with side as the repeated measure showed a main effect for treatment related to a 4.6% increase in mean hippocampal volume (1857.3 mm³ [SD 225.6] to 1906.2 mm³, [SD 243.2]) with treatment ($F = 8.775$ $df = 1, 36$; $P = 0.005$). Increased hippocampal volume was seen for both left (5.6%) (1807.6 mm³ [SD 255.5] to 1909.3 mm³ [SD 236.9]) and right (3.7%) (1906.9 mm³ [SD 195.8] to 1976.7 mm³ [SD 249.6]) hippocampus. There was no change in whole brain volume with treatment. Increase in hippocampal volume was significant after adding whole brain volume before and after treatment to the model.

Discussion

Traumatic stress has a broad range of effects on brain function and structure, as well as on neuropsychological components of memory. Brain areas implicated in the stress response include the amygdala, hippocampus, and prefrontal cortex. Neurochemical systems, including cortisol and norepinephrine, play a critical role in the stress response. These brain areas play an important role in the stress response. They also play a critical role in memory, highlighting the important interplay between memory and the traumatic stress response. Preclinical studies show that stress affects these brain areas. Furthermore, antidepressants have effects on the hippocampus that counteract the effects of stress. In fact, promotion of nerve growth (neurogenesis) in the hippocampus may be central to the efficacy of the antidepressants. Studies in patients with PTSD show alterations in brain areas implicated in animal studies, including the amygdala, hippocampus, and prefrontal cortex, as well as in neurochemical stress response systems, including cortisol and norepinephrine. Treatments that are efficacious for PTSD show a promotion of neurogenesis in animal studies, as well as promotion of memory and increased hippocampal volume in PTSD. Future studies are needed to assess neural mechanisms in treatment response in PTSD. □

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