

Does Stress Damage the Brain? Understanding Trauma-related Disorders from a Mind-Body Perspective

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Learning Objective

In this lesson, clinicians will learn about (1) brain regions and functions sensitive to stress and hypothesized to underlie certain symptoms of trauma-related disorders; (2) how stress produces emotional and behavioral dysfunction as well as physical illness; and (3) how selective serotonin reuptake inhibitors seem to have a beneficial effect in the treatment of such patients.

Editor's Note

Many of us have always assumed that severe and chronic stress can have a destructive effect on brain function, sometimes reversible, sometimes not. Now, with more sophisticated methods of investigation, we are able to identify what these are and how they may come about. In this lesson, Dr. Bremner begins by emphasizing the frequency of comorbidity in patients with posttraumatic stress disorder; a significant number of them also suffer with diagnosed anxiety, depression, alcohol and drug abuse, dissociative, and borderline personality disorders. He suggests the term "trauma-related disorder" for this group. As I see it, this goes a long way toward acknowledging that many psychiatric disorders have important features in common that run across DSM-IV lines and that understanding these can open the doors to new concepts of etiology and treatment.

The author identifies the hippocampus, the seat of memory integration, and the pre-frontal cortex, as being centrally involved in some of the deficits seen in PTSD. Hippocampal dysfunction or damage may account for dissociation; changes in the frontal cortex may be associated with emotional and interpersonal difficulties. Norepinephrine is released under stress to ready the person to deal with real or perceived danger; in lesser amounts, this hormone improves cognition and attention, stimulating activity in the frontal cortex, but at very high levels, the brain begins to shut down. Increased cortisol production is vital for short-term survival because it enables humans and animals to shunt energy to the brain and muscles, thus speeding up thinking and action; however, if cortisol levels are too high for too long a time, physical damage and possible damage to the brain can ensue. PTSD has long been associated with long-term dysregulation of the corticotropin releasing factor/hypothalamic-pituitary-adrenal axis system.

Stress results in a reduction in neurotrophins, such as “brain-derived neurotrophic factor,” in the hippocampus and an inhibition of hippocampal neurogenesis. Using magnetic resonance imaging (MRI), Dr. Bremner and his colleagues demonstrated a much smaller hippocampus in combat-related PTSD patients, who also showed deficits in verbal declarative memory function. In another study, survivors of childhood abuse with PTSD were found to have smaller hippocampal volume and demonstrable deficits in short-term memory.

The author concludes by reporting a 5% increase in hippocampal volume and a 20% increase in hippocampal-based declarative memory function in these patients after a year of treatment with the SSRI paroxetine. —FF

Introduction

Stress has effects on brain areas that play a critical role in learning and memory, including the hippocampus and prefrontal cortex. Other brain areas that are connected with these regions, including the amygdala and cingulate, are hypothesized to play a role in stress-related psychiatric symptoms. Stress also results in long-term dysregulation of stress hormones, such as cortisol and norepinephrine, that in turn modulate the laying down and recall of memory traces at the level of the hippocampus and other brain structures. In this lesson a model will be proposed for how stress results in long-term changes in these brain structures and systems that lead to symptoms of stress-related psychiatric disorders, including posttraumatic stress disorder (PTSD), depression, borderline personality disorder (BPD), substance abuse, and dissociative disorders.

Stress results in long-term problems with learning and memory that have a neurological basis. **Stress patients of the brain begin to resemble patients with organic memory problems or early dementia. In fact, PTSD has been described as a disorder in which there is accelerated aging, which may include both an acceleration of the memory deficits that are seen in a subgroup of the elderly as well as increased risk for atherosclerotic diseases, including stroke or heart disease, and metabolic diseases,**

including diabetes. One of my patients who had been sexually abused and had PTSD said: *“Lately I feel like my mind is degenerating, like I have some horrible dementing illness. I can’t remember anything or think about anything normally. I walk into a room and I see something I’ve never seen before, and I say to myself, ‘I’ve never seen that before, where did that come from?’ I feel like I am falling apart.”* **We have hypothesized that these problems are due to the negative effects of stress on the hippocampus, a brain area that plays a critical role in learning and memory.**

In my recent book, *Does Stress Damage the Brain?*,¹ I outlined a **model of trauma-spectrum disorders that are linked to one another and have a common basis in exposure to trauma. These disorders include posttraumatic stress disorder (PTSD), depression, borderline personality disorder (BPD), substance abuse, anxiety, somatization, eating, and dissociative disorders.** In many cases these disorders share more in common than the disorders with which they are currently grouped in the *Diagnostic and Statistical Manual (DSM-IV)* classification system. For example, PTSD is currently classified in the anxiety disorders with obsessive compulsive disorder; however it shares more in common with the dissociative disorders in terms of comorbidity and the similarity and overlap of symptoms in the two disorders.

Consider the Data on Comorbidity of Psychiatric Disorders:

There is high comorbidity between PTSD and other psychiatric disorders, with 99% of Vietnam veterans with PTSD meeting criteria for lifetime *Diagnostic Interview Schedule* (DIS)-based diagnosis versus 41% of non-PTSD veterans and 80% of PTSD patients having a history of lifetime alcohol or substance abuse/dependence, representing higher rates than veterans without PTSD.² Twenty-eight percent of women with PTSD have alcohol abuse/dependence disorders compared with 14% of women without PTSD.³ In patients with early childhood sexual abuse and PTSD, rates of lifetime depression approaches 100%.⁴ We found that PTSD patients had 86% comorbidity of a dissociative disorder,⁵ and 100% of patients with severe dissociative disorders had comorbid PTSD. Combat veterans with PTSD have been found to have higher rates of all of the anxiety disorders compared with the general population.² Women with borderline personality disorder were reported to have comorbid PTSD in 50% of cases,⁶ and 71% have a history of childhood sexual trauma.⁶ These findings highlight the overlap in symptoms of the disorders I have described¹ as “trauma spectrum psychiatric disorders.”

How the Brain Influences Posttraumatic Symptom Expression

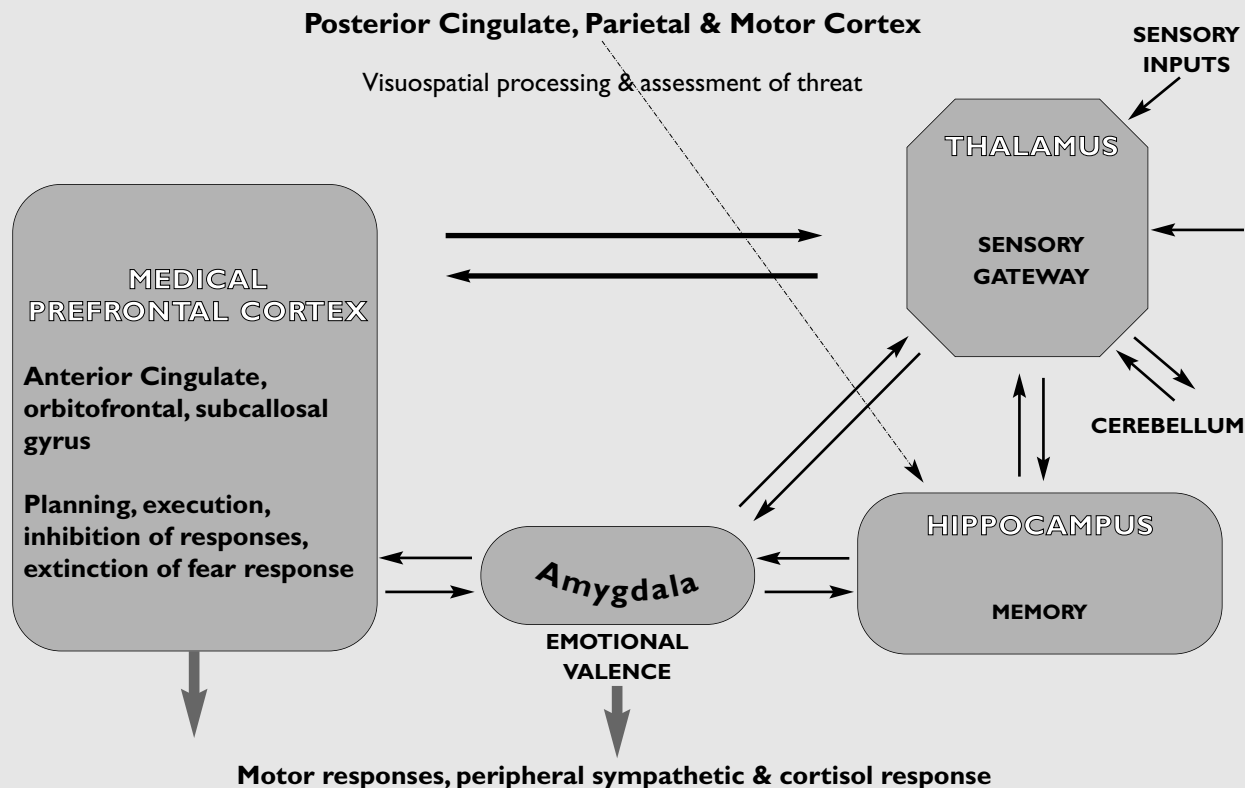
Hippocampal dysfunction may play a role in PTSD and dissociative symptoms related to trauma. The hippocampus plays an important role in integrating or binding together different aspects of a memory at the time of recollection. It is thought to be responsible for locating the memory of an event in time, place, and context. The hippocampus is also involved in memory for the context of a stressful event and possibly in the inhibition of fear responses. Dissociation is defined as a breakdown in normal memory, consciousness, or identity, and hippocampal damage may be responsible for this breakdown. Moreover, dissociation at the time of trauma is associated with long-term psy-

chopathology.⁷ This dissociation may represent not a risk factor for later pathology, but instead the initial onset of a PTSD-dissociative spectrum disorder. **Dissociation at the time of trauma may represent the subjective sensation of hippocampal damage—reviewed below—at the time of stress, given the critical role the hippocampus plays in the integration of both memory encoding and retrieval.**

Another difficulty that trauma patients have is trouble relating to others and fitting into society, which I believe is related at least in part to problems with the frontal cortex. The medial prefrontal cortex has been shown to play a critical role in emotion. This includes both emotional responses in a social situation and relating to others as well as the modulation of fear-related emotions that may be recalled during a life-threatening event and which are thought to be mediated by a part of the brain called the amygdala. *Phineas Gage, who had a railroad spike driven through those parts of his frontal cortex, was able to reason and converse normally; however he was completely disabled in that he was unable to work or have social relationships because he could not read the social cues of others and respond in an appropriate way.*⁹ In a similar way, PTSD patients are unable to respond normally to others and to read social cues. For instance, PTSD patients may be more likely to interpret social cues as being hostile or threatening, which can make it difficult to get along with supervisors or co-workers. This results in situations in which they feel misunderstood and cut off from others, and society is unable to integrate them in the larger whole.¹⁰ **Our brain imaging studies have shown that this part of the brain—compared with healthy controls—has a decrease in function when PTSD patients are exposed to a reminder of their trauma⁸⁻¹¹ or when BPD patients hear scripts of abandonment situations.¹²**

Psychological trauma has lasting effects on the individual that are not easily captured in our psychiatric diagnostic categories. These include the effects of trauma on the individual's perception of society, the world, and the meaning of his or her relationship with the world and with others. The psychiatric disorder PTSD is perhaps unique in representing

Figure 1
Functional Neuroanatomy of Trauma Spectrum Disorders



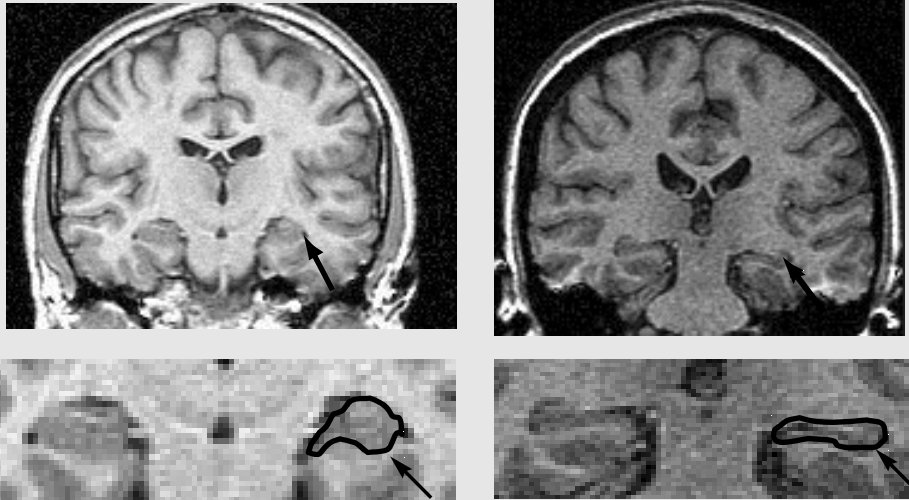
Stress has effect on multiple brain areas that are responsible for mediating the stress response. These include amygdala, hippocampus, medial and orbitofrontal cortex, cerebral cortex, hypothalamus, and the brain stem. These regions are functionally inter-related and represent important substrates for neurochemical systems involved in the stress response. Long-term changes in function and structure of these regions leads to symptoms of PTSD.

interplay between psychiatric and neurophysiological dysfunction and a profound alteration in the individual's existential view of the world and his or her place in it. Trauma victims frequently suffer from "survival guilt," the feeling that they should not have survived when so many others died. The fact that the person survived when so many others perished adds to the feeling that the world is meaningless and nothing makes sense. Victims often believe that they do not deserve to "leave all of this behind them" and "get on with their lives" when only a fluke of chance led to their survival. They may feel that they have more in common with the dead victims from their past than the people in their current life.

Stress Responsive Hormonal Systems

Hormones, including norepinephrine and cortisol, play a crucial role in the stress response. **Norepinephrine is released in the brain and throughout the body and has several functions that are critical for survival. Norepinephrine sharpens the senses, focuses attention, raises the level of fear, increases heart rate and blood pressure, and, in general, prepares us for fight or flight. The norepinephrine system is similar to a fire alarm that alerts all areas of the brain simultaneously. This system sacrifices the ability to convey specific information to specific parts of the brain in order to obtain more speed.**^{16,17}

Figure 2
Hippocampal Volume Reduction in PTSD



(MRI) scan shows a visible reduction in the hippocampus in a patient with PTSD relative to a healthy individual.

Norepinephrine focuses the senses by activating the neurons that collect information obtained by the senses in order to rapidly and efficiently obtain information about dangers in the environment. At the same time it stimulates the cells of the brain to more efficiently collect information about what dangers are out there. It also stimulates the heart to beat more rapidly and blood pressure to increase, which leads to emergency transfer of oxygen and nutrients needed for survival to all the cells of the body. The beauty of the system is that the same chemical messenger that “turns on” the brain also stimulates the heart (as well as other bodily organs) in order to facilitate survival. Acute stressors in animals lead to release of norepinephrine and chronic stress to potentiated release with re-exposure to stressors, compared to previously unstressed animals.¹³

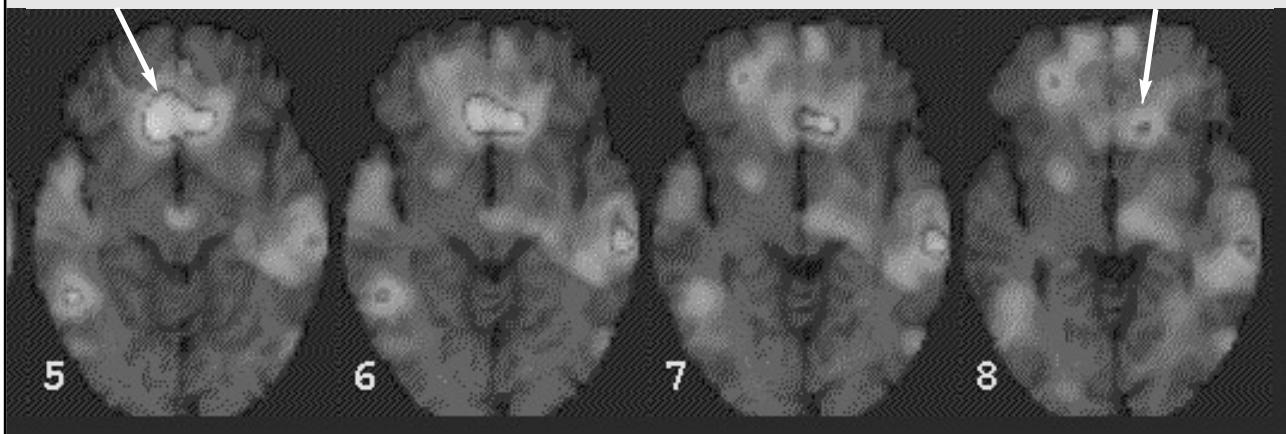
A variety of studies have shown long-term dysregulation of the noradrenergic system in PTSD.¹⁴ Psychophysiology studies have demonstrated an increase in sympathetic responses (heart rate, blood pressure, and galvanic skin response) to traumatic reminders, such as traumatic slides and sounds or traumatic scripts, in PTSD.¹⁵ Studies of norepinephrine in plasma and urine have shown increased lev-

els at baseline, while traumatic reminders result in a potentiated release of norepinephrine in PTSD.¹⁶ Administration of the α_2 antagonist yohimbine has been demonstrated to increase the release of norepinephrine in the brain, which resulted in increased PTSD-specific symptomatology as well as increased release of norepinephrine metabolites in plasma in PTSD patients.¹⁷ Alterations in central metabolic responses to yohimbine

were also found in PTSD patients as measured with positron emission tomography (PET) scans.¹⁸

Animal studies have shown that increasing norepinephrine release up to a certain level improves cognition and attention but beyond that point there is a reduction in performance. Using PET, which permits the measurement of brain activity during artificial stimulation of norepinephrine release in the brain using yohimbine, we found that lower levels of norepinephrine stimulate brain activity in prefrontal cortex but that the brain tends to shut down at very high levels (as seen in PTSD). These findings are consistent with an inverted U-curve for norepinephrine, where lower levels of norepinephrine stimulation increase brain efficiency whereas very high levels decrease brain efficiency. It is commonly agreed that a small amount of stress can be advantageous but that too much can have an adverse effect. For instance, sometimes it is difficult to study if there is no reason to learn the material, especially if the material is not interesting. If there is an important exam, it becomes easier. However, when individuals get “stressed out” and “choke,” they perform worse. This occurs when too much norepinephrine is released in their brains,

Figure 3
Medical Prefrontal Cortical Dysfunction with Traumatic Memories in PTSD



Effects of exposure to traumatic reminders in the form of combat slides and sounds on brain blood flow in PTSD. There was a decrease in medial prefrontal cortical (mPFC) and anterior cingulate (AC) function with traumatic reminder exposure in PTSD areas in light grey

which is why some individuals with public speaking fears take a drug (propranolol) to block the effects of norepinephrine in the brain in order to improve their performances during public speaking events.

The *cortisol* system also plays an important role in the stress response. Like norepinephrine, cortisol is released during times of threat and is critical to survival. **Cortisol aids in survival by redistributing energy when an individual is under attack. To do so, it suppresses functions not needed for immediate survival, including reproduction, immune response, digestion, and the pain. Cortisol promotes vital functions, including increased heart rate and blood pressure, while shunting energy to the brain and muscles to speed up thought processes and fight or flee.** Although cortisol has actions that are beneficial for short-term survival, it may perform these functions at the expense of long-term viability of the body. For instance, chronically high cortisol levels cause gastric ulcers, thinning of the bones, and, possibly, brain damage.²³

Evolution may have favored the caveman who could survive attacks by woolly mammoths long enough to pass his genes to the next generation, even if it meant that he couldn't remember where he left his favorite spear when his was old. In other words, evolu-

tion favors short-term survival at the expense of long-term function.²⁴

The *corticotropin releasing factor (CRF)/hypothalamic-pituitary-adrenal (HPA) axis* system plays an important role in the stress response.²⁴ Exposure to stressful situations is associated with a marked increase in cortisol release from the adrenal glands. *Glucocorticoid* release from the adrenal glands is regulated by *adrenocorticotropin releasing hormone (ACTH)* released from the pituitary, which in turn is primarily regulated by CRF released from the *paraventricular nucleus (PVN)* of the hypothalamus. Intraventricular injection of CRF results in stress-related behaviors such as decreased exploration of novel environments, and increased defecation. *Stressors early in life may have long-term effects on the CRF/HPA axis, including increased glucocorticoid response to subsequent stressors.*²⁵

PTSD has been associated with long-term dysregulation of the HPA axis. Baseline levels of urinary cortisol were either decreased or unchanged in chronic PTSD; decreased 24-hour samples of plasma cortisol levels were found in the same group of patients.^{19,20} However, in PTSD patients, exposure to a stressor²¹ or a traumatic reminder²² was associated with a potentiated release of cortisol. Cortisol also may be elevated in the more acute

phase of PTSD,²⁹ although further research is needed in this area. **A replicated finding has been a super-suppression of the cortisol** response to lower doses of DST (0.5 mg); this finding is in direct contrast with those of patients with major depression who are non-suppressors with the standard 1 mg DST test.²³ PTSD patients had elevated levels of CRF in the cerebrospinal fluid under resting conditions.^{24,25} One possible explanation of the findings to date related to HPA axis function in PTSD is an increase in neuronal CRF release, increased central glucocorticoid receptor responsiveness, and resultant low levels of peripheral cortisol due to enhanced negative feedback. When at rest, cortisol levels are normal or low, as stated in the beginning of this section.

Effects of Stress on the Hippocampus

Work from the laboratories of Robert Sapolsky at Stanford University and Bruce McEwen at Rockefeller University provided evidence for the startling observation that **cortisol** (or glucocorticoids, the generic term that applies across all animal species) **released during stress may damage the brain.**^{26,27} Stress has important effects on impairing memory—an important function of the hippocampus. *Neurotrophins*, such as brain-derived neurotrophic factor (BDNF), a recently isolated neuropeptide that has important trophic effects on the hippocampus and other brain regions, may also play a role in stress-related changes in the hippocampus. Stress in animals resulted in a reduction in BDNF in the hippocampus.²⁸ **Stress also inhibits neurogenesis, the growth of new neurons, in the hippocampus.**²⁹

In 1990, my colleagues and I saw these findings presented at a scientific meeting and wondered if they were applicable to humans exposed to psychological trauma. If so, this would have profound implications. We wondered if it was possible that being abused as a child or being a war veteran could cause brain damage, just from the things that one saw, heard, smelled? We administered tests of memory, such as remembering a story or a list of words, that had been shown to be related to neuronal loss in the hippocampus. We used

neuropsychological testing to measure declarative memory function in PTSD. In an initial study we found statistically significant deficits in verbal declarative memory function in combat-related PTSD, including deficits in paragraph recall, but no deficits in IQ or visual memory.³⁰ Next we tested survivors of childhood physical and/or sexual abuse with the diagnosis of PTSD and found similar memory deficits. Deficits in short-term memory in the childhood abuse patients were observed to be correlated with level of abuse as measured using the composite severity score on the *Early Trauma Inventory*.³¹

Based on the animal studies mentioned earlier, we were interested in looking at hippocampal morphology in patients with a history of traumatic stress exposure and PTSD. Using magnetic resonance imaging (MRI) we found that the hippocampus was smaller in the PTSD patients than in the comparison group, 8% smaller for the right hippocampus. The left hippocampus was not significantly smaller. We also found that the more difficulties the veterans had with memory, the smaller the hippocampus.³² In a second study, adult survivors of childhood abuse with PTSD were found to have even smaller hippocampal volume than those without PTSD.⁴ Other studies have had similar results.³³⁻³⁵

Work by Ron Duman and his group showed that selective serotonin reuptake inhibitors (SSRIs), which are used in the treatment of psychiatric disorders, can counteract the negative effects of stress on the hippocampus.³⁶ Based on this work, our group tested these medications on 20 patients with PTSD treated in an open label fashion with paroxetine, (Paxil) in order to see if they could reverse the memory deficits and hippocampal atrophy associated with PTSD and depression. We showed that a year of treatment with paroxetine in PTSD patients resulted in a 5% increase in hippocampal volume and a 20% increase in hippocampal-based declarative memory function.³⁷ Applying findings from animal studies to humans, our studies corroborated the beneficial effects of SSRIs on hippocampal structure and function following traumatic stress.

Effects of Stress on Health

Although the body's stress response plays a critical role in short-term survival, this is often at the expense of long-term function. In addition to its effects on memory and the hippocampus, chronically elevated levels of cortisol may also affect mood, leading to depression and feelings of fatigue. Stress also impairs the immune system, which can lead to an increase in infections and, possibly, increased rates of cancer.⁴⁵ Elevations in cortisol lead to increased deposition of intra-abdominal fat;⁴⁵ this type of fat is associated with a

higher mortality than obesity in general.⁴⁵ Stress also has effects on the cardiovascular system, which increase the risk for heart disease.^{46,47} Cortisol adversely affects atherosclerosis, and elevations in norepinephrine may have direct effects on heart rhythms, leading to sudden death.⁴⁷ Patients with depression (which is related to stress in many cases) and heart disease are about five times more likely to have sudden death relative to patients with heart disease without depression.⁴⁸ PTSD also has been associated with an increased risk for cardiovascular disease.⁴⁹

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Questions Based On This Lesson

To earn CME credits, answer the following questions on your quiz response form.

43. Which one of the following statements is *not* correct?

- A. The author suggests a unifying concept of “trauma-spectrum disorder,” consisting of PTSD and DSM-IV-defined common comorbid disorders.
- B. Dissociation at the time of a trauma—defined as a breakdown in normal memory, consciousness, or identity, possibly caused by hippocampal damage—may actually protect against the development of long-term psychopathology.
- C. Lower levels of norepinephrine stimulate brain activity in the prefrontal cortex, but at very high levels (as seen in PTSD), the brain tends to shut down.
- D. Increased cortisol release has beneficial actions for short-term survival, but chronically high cortisol levels can be destructive to the body, perhaps even to the brain.

44. Stress has been shown to:

- A. Increase the brain-derived neurotrophic factor (BDNF) in the hippocampus, which regulates memory function
- B. Accelerate hippocampal neurogenesis
- C. Induce short-term memory deficits in adult survivors of childhood abuse that are correlated with the assessed severity of the abuse
- D. Significantly enlarge the hippocampus, as shown via MRI studies, in combat veterans who displayed deficits in verbal declarative memory and paragraph recall

45. Which of the following psychopharmacologic agents appear to counteract the negative effect of stress on the hippocampus?

- A. Atypical antipsychotics
- B. Selective serotonin reuptake inhibitors
- C. Benzodiazepines
- D. Lithium and other mood stabilizers

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