REVIEW ARTICLE

Does Stress Damage the Brain?

J. Douglas Bremner

Studies in animals showed that stress results in damage to the hippocampus, a brain area involved in learning and memory, with associated memory deficits. The mechanism involves glucocorticoids and possibly serotonin acting through excitatory amino acids to mediate hippocampal atrophy. Patients with posttraumatic stress disorder (PTSD) from Vietnam combat and childhood abuse had deficits on neuropsychological measures that have been validated as probes of hippocampal function. In addition, magnetic resonance imaging (MRI) showed reduction in volume of the hippocampus in both combat veterans and victims of childhood abuse. In combat veterans, hippocampal volume reduction was correlated with deficits in verbal memory on neuropsychological testing. These studies introduce the possibility that experiences in the form of traumatic stressors can have long-term effects on the structure and function of the brain. Biol Psychiatry 1999;45:797–805 © *1999 Society of Biological Psychiatry*

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Introduction

One hundred years of psychiatry has brought us back to our starting point. At the end of the 19th century, Sigmund Freud made the famous case study of Anna O., who was suffering from hysterical symptoms that appeared to be related to the witnessing of sexual events as a child. Freud originally believed that Anna O. was a victim of exposure to traumatic sexual experiences in childhood. Following this initial observation, he noticed an increasing number of women in his practice who reported exposure to sexual events in childhood. Could it be that Vienna was suffering from an epidemic of childhood sexual abuse? At the time, childhood sexual abuse was considered to be a rare phenomenon. Freud changed his views into the theory that fantasies of childhood sexuality were leading to neurotic behavior in his patients, rather than the reality of childhood sexual abuse (Nemiah 1998). The rest of the story is the history of American psychiatry for a good part of the 20th century.

American psychiatry was dominated by Freud's theories for the first half of the 20th century. These views held sway until the advance of biologic approaches to psychiatry, which have become increasingly prominent over the past 30 years. Biological psychiatrists aimed to replace Freud's theories of psychopathology (based on ideas of imbalances of psychological forces) with what they felt was a more scientific approach. In their view, psychopathology was secondary to disruptions of physiology that had their foundation in genetic vulnerability. This framework placed greater emphasis on genetic abnormalities leading to physiologic changes, with their phenomenologic expression in psychiatric disorders. In the early phase of biological psychiatry, there was a great emphasis on finding the genetic basis for psychiatric disorders, and little emphasis on the role of environment in the genesis of psychopathology. As is often true in the history of the development of ideas, the biological psychiatrists effectively leaped backward over 50 years of psychoanalysis to psychiatrists such as Kraepelin (1919). He also believed that psychiatric disorders had their basis in constitutional abnormalities that had their expression in the brain, and performed neuroanatomic studies of the brains of schizophrenics in order to find a lesion to explain their illness.

The biological psychiatrists who used this model, however, were really not much different from the psychoanalysts who preceded them. Both groups gave little or no credence to the role that environment could play in the development of psychiatric illness. Biological psychiatry emphasized the deterministic effects of genetics, while psychoanalysts focused on unconscious mechanisms upon which the environment had little impact (e.g., at one time the idea that children should be observed in order to understand their internal psychology was considered radical). Thirty years after the start of the biologic revolution in psychiatry, we still have not found the gene for schizophrenia or mania. It is clear that genetic factors do play an important role in psychiatric disorders. Most likely, a combination of genetic and environmental factors, of nature and nurture, is involved in the development of psychopathology. In terms of possible environmental causes of psychopathology, stress is a good candidate.

One of the most important brain areas that mediates, and in turn is affected by, the stress response is the hippocam-

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pus. The hippocampus plays an important role in new learning and memory (Zola-Morgan and Squire 1990). This function is critical to the stress response, for example in assessing potential threat during a life-threatening situation, as occurs with exposure to a predator. Alterations in memory form an important part of the clinical presentation of patients with stress-related psychopathology. PTSD patients demonstrate a variety of memory problems including deficits in declarative memory (remembering facts or lists, as reviewed below), and fragmentation of memories (both autobiographic and trauma-related). PTSD is also associated with alterations in nondeclarative memory (i.e., types of memory that cannot be willfully brought up into the conscious mind, including motor memory such as how to ride a bicycle). These types of nondeclarative memories include conditioned responses and abnormal reliving of traumatic memories following exposure to situationally appropriate cues (Brewin et al 1996).

The important effects of the stress hormones, glucocorticoids, on the hippocampus is consistent with the hypothesis that the hippocampus likely plays a role in stress-related psychiatric disorders. The hippocampus has a rich concentration of receptors for glucocorticoids (McEwen et al 1986). Corticosteroid receptors within the hippocampus include Type I (mineralocorticoid) and Type II (glucocorticoid). Type II receptors have a low affinity for glucocorticoids, but tissues with Type I receptors contain an enzyme which metabolizes cortisol so that the receptor is not exposed to high concentrations of cortisol that is available for binding. This binary system of receptors may allow a more flexible responsiveness of the system, with Type II receptors playing a more important role in modulation of hippocampal function during high release of glucocorticoids as is seen during acute stress (Trapp and Holsboer 1996). The hippocampus also modulates glucocorticoid release through inhibitory effects on the hypothalamic–pituitary–adrenal (HPA) axis. These findings indicate that the hippocampus is an important center piece for integrating cognitive, neurohormonal, and neurochemical responses to stress. We hypothesized that hippocampal dysfunction represents the anatomic basis for alterations in memory, such as fragmented or delayed recall of traumatic memories of childhood abuse (Bremner et al 1996a). The hippocampus may also play a role in other symptoms of PTSD.

Studies in normal human subjects showed that glucocorticoids have direct effects on memory function. Administration of commonly used therapeutic doses of glucocorticoids (Keenan et al 1995), dexamethasone (Wolkowitz et al 1990; Newcomer et al 1994), or cortisol (Kirschbaum et al 1996) resulted in impairments in verbal declarative memory function in healthy human subjects. Cortisol levels were related to memory function, with evidence of exacerbation of memory deficits with stress-induced cortisol elevations (Kirschbaum et al 1996; Lupien et al 1997) and improvement in memory function with reduction in cortisol levels (Seeman et al 1997; Wolkowitz et al 1997). ACTH (Born et al 1990) and cortisol (Born et al 1987) have effects on a component of the event related potential (ERP) that is a marker for selective attention. Patients with Cushing's Disease, which involves excessive release of cortisol over long periods of time, have deficits in verbal declarative memory that are correlated with hippocampal volume reduction on magnetic resonance imaging (MRI) (Starkman et al 1992). These findings showed that glucocorticoids have direct and reversible effects on memory and cognition that are at least partially mediated through the hippocampus.

Cortisol also represents an important part of the response to stress in human subjects. Healthy human subjects undergoing psychological stressors demonstrate a robust increase in cortisol levels in the periphery (Rose et al 1968; Seeman et al 1995a; Seeman et al 1995b). Soldiers in the Korean War undergoing random artillery bombardment had markedly increased levels of urinary cortisol, with the highest levels in soldiers under the greatest danger, in comparison with their own cortisol levels when away from the battle zone area (Howard et al 1955). These studies showed that extreme stress results in an acute increase in cortisol levels in human subjects.

Work from the laboratories of Robert Sapolsky at Stanford University, Bruce McEwen at Rockefeller University, and others demonstrated in a variety of animal species that high levels of glucocorticoids seen in stress is associated with damage to the hippocampus. When male and female vervet monkeys are caged together, the female monkeys attack the males, leading to extreme stress in the males, which is often fatal. Monkeys who were improperly caged and died spontaneously following exposure to severe stress had multiple gastric ulcers on autopsy, consistent with exposure to chronic stress, and hyperplastic adrenal cortices, consistent with sustained glucocorticoid release. These monkeys also had damage to the CA3 subfield of the hippocampus (Uno et al 1989).

Follow-up studies suggested that hippocampal damage was associated with direct exposure of glucocorticoids to the hippocampus (Sapolsky et al 1990). Studies in a variety of animal species (Sapolsky et al 1988) showed that direct glucocorticoid exposure results in decreased dendritic branching (Wooley et al 1990; Watanabe et al 1992c), alterations in synaptic terminal structure (Magarinos et al 1997), a loss of neurons (Uno et al 1990), and an inhibition of neuronal regeneration (Gould et al 1998) within the CA3 region of the hippocampus. These effects are steroid and tissue specific (Sapolsky et al 1985; Packan

and Sapolsky 1990). Prenatal exposure to elevated levels of glucocorticoids also resulted in hippocampal damage (Uno et al 1990), a finding which has implications for the common practice in pediatric medicine of administering dexamethasone to premature infants to prevent intraventricular hemorrhage. Glucocorticoids exert their effect through disruption of cellular metabolism (Lawrence and Sapolsky 1994) and by increasing the vulnerability of hippocampal neurons to a variety of insults, including endogenously released excitatory amino acids (Sapolsky and Pusinelli 1985; Armanini et al 1990; Virgin et al 1991). Glucocorticoids have also been shown to augment extracellular glutamate accumulation (Stein-Behrens et al 1994). Furthermore, reduction of glucocorticoid exposure prevents the hippocampal cell loss associated with chronic stress (Landfield et al 1981; Meaney et al 1988).

Stress also has effects on functions of new learning and memory that are mediated by the hippocampus. Exposure to the stress of an unfamiliar environment resulted in deficits in working memory indicative of hippocampal dysfunction (Diamond et al 1996). High levels of glucocorticoids seen with stress were associated with deficits in new learning, in addition to damage to the hippocampus (Luine et al 1994). Long-term subcutaneous implants of glucocorticoids that mimic the chronic stress situation resulted in deficits in new learning and memory for maze escape behaviors. Moreover, the magnitude of deficits in new learning of maze escape behaviors was correlated with the number of damaged cells in the CA3 region of the hippocampus (Arbel et al 1994). Stress was also shown to affect long-term potentiation (LTP), which is used as a model for the molecular basis of new learning and memory (Diamond et al 1995). These effects may be mediated by glucocorticoids acting through the Type II receptor within the hippocampus (Pavlides et al 1995).

Other neurochemical systems interact with glucocorticoids to mediate the effects of stress on memory and the hippocampus. Stress resulted in a decrease in $5HT_{1A}$ binding within the hippocampus with associated atrophy in the CA3 region of the hippocampus and memory impairment. Tianeptine, which decreases serotonin levels within the hippocampus, blocked the effect of stress on memory and the hippocampus, suggesting that serotonin released during stress may also play a role in the etiology of hippocampal damage (McEwen et al 1997). Brain-derived neurotrophic factor (BDNF) is a recently isolated neuropeptide which has important trophic effects on the hippocampus and other brain regions. Stress resulted in a reduction in brain-derived neurotrophic factor (BDNF) mRNA in the hippocampus, an effect which may be partially related to glucocorticoid release (Smith et al 1995). These effects were blocked by antidepressant drugs and electroconvulsive therapy (Nibuya et al 1995). Stress-induced reductions in BDNF may contribute to hippocampal atrophy associated with stress.

Stress-mediated hippocampal damage may lead to dysregulation of others aspects of the organism's stress response system. The hippocampus has an inhibitory effect on the corticotropin releasing factor (CRF) and the hypothalamic–pituitary–adrenal (HPA) axis (Jacobson and Sapolsky 1991). Intraventricular injection of CRF, which is physiologically released during stress, resulted in a series of physiologic and behavioral responses that are adaptive during stress and are considered to be characteristic of anxiety responses. Stress-induced damage to the hippocampus resulted in increased levels of corticotropin releasing factor (CRF) mRNA in the paraventricular nuclei of the hypothalamus (Herman et al 1989) as well as a decrease in the sensitivity of rats to dexamethasone suppression of HPA function (Feldman and Conforti 1980; Magarinos et al 1988). In human subjects with combat-related PTSD, we found elevated CRF levels in cerebrospinal fluid based on a single lumbar puncture determination (Bremner et al 1997a). CRF is distributed in a number of locations outside of the hypothalamus. The behavioral effects of CRF are not likely to be mediated by hypothalamic CRF, however, and the functional significance of elevations in CRF derived from the hypothalamus for stress-related psychiatric disorders is unclear.

The effects of glucocorticoids on the physiology of the organism exposed to stress are more complex than a simple mediation of hippocampal neuronal cell death. Glucocorticoids have a variety of effects on physiologic systems in addition to effects on the brain, including the modulation of gene expression, immunity, reproduction, and bone formation. These effects may have a protective effect on the organism during certain situations of stress, but in other situations, the effects of glucocorticoids may be damaging (McEwen et al 1992). Stress-induced hippocampal damage may be an example of sacrificing long-term function (i.e., memory function) for the sake of short-term survival. Elevations in glucocorticoids are not invariably associated with hippocampal damage. For instance, the absence of glucocorticoids following adrenalectomy resulted in damage to neurons of the dentate gyrus of the hippocampus (distinct from the CA3 region most commonly affected by stress) (Vaher et al 1994). The authors argued for a more dynamic role of glucocorticoids in sculpting neurons of the hippocampus, with glucocorticoids having the potential to have both protective and damaging effects depending on a variety of factors (McEwen et al 1995).

These studies raised the question, do glucocorticoids result in hippocampal damage and associated memory deficits in humans? With this in mind, we initially used neuropsychological testing to measure declarative mem-

ory function in Vietnam combat veterans with PTSD. We selected measures that were validated in studies of patients with epilepsy to be specific probes of hippocampal function. Sass and colleagues in the Yale Neurosurgery Program administered the Wechsler Memory Scale (WMS)-Logical Subscale (paragraph recall) and verbal Selective Reminding Test (vSRT) to patients with epilepsy who subsequently underwent surgical resection of the hippocampus. The investigators found that decreases in percent retention of the WMS paragraph after delayed recall and deficits on the Long Term Retrieval (LTR) subscale of the vSRT were correlated with decreases in neuronal number of the CA3 region of the left hippocampus (Sass et al 1990; Sass et al 1992). The findings were specific to verbal, and not visual, memory. In a study using these measures, we compared Vietnam combat veterans with PTSD ($n = 26$) to control subjects ($n = 16$) matched for gender, age, race, years of alcohol abuse, years of education, handedness, and socioeconomic status. We found deficits in paragraph recall as measured by the WMS-Logical Component, for immediate and delayed recall, as well as percent retention. We also found deficits in short-term verbal memory as measured with the vSRT LTR. There was no difference in IQ between patients and control subjects in this study as measured by the Wechsler Adult Intelligence Sale-Revised (WAIS-R) or visual memory as measured by the WMS-Figural Component (Bremner et al 1993). We followed up studies of memory in male combat veterans with PTSD by examining men and women with PTSD related to severe childhood physical and/or sexual abuse. We studied patients with PTSD related to a history of severe childhood abuse as measured by the Early Trauma Inventory (ETI) ($n = 18$), and compared them to healthy subjects ($n = 17$) matched for age, gender, race, years of education, and years of alcohol abuse. We found deficits in immediate and delayed recall and percent retention on the WMS-Logical Component, as well as the vSRT LTR, in the patients with abuse-related PTSD in comparison to controls. Deficits in short-term memory in the childhood abuse patients were significantly correlated with level of abuse as measured with the composite severity score on the ETI ($r = -.48$; $p < .05$). There was no difference in IQ as measured by the WAIS-R or visual memory as measured by the WMS-Figural Component in early trauma patients in comparison to control subjects (Bremner et al 1995b). Other groups also found deficits in verbal declarative memory in Vietnam combat veterans with PTSD using other measures of verbal declarative memory function (Uddo et al 1993; Yehuda et al 1995) (although see Gurvits et al 1993). Recently, deficits in verbal declarative memory were also reported in Desert Storm veterans with PTSD (Vasterling et al 1997). Future studies are needed to demonstrate that verbal memory deficits are specifically associated with PTSD, and are not a nonspecific result of exposure to traumatic stress.

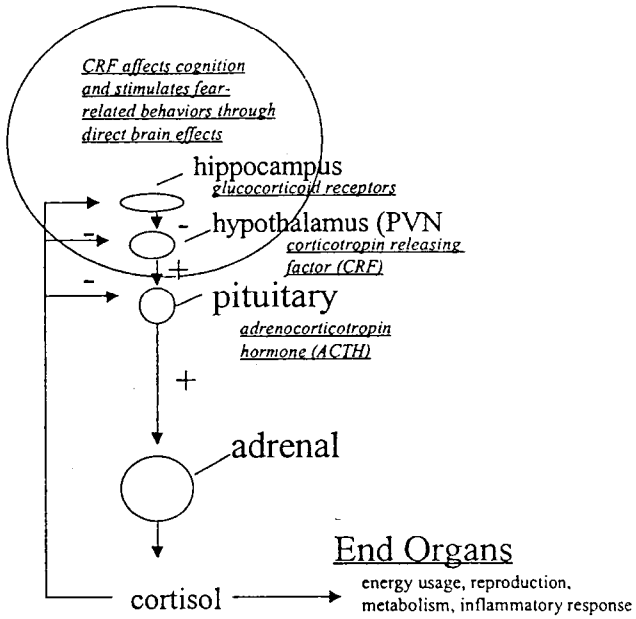

Figure 1. Diagrammatic representation of the relationship between the hippocampus and the hypothalamic–pituitary–adrenal (HPA) axis response to stress in PTSD. Activation of the HPA axis in acute stress results in elevated cortisol in the periphery, which may lead to hippocampal damage. Hippocampal atrophy may cause a release of hypothalamic inhibition, resulting in elevated CRF with associated blunted ACTH response to CRF. Long-term dysregulation in PTSD may lead to decreases in cortisol (the mechanism of which is unclear) or no change.

In order to test the hypothesis that traumatic stress results in hippocampal damage, we used magnetic resonance imaging (MRI) to quantitate hippocampal volume in living human subjects with a history of traumatic stress and the diagnosis of PTSD. We first looked at hippocampal volume in Vietnam veterans with combat-related PTSD. Healthy control subjects were matched for gender, age, race, years of alcohol abuse, years of education, height, weight, and socioeconomic status. Measurements of the hippocampus were performed using a reliable technique for measurement of hippocampal volume that has been validated by correlating MRI-based volumetrics with hippocampal neuronal number obtained from surgical specimens of the hippocampus in patients with epilepsy. We found an 8% decrease in MRI-based measurement of right hippocampal volume in patients with PTSD ($n = 26$) in comparison to matched control subjects ($n = 22$) [1184 vs 1286 mm^3; 95% confidence interval (CI) 10 to 195 mm^3; $p < .05$]. Decreases in right hippocampal volume in the PTSD patients were associated with deficits in short-term memory as measured by the WMS-Logical,

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percent retention subcomponent ($r = .64$; $p < .05$). There was no difference in volume of bilateral left temporal lobe (minus hippocampus) or caudate between patients and controls in this study (Bremner et al 1995c). We have subsequently not found a difference in volume of the amygdala between patients with combat-related PTSD and control subjects (Bremner et al 1998). Multiple linear regression including potential confounders not addressed by the matching methodology, years of alcohol abuse, education, and age, did not show a significant relationship between these variables and hippocampal volume (Bremner et al 1996b).

A subsequent study examined hippocampal volume in 17 male and female adults with a history of severe childhood physical and/or sexual abuse and long-term psychiatric consequences in the form of PTSD. They were compared to 17 healthy control subjects matched on a case-by-case basis for age, gender, handedness, race, years of education, and years of alcohol abuse. There was a 12% reduction in left hippocampal volume in the patients with abuse-related PTSD in relation to comparison subjects, which was statistically significant ($p < .05$). A 3.8% reduction in volume of the right hippocampus was not significant. Multivariate analyses utilizing stepwise linear regression continued to show a significant relationship between PTSD and decreased hippocampal volume when the potential confounders of age, education, and alcohol abuse were entered in the model. There were no significant differences between patients and controls for temporal lobe, caudate, or amygdala volumes in this study (Bremner et al 1997b).

Other studies found reductions in hippocampal volume in clinical populations of traumatized subjects. Gurvits and co-workers (1996) compared hippocampal volume in seven patients with Vietnam combat-related PTSD to seven Vietnam combat veterans without PTSD, and eight healthy nonveteran control subjects. The authors found a 26% bilateral decrease in hippocampal volume, which was statistically significant for both left and right hippocampal volume considered separately. Although subjects were not case matched for alcohol abuse, there continued to be a significant difference in hippocampal volume after adjusting for years of alcohol abuse using analysis of covariance. There was no difference in ventricular, amygdala, or whole brain volume between the groups. This study also found a significant correlation between level of combat exposure (measured with the Combat Exposure Scale) and combat exposure, as well as visual delayed recall errors. Stein and colleagues (1997) found a statistically significant 5% reduction in left hippocampal volume in 21 sexually abused women relative to 21 nonabused female control subjects. Hippocampal atrophy in this study was correlated with level of dissociative symptomatology in the abused women. Most (although not all) of the abused women had a current diagnosis of PTSD. In summary, there are several replicated studies in more than one population of traumatized patients showing atrophy of the hippocampus, which appears to be specific to PTSD diagnosis. PTSD patients with early life trauma had a greater reduction in left hippocampal volume, while patients with PTSD from later life (Vietnam combat) had bilateral or right hippocampal atrophy. One possible explanation for this finding is related to the fact that the hippocampus continues to develop after birth. Insults to the hippocampus as different stage of development may have different effects on the hippocampus.

Hippocampal atrophy was also found in patients with major depression. Exposure to stress has been temporally related to the onset of depressive episodes (reviewed in Mazure 1994), and many patients with depression have elevations in plasma cortisol levels. Cognitive deficits consistent with hippocampal dysfunction were also associated with depression. Recently, Sheline and co-workers (1996) found atrophy of the hippocampus in a group of treated patients with major depression compared to control subjects. Our group has also found statistically significant reductions in hippocampal volume after controlling for differences in whole brain volume (Bremner et al, unpublished data, 2/16/98). A previous study, however, did not find evidence for hippocampal atrophy in depression in patients with current depression (Axelson et al 1993). This negative finding may be related in part to limited resolution of early MR imaging techniques and inability to distinguish hippocampus from amygdala. Hippocampal volume reductions in depression could be related to either stress resulting in an increase in cortisol, or to elevated cortisol levels that are associated with depressive episodes in 40% to 50% of patients. More work is needed to comprehensively examine cortisol, memory, and the hippocampus in depressed patients before and after treatment.

The functional implications of hippocampal volume reduction in PTSD are unclear. Volume reductions of 5% to 12% are of a lesser magnitude than in other disorders involving hippocampal pathology such as epilepsy and Alzheimer's dementia. The fact that volume reduction correlated with memory dysfunction in at least two studies indicates that these findings are related to declarative memory dysfunction. The hippocampus may also be involved in fear responding and other behaviors that are relevant to the clinical presentation of PTSD.

There are alternative possible explanations for memory deficits and hippocampal volume reduction in PTSD. Small hippocampal volume and poor memory function that is present from birth could represent a risk factor for the development of PTSD. Consistent with this idea, McNally and Shin (1995) reported that low IQ at the time

of entering the service was a risk factor for development of combat-related PTSD. Studies in monozygotic twins (who have identical genetic constitution) are needed in order to assess the relative contribution of genetic and environmental factors to memory deficits and hippocampal volume reduction in PTSD.

The possibility that cortisol may be low in chronic PTSD raises the question of how elevations in cortisol can represent the mechanisms of hippocampal atrophy in PTSD. Several early studies showed decreased cortisol in chronic PTSD (Mason et al 1986; Yehuda et al 1991; reviewed in Yehuda et al 1995b). These findings have not been uniformly replicated, however (Pitman and Orr 1990; Lemieux and Coe 1995), in some cases with larger sample sizes than earlier studies (Mason et al, unpublished data, 9/1/98). We hypothesized that high levels of cortisol at the time of the stressor result in damage to hippocampal neurons, which can persist for many years after the original trauma, leading to reductions in hippocampal volume as measured with MRI (Bremner et al 1995a, 1996; 1998). In this scenario, decreased cortisol characterizes the chronic stages of the disorder due to adaptation and long-term changes in cortisol regulation. The studies reviewed above suggest that acute traumatic stress results in hyperactivity of the CRF/HPA system, while chronic PTSD may lead to long-term dysregulation, which results in a different HPA/cortisol system. It is also possible that sensitivity of hippocampal glucocorticoid receptors to circulating cortisol represents the critical variable in determining vulnerability to stress-induced hippocampal atrophy.

Findings of no increase in cortisol levels in the aftermath of rape in women who subsequently develop PTSD (Resnick et al 1995; Yehuda et al 1998) have also been used to argue against the glucocorticoid hypothesis of stress-induced hippocampal damage. In an initial report, cortisol samples obtained days to weeks after exposure to the trauma of rape found a relationship between low cortisol in the aftermath of rape and prior history of trauma (Resnick et al 1995). In a subsequent analysis of samples obtained 8 to 48 hours after the rape, the authors found a relationship between low cortisol levels in the aftermath of rape and prior history of trauma. However, there was there was no relationship between cortisol and risk for subsequent development of PTSD (Yehuda et al 1998). Given the finding that history of prior trauma increases the risk for PTSD with subsequent victimization, this raises the question of whether these patients had prior PTSD, or were physiologically distinct from the nonstress exposed subjects. The studies also provide no information about cortisol levels at the time of the rape. Studies are needed to examine the relationship between cortisol at the time of the trauma, hippocampal volume, and PTSD.

Findings of memory deficits and hippocampal volume reduction in PTSD have implications for the controversy surrounding delayed recall of childhood abuse (Bremner et al 1996). The hippocampus has been hypothesized to play a role in the binding of individual memory elements at the time of memory retrieval. If the hippocampus is dysfunctional, this may represent the anatomic basis of the fragmentation of memory often seen in patients with PTSD related to childhood abuse. Memory dysfunction in PTSD is also relevant to clinical management. Clinicians should be aware that problems with learning and memory may affect the performance of patients at work or school.

If stress results in hippocampal damage and associated problems with memory, this could have far reaching implications. Our inner cities are plagued by an epidemic of urban violence that affects our nation's children on a daily basis. The hippocampus plays a role in new learning and memory. If stress impairs the ability of children to learn, this could have important public health implications. Consistent with this, one recent study showed that Lebanese teenagers with PTSD related to exposure to bombings and violence in civil war had deficits in academic achievement as measured with the Metropolitan Achievement Test (MAT) in comparison to stressed nonPTSD youths and nonstressed control subjects (Saigh et al 1996).

The question arises, if stress can damage the brain, is there anything that can be done to prevent or reverse this process? The good news is that studies in animals demonstrated several agents with potentially beneficial effects. The group at Rockefeller University found that phenytoin (Dilantin) reverses stress induced hippocampal atrophy, probably through modulation of excitatory amino acid-induced neurotoxicity (Watanabe et al 1992a). Other agents, including tianeptine and dihydroepiandosterone (DHEA), have similar effects (Watanabe et al 1992b). Serotonin reuptake inhibitor administration was shown to result in an increase in dendritic branching within the hippocampus (Duman et al 1997). We still do not know if hippocampal atrophy is reversible in humans. However, findings that cognitive therapy results in reversal of memory dysfunction in traumatized Lebanese youths with PTSD offers some grounds for hope (Saigh 1988). In addition, studies showing that the hippocampus is unique within the brain in its capacity to regenerate neurons (Gould et al 1998) suggest that reversibility may be possible even in the setting of neuronal death.

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