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The effects of stress on memory and the hippocampus throughout the life cycle: Implications for childhood development and aging

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Abstract
Studies in animals showing hippocampal atrophy and associated memory deficits in stress and aging have implications for stress and aging in humans. Clinical studies in traumatized human populations with posttraumatic stress disorder (PTSD) have replicated studies in animals, showing reduction in volume of the hippocampus measured with magnetic resonance imaging and associated memory deficits. Trauma at different stages of development (early childhood abuse versus trauma in later life due to combat) may influence the nature of memory deficits and hippocampal atrophy. Studies in aging human subjects are consistent with animal studies, although future research is needed in this area. The similarities between biological findings related to cortisol and the hippocampus in stress and aging in both animal and human studies raises the question of whether PTSD can be seen as a form of accelerated aging. Evidence that stress affects the hippocampus and the capacity for learning has broad implications for public health policy, underlying the need for additional resources in this important area and a reexamination of our understanding of factors influencing academic achievement.

It was over a decade ago that Robert Sapolsky, Bruce McEwen, and colleagues at Stanford and Rockefeller Universities made the startling observation that stress may damage the brain. These scientists found that high levels of glucocorticoids seen in stress result in damage to the hippocampus, a brain area involved in learning and memory (McEwen et al., 1992; Sapolsky, 1996). 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 were found to have damage to the CA3 subfield of the hippocampus (Uno, Tarara, Else, Suleman, & Sapolsky, 1989). This hippocampal damage was reproducible when glucocorticoids were implanted directly into the hippocampus (Sapolsky, Packan, & Vale, 1988; Sapolsky, Uno, Rebert, & Finch, 1990).

Exposure to glucocorticoids resulted in decreased dendritic branching (Watanabe, Gould, & McEwen, 1992; Wooley, Gould, & McEwen, 1990) and a loss of neurons (Uno, Lohmiller, Thieme, Kernitz, Engle, & Roecker, 1990) which were specific to the hippocampus (Packan & Sapolsky, 1990). Glucocorticoids exerted their effect through disruption of cellular metabolism, increasing the vulnerability of hippocampal neurons to a variety of insults, including endogenously released excitatory amino acids (Armanini,

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Hutchins, Stein, & Sapolsky, 1990; Sapolsky, Krey, & McEwen, 1986; Sapolsky & Pusinelli, 1985; Virgin et al., 1991), and augmenting extracellular glutamate accumulation (Stein–Behrens, Lin, & Sapolsky, 1994). More recently, emerging studies have found evidence for the idea that other factors besides glucocorticoids, such as Nerve Growth Factor (NGF), which has an effect on neuronal morphology and proliferation, may mediate stress-induced alterations in hippocampal morphology (Nibuya, Morinubo, & Duman, in press). Stress induced hippocampal atrophy was also associated with deficits in memory function (Luine, Villages, Martinex, & McEwen, 1994) with the magnitude of deficits in new learning of maze escape behaviors being correlated with the number of damaged cells in the CA3 region of the hippocampus (Arbel, Kadar, Silberman, & Levy, 1994).

These studies raised the question, does severe stress result in hippocampal damage and associated memory deficits in humans? With this in mind, neuropsychological testing was used to measure declarative memory function in posttraumatic stress syndrome (PTSD). We used the Selective Reminding Test (Hannay & Levin, 1995) and the Wechsler Memory Scale (Russell, 1978) as measures that are known to be related to hippocampal neuronal number. Seminal studies from the Yale Neurosurgery Department using patients with epilepsy undergoing temporal lobectomy showed significant correlations between number of neurons in the CA3 region of the left hippocampus and performance on the verbal Selective Reminding Test (vSRT) Long Term Retrieval (LTR) component (Sass et al., 1990), as well as percent retention on the Logical Memory Portion of the Wechsler Memory Scale (WMS) (Sass et al., 1994). These findings indicate that the left hippocampus plays an important role in verbal memory. However, observations that verbal memory impairment is more severe with bilateral hippocampal lesions compared to unilateral lesions indicates that both hippocampi play a role in verbal memory. In a study comparing Vietnam combat veterans with PTSD ($N = 26$) to healthy controls ($N = 16$) matched for age, race, years of alcohol abuse, years of education, handedness, and socioeconomic status, PTSD patients had deficits in verbal memory as measured by the Wechsler Memory Scale (WMS)-Logical Component (Russell, 1978) (Figure 1). PTSD patients also had deficits in verbal memory as measured with the Selective Reminding Test-Verbal Component (Hannay & Levin, 1985). There was no difference in IQ or visual memory (Bremner et al., 1993). Other studies also found deficits in verbal declarative memory in Vietnam combat veterans with PTSD using other measures of verbal declarative memory function (Uddo, Vasterling, Brailey, & Sutker, 1993; Yehuda et al., 1995), and in survivors of childhood abuse (Bremner, Randall, Capelli, Scott, McCarthy, & Charney, 1995) (described below). Recently, deficits in verbal declarative memory were also reported in Desert Storm veterans with PTSD.

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 controls were matched for 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 controls ($n = 22$) (1184 vs. 1286 mm^3) (95% confidence interval [C.I.] 10–195 mm^3) ($p < 0.05$) (Figure 2). Decreases in right hippocampal volume in the PTSD patients were associated with deficits in short-term memory as measured by the WMS-Logical, percent retention subcomponent ($r = 0.64$; $p < 0.05$) (Figure 3). There was no difference in volume of bilateral left temporal lobe (minus hippocampus), caudate, or amygdala between patients and controls in this study (Bremner et al., 1995a). Multiple linear regression including potential confounders not addressed by the matching

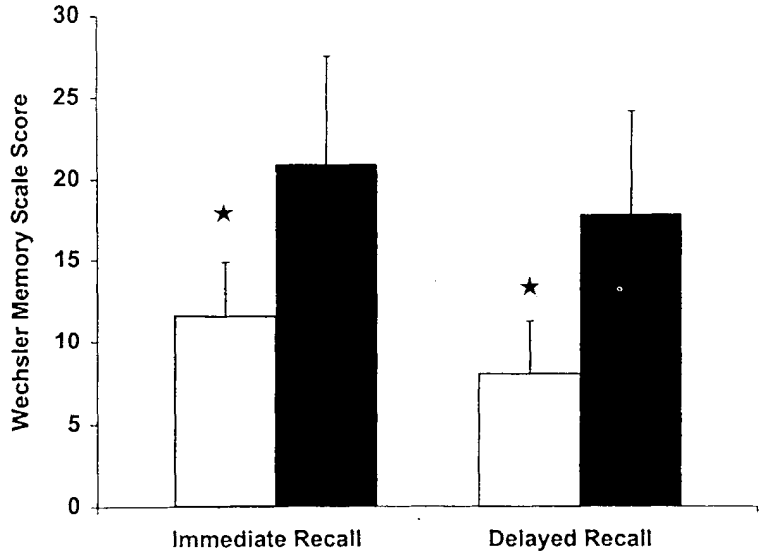

Figure 1. Verbal memory function as assessed with the Wechsler Memory Scale–Logical Component. There was a significant decrease in verbal memory scores for both immediate and delayed recall in Vietnam veterans with combat-related PTSD compared to healthy controls. (□) PTSD ($n = 26$); (■) controls ($n = 15$). $^{*}p < .05$.

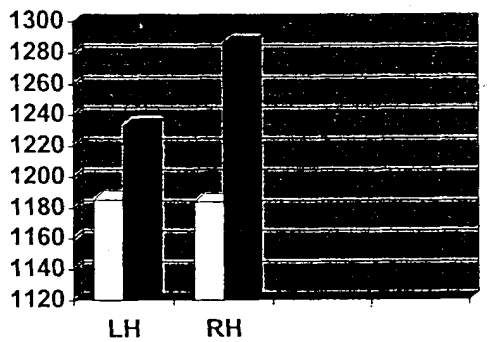

Figure 2. Hippocampal volume in combat-related PTSD. There was an 8% decrease in right hippocampal volume in patients with Vietnam combat-related PTSD in comparison to controls ($p < .05$). (□) PTSD, $n = 26$; (■) controls, $n = 22$.

methodology, years of alcohol abuse, education, and age did not show a significant relationship between these variables and hippocampal volume.

Gurvits et al. (1996) compared hippocampal volume in seven patients with Vietnam combat-related PTSD to seven Vietnam combat veterans without PTSD and eight healthy nonveteran controls. The authors found a statistically significant 26% bilateral decrease in hippocampal volume that 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 hippocampal volume, as well as visual delayed recall errors. Findings of hippocampal atrophy were replicated in two additional studies of survivors of childhood abuse (Bremner et al., 1997b; Stein, Koverola, Harna, Torchia, & McCarty, 1997), which are described in greater detail below. The hippocampus is felt to have an inhibitory effect on CRF release from the hypothalamus (Feldman & Conforti, 1980; Herman et al., 1989), and chronic stress in animals was associated with elevations in CRF. Consistent with this, in a study of Vietnam combat veterans with posttraumatic stress disorder ($n = 11$) compared to age and sex matched healthy subjects ($n = 17$), there was a significant increase in concentrations of CRF in the cerebrospinal fluid based on lumbar puncture (Bremner et al., 1997a).

A decrease in cortisol has been reported in chronic PTSD (Mason, Giller, Kosten, &

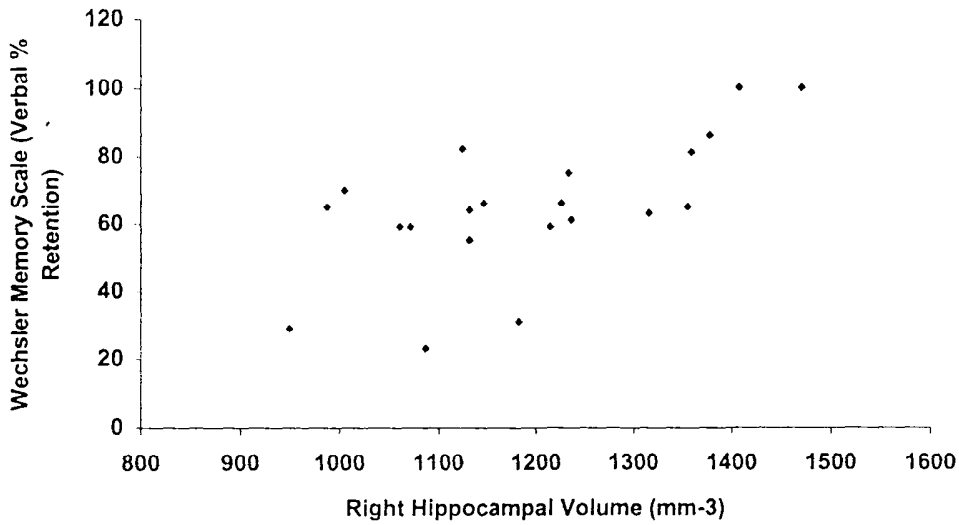

Figure 3. Relationship between right hippocampal volume and verbal memory function as assessed with the Wechsler Memory Scale. There was a significant correlation between deficits in verbal memory and reduced hippocampal volume in patients with Vietnam combat-related PTSD ($r = .64$; $p < .05$).

Harkness, 1986; Yehuda, Southwick, Nussbaum, Giller, & Mason, 1991; reviewed in Yehuda, Giller, Levenwood, Southwick, & Siever, 1995a, although see Pitman & Orr, 1990, and Lemieux & Coe, 1995). In addition, women with low cortisol 17–151 days after rape assault were reported to have higher histories of previous trauma, and greater risk of developing PTSD (Resnick, Yehuda, Pitman, & Foy, 1995). There was no direct relationship, however, between low cortisol and subsequent development of PTSD in this study or in a subsequent analysis of this sample using cortisol samples obtained within 50 hr of the time of the rape trauma (Yehuda, Resnick, Schmeidler, Yang, & Pitman, 1998). These findings do raise the question of how elevated cortisol can represent the etiology of hippocampal atrophy in PTSD. One possibility is that high levels of cortisol at the time of the stressor result in damage to hippocampal neurons which persist for many years after the original trauma, leading to reductions in hippocampal volume as measured with MRI (Bremner, Krystal, Southwick, & Charney, 1995; Bremner, Krystal, Charney, & Southwick, 1996; Bremner, Vermetten, Southwick, Krystal, & Charney, 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. Evidence in support of glucocorticoid mediated toxicity in humans comes from studies in patients with abnormal elevations of cortisol due to Cushing's disease showing hippocampal atrophy and cognitive memory deficits (Starkman, Gebarski, Berent, & Schteingart, 1992). However, an alternative hypothesis for hippocampal atrophy is that small hippocampal volume, which is present from birth, is a risk factor for the development of PTSD.

If these findings are related to glucocorticoid-mediated hippocampal toxicity, this raises the question of how is it possible that a hormonal system required for survival can actually be toxic to the brain in some situations? During an acute stress, it may be more important for the organism to release large amounts of glucocorticoids for survival than to preserve the hippocampus and memory

function. Memory dysfunction may not be a problem until later in the life span of the organism, when it has little impact on that most important event from an evolutionary perspective, passing genetic material on to the next generation. According to this idea, long-term function is sacrificed for the sake of short-term survival.

The Long-Term Effects of Trauma Early in Life on Hippocampal Function and Memory: Clinical Implications

An important question is whether stress at different stages of development will have different effects on the individual. Studies in animals suggest that stress early in life can have an impact on the individual that persists throughout the life span. Both prenatal (light and noise) (Fride, Dan, Feldon, Halevy, & Weinstock, 1986) and early maternal deprivation (Levine, Weiner, & Coe, 1993; Stanton, Gutierrez, & Levine, 1988) and early manipulation stress (Levine, 1962) resulted in increased glucocorticoid response to subsequent stressors. Prenatal stress was associated with a failure of habituation of glucocorticoid responsiveness to novel stimuli (Fride et al., 1986). Increased glucocorticoid responsivity to ACTH challenge in maternal deprivation stress suggested an increase in adrenocortical responsivity with early stress (Stanton, Gutierrez, & Levine, 1988). Early postnatal adverse experiences altered hypothalamic CRF mRNA, median eminence CRF content, and stress induced CRF release (Plotsky & Meaney, 1993) and ACTH release (Ladd, Owens, & Nemeroff, 1996) in male rats. Maternally deprived rats had decreased numbers of glucocorticoid receptors, as measured by dexamethasone binding, in the hippocampus, hypothalamus and frontal cortex. They also had increased norepinephrine levels in the paraventricular nucleus (PVN) of the hypothalamus as determined by microdialysis. In nonhuman primates, adverse early experiences induced by variable maternal foraging requirements resulted in profound behavioral disturbances (more timid, less social, and more subordinate) years later. Adult monkeys raised in the variable foraging maternal environment also had elevated levels of corticotropin releasing factor (CRF) in the cerebrospinal fluid (Coplan et al., 1996). These observations suggest early adverse experience permanently affects the HPA axis.

It is also possible that positive early life experiences during critical periods of development may have long term beneficial consequences on an animal's ability to mount adaptive responses to stress or threat. An animal model that appears to be of use in studying this phenomena is postnatal handling. Postnatal handling has important effects on the development of behavioral and endocrine responses to stress. For example, daily handling within the first few weeks of life (picking up rat pups and then returning them to their mother) resulted in increased Type II glucocorticoid receptor binding which persisted throughout life. This was associated with increased feedback sensitivity to glucocorticoids and reduced glucocorticoid-mediated hippocampal damage in later life (Meaney, Aitken, Van Beekel, Bhatnagar, & Sapolsky, 1988; Meaney, Aitken, Sharma, & Sarrieau, 1989). These effects appear to be due to a type of "stress inoculation" from the mother's repeated licking of the handled pups (Liu et al., 1997). 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 organisms biological response to threatening stimuli.

Studies in animals showing glucocorticoid-mediated hippocampal toxicity and memory dysfunction with stress raised the question, does early stress such as childhood abuse result in similar deficits in human subjects? To answer this question we looked at survivors of childhood physical and/or sexual abuse with the diagnosis of PTSD ($n = 18$) and compared them to healthy subjects ($n = 17$) matched for age, sex, race, years of education, and years of alcohol abuse. We found deficits in short-term memory as measured by the Wechsler Memory Scale (WMS)-Logical Component (verbal memory), for immediate and delayed recall, as well as the Verbal Selective Reminding Test, in the patients with abuse-related PTSD in comparison to controls

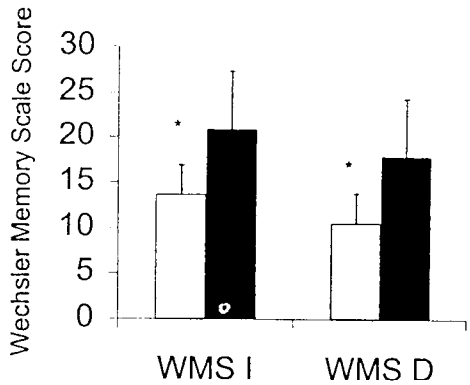

Figure 4. Verbal memory function as assessed with the Wechsler Memory Scale–Logical Component. There was a significant decrease in verbal memory scores for both immediate and delayed recall in adult survivors of childhood abuse with PSTD compared to healthy controls. (□) PTSD, $n = 21$; (■) controls, $n = 20$. $^{*}p < .05$.

($p < 0.01$) (Figure 4). 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 Early Trauma Inventory (Bremner, Vermetten, & Mazure, 1998) ($r = -0.48$; $p < .0.05$) (Figure 5). 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 controls (Bremner, Randell, Capelli, Scott, McCarthy, & Charney, 1995). Using MRI we measured 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, who were compared to 17 healthy controls matched on a case-by-case basis for age, sex, handedness, race, years of education, and years of alcohol abuse. There was an 12% reduction in left hippocampal volume in the patients with abuse-related PTSD in relation to comparison subjects which was statistically significant ($p < 0.05$) (Table 1). A 3.8% reduction in volume of the right hippocampus was not significant (Table 1). 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) (Table 1).

Stein, Koverola, Hanna, Torchia, and McClarty (1997) found a statistically significant 5% reduction in left hippocampal volume in 21 sexually abused women relative to 21 nonabused female controls. 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. Hippocampal atrophy was also related to another psychiatric disorder felt to be related to stress, major depression. A number of studies found a temporal relationship between stress and the onset of depressive episodes (reviewed in Mazure, 1994). Hypercortisolemia accompanies depressive episodes in a number of instances. Recently, Sheline, Wang, Godo, Csernansky, and Vannier (1996) reported hippocampal atrophy based on MRI measurements in patients who had recovered from an episode of depression. Our group also found a reduction in hippocampal volume in patients with treated depression, which was statistically significant after controlling for differences in whole brain volume with analysis of covariance. In summary, there are now four replicated studies showing hippocampal atrophy in PTSD and two studies in patients with depression. There are also multiple replicated studies showing deficits in verbal declarative memory function in PTSD.

There were several differences in the effects of stress at different stages of development on memory and the hippocampus in the studies reviewed above. Patients with PTSD secondary to trauma later in life (Vietnam combat) had atrophy of the right hippocampus while those with PTSD secondary to early life trauma had greater left hippocampal atrophy. Why is there the difference in laterality of these findings? One possibility is that trauma at different stages of development has different effects on the hippocampus. The brain continues to develop after birth, which may explain differences in the effects of trauma at

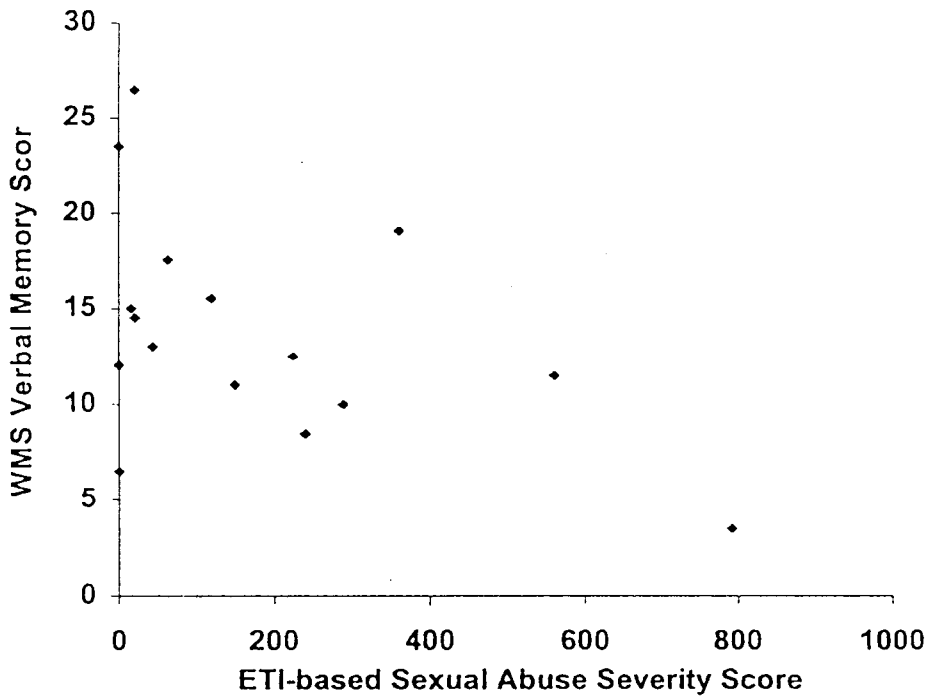

Figure 5. Relationship between severity of abuse as measured with the Early Trauma Inventory and verbal memory function as assessed with the Wechsler Memory Scale–Logical Component. There was a significant correlation between severity of abuse and deficits in verbal memory in adult survivors of childhood abuse with PTSD ($r = -.48$; $p < .05$).

Table 1. *Volume of the hippocampus (mm^3) in abuse patients and controls*

	Patients ($n = 17$)		Controls ($n = 17$)			
Brain Region	Mean	*SD*	Mean	*SD*	*F*	*p* Value
Hippocampus						
Left	1,050	152	1,193	142	8.07	0.0077
Right	1,062	169	1,116	190	0.74	0.40
Mean	1,056	160	1,155	160	3.57	0.07

different stages of development. Patients with early trauma showed a correlation between deficits in memory and severity of abuse, which was not seen in patients with later life trauma (Bremner et al., 1995). Previous studies in children with a history of severe abuse found a relationship between the arithmetic subscale of the IQ test and markers of abuse (Lewis, Shanok, Pincus, & Glaser, 1979). Trauma at early stages of development may have an effect on IQ that is not seen in patients exposed to traumatic stress at later periods of development. It is also possible that genetically transmitted low IQ is a risk factor for childhood abuse and/or PTSD (McNally & Shin, 1995).

The current plague of traumatic stress affecting our children could have critical implications for public health policy. Sixteen percent of women had a history of childhood sexual abuse (rape, attempted rape, or unwanted molestation) before their 18th birthday (McCauley et al., 1997). Nine percent of inner city youths in Detroit were found to be

suffering from PTSD related to traumas such as witnessing shooting, childhood abuse, and domestic violence (Breslau et al., 1991). These figures suggest that there are several hundred thousand youths in our country currently suffering from PTSD. Childhood maltreatment and victimization could affect academic achievement which could have far reaching ramifications on our society (Cicchetti, Toth, & Hennessy, 1993). Consistent with this, Saigh, Mroweh, and Bremner (1997) found that adolescents in Lebanon with civil war-related PTSD ($n = 12$) had deficits in academic achievement as measured with the Metropolitan Academic Achievement Test (Prescott, Balow, Hogan, & Farr, 1986) in comparison to stressed non-PTSD ($n = 16$) and nonstressed Lebanese adolescents ($n = 15$). Deficits included scholastic performance in the areas of vocabulary, reading, mathematics, spelling, language, and science subtests. If traumatized children are suffering from stress-induced hippocampal toxicity with associated memory dysfunction, this could have enormous implications for public health policy. These children will be expected to have difficulties in learning that will impair their academic performance and affect them throughout their lives.

Alterations in memory in patients with a history of childhood abuse are currently a topic of considerable controversy. Fragmentation of memory and dissociation are common outcomes associated with childhood abuse. It is common for abuse victims to remember only certain aspects of the abuse event. For instance, a patient who was locked in the closet had an isolated memory of the smell of old clothes and the sound of a clock ticking. Later she connected that with feelings of intense fear and then the entire circumstances relating to the abusive events. Such examples of the gradual recovery of memory, however, have been quite controversial over the past 5 years (Bremner & Marmar, 1998). In a number of litigation suits it has been claimed that episodes of "delayed recall" really represent memories that were "implanted" by overzealous therapists, due to excessive urging or the use of techniques such as hypnosis. It has been argued that these therapists insisted to their patients that they had been abused, to the point where patients could not distinguish whether they were having memories of true abuse or memories of what their therapists had told them. Clearly there is a wide range of competency, professionalism, and training amongst mental health professionals currently in practice. Undoubtedly some overzealous therapists have in the past insisted to their patients that they were abused. However, the current chill in this area has reduced this type of activity. Many therapists and clinicians are even afraid to question their patients about their trauma histories, which is unfortunate.

Empirical studies on memory and the hippocampus may shed some light on controversial topics such as delayed recall of memories of childhood abuse. The hippocampus plays an important role in integrating or binding together different aspects of a memory at the time of recollection. It is felt to be responsible for locating the memory of an event in time, place, and context. We have hypothesized that atrophy and dysfunction of the hippocampus following exposure to childhood abuse may lead to distortion and fragmentation of memories (Bremner, Krystal, Charney, & Southwick, 1996). For instance, in the example given above, in an abused patient who was locked in the closet, there is a memory of the smell of old clothes, but no visual memory of being in the closet and no affective memory of the feeling of fear. Perhaps with psychotherapy there is a facilitation of associations to related events that may bring all of the aspects of the memory together. Or if the patient has an event such as being trapped in a dark elevator, the feeling of fear with darkness and the enclosed space may be enough to trigger a recollection of the entire memory. According to the model which we are describing, fragmentation of memory and delayed recall of traumatic events would not be expected to occur in all individuals who were exposed to traumatic stress, but only in those who developed psychopathology (PTSD) with associated hippocampal atrophy and dysfunction.

The Interaction of Stress and Aging in Producing Hippocampal Toxicity and Memory Impairments

Aging and stress may interact to promote hippocampal toxicity with related memory dysfunction. Sapolsky, Krey, and McEwen (1985) outlined a "glucocorticoid cascade" model for age-related memory deficits. They found that in rodents there is a progressive increase in peripheral levels of glucocorticoids with age. These elevations lead to progressive hippocampal atrophy, further increases (due to a loss of hippocampal inhibition of glucocorticoid release) in peripheral glucocorticoid levels, and progressive memory deterioration. These rats also showed a delay in return of glucocorticoid levels to baseline after stress, possibly secondary to a down regulation of glucocorticoid receptors in the hippocampus with aging (Sapolsky, Krey, & McEwen, 1983a, 1983b). Aging was associated with a loss of the normal plasticity of these receptors (Eldridge, Brodish, & Kute, 1989; Eldridge, Fleenor, & Kerr, 1989).

Studies in elderly human subjects relating to glucocorticoids, memory, and the hippocampus have been few and typically do not include comprehensive assessments. Findings from these studies are mixed (Stein–Behrens & Sapolsky, 1992; Urban, 1992), although there is some evidence to support the idea that elevations in cortisol (Armanini et al., 1993; Lupien et al., 1994; Swaab et al., 1994; Van Cauter, Leproult, & Kupfer, 1996) and impairment in feedback sensitivity to cortisol (O'Brien, Schweitzer, Ames, Tuckwell, & Mastwyk, 1994) occur with aging. Aging individuals had decreased numbers of glucocorticoid receptors measured on leukocytes (Armanini et al., 1992, 1993) and altered cortisol responsiveness to stressors (Gotthardt et al., 1995; Raskind et al., 1995; Seeman et al., 1995). Increases in cortisol (Lupien et al., 1994) and decreased sensitivity to the feedback inhibition of cortisol (O'Brien et al., 1994) with aging were correlated with progressive memory impairment. Acute administration of glucocorticoids resulted in greater memory impairment in young individuals compared to elderly individuals, which suggested decreased glucocorticoid binding in the hippocampus in the elderly (Newcomer, Craft, Hershey, Askins, & Bardgett, 1994). Some studies (Convit et al., 1995), but not others (Sullivan, Marsh, Mathalon, Lim, & Pfefferbaum, 1995), found a decrease in volume of the hippocampus measured with MRI in elderly subjects. Studies in individuals with age-associated memory impairment (AAMI) demonstrated alterations in hippocampal structure (Soininen et al., 1994; Parnetti et al., 1996) which were correlated with memory impairment (Soininen et al., 1994). It is clear that hippocampal atrophy, hypercortisolemia, and memory impairment do not progress as rapidly in humans as in rodents, although there is evidence to suggest that a similar process is taking place at a slower rate in at least a subgroup of the elderly. Future studies should focus on populations of "super elderly" individuals (e.g., subjects who are 75 or greater, rather than using conventional definitions of the elderly, such as greater than age 65). This type of study design may be more strategically designed to accentuate age-related effects on the hippocampus.

In the only study we are aware of to look at the relationship between stress and cortisol in the elderly, Seeman et al. (1995) measured cortisol and ACTH response to the stress of a driving simulation challenge test in 16 healthy men and women between 70 and 79 years of age. They found significant elevations in ACTH and cortisol with stress in the elderly subjects. Furthermore, those subjects with a low self esteem exhibited a nearly six-fold greater cortisol response to the driving challenge compared to those reporting a high self esteem.

There is a paucity of research on the relationship between aging and PTSD (reviewed in Ruskin & Talbot, 1996) and most of these studies have been epidemiological. Kato, Asukai, Miyake, Minadawa, and Nishiyama (1996) measured the frequency of short-term PTSD symptoms amongst evacuees of the Hanshin–Awaji earthquake. Fifty subjects under the age of 60 years and 73 subjects over the age of 60 years were interviewed at 3 and

8 weeks after the earthquake. At the 3-week time point, all subjects from both age groups experienced sleep disturbances, depression, hypersensitivity, and irritability. At the 8-week time point, elderly subjects showed a significant decrease in 8 of 10 symptoms, while there was no change in the younger subjects. Goenjian et al. (1994) evaluated 179 subjects 1.5 years after the 1988 earthquake. Although the total mean score on the PTSD reaction index was not significantly different between elderly and younger adults, there was a significant difference in the symptom profile, with the elderly scoring higher on arousal symptoms and lower on intrusive symptoms than younger subjects. Even fewer biological studies were performed on aging and PTSD. One study found decreased cortisol levels in 24-hr urine samples in elderly Holocaust survivors with PTSD (Yehuda et al., 1995b) and in middle aged Vietnam combat veterans with PTSD, while younger individuals with abuse-related PTSD actually had elevated cortisol levels (Lemieux & Coe, 1995). It may be that PTSD in younger individuals is associated with hypercortisolemia, while with aging there is hypocortisolemia, possibly secondary to long-term dysregulation of the HPA axis.

The findings reviewed up to this point raise the question, can PTSD be considered to represent a form of accelerated aging? Will biological findings in PTSD be predicted to be identical to aging? In animal studies both stress and aging are associated with declarative memory dysfunction and hippocampal atrophy. These findings hold based on human research in populations of stress and probably aging as well. Stress and aging may also interact to increase the vulnerability of the hippocampus to glucocorticoid mediated toxicity. For example, continuous administration of slow-release corticosterone to simulate mild stress in young (3 months old) and middle aged (12 months old) rats resulted in greater cognitive deficits in the middle aged rats (Levy, Dachir, Arbel, & Kadar, 1994). Findings related to the HPA axis may also be relevant to understanding the relationship between stress and aging. In animal studies, both chronic stress (Ladd, Owens, & Nemeroff, 1996) and aging (Sapolsky, Krey, & McEwen, 1983a, 1983b) are associated with downregulation of glucocorticoid receptors and impaired return of baseline of glucocorticoids after reintroduction of stress. These findings also support the hypothesis that chronic stress can be thought of as a type of "accelerated aging." Clinical studies in PTSD patients, however, showed an increase in glucocorticoid receptors on peripheral lymphocytes. A clue about these apparent discrepancies may come from the results of a current study looking at the effect of dexamethasone on memory function. Dexamethasone impaired memory function in normal younger subjects, but not in normal older subjects, consistent with a loss of hippocampal glucocorticoid receptors with normal aging (Newcomer et al., 1994). A current study in our laboratory is looking at the effects of dexamethasone on memory function in PTSD. If there is a loss of hippocampal glucocorticoid receptors, as is seen in normal aging, then there should be no effect of dexamethasone on memory in PTSD (making it like a form of "accelerated aging"). If there is increased glucocorticoid receptors in the hippocampus, as suggested by the results of Yehuda and colleagues (1995b), then there should be greater impairment of memory with dexamethasone.

Treatment and Prevention of Glucocorticoid Mediated Hippocampal Toxicity and Memory Deficits Throughout the Life Cycle

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, Gould, Cameron, Daniels, & McEwen, 1992). Other agents, including tianeptine and dihydroepiandosterone

(DHEA), have similar effects (Watanabe, Gould, Daniels, Cameron, & McEwen, 1992). Neurons within the hippocampus were found to be unique within the brain in showing the capacity to regenerate themselves (Gould, Tanapat, McEwen, Flugge, & Fuchs, 1998). 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). Psychotherapy is useful in the treatment of other consequences of childhood abuse, and these effects may be mediated through effects on the brain (Cicchetti & Toth, 1995; Toth & Cicchetti, 1993).

Perhaps more salient is to consider ways that can prevent glucocorticoid mediated toxicity to the hippocampus. We are currently suffering from a virtual epidemic of childhood abuse (Cicchetti & Toth, 1995; Lynch & Cicchetti, 1998; McCauley et al., 1997). This epidemic has critical implications for public health policy (Barnett, Manly, & Cicchetti, 1993). If childhood abuse and neglect is resulting in glucocorticoid mediated hippocampal toxicity, then this could lead to problems with learning that will have a major impact on the child's development. In addition, symptoms of PTSD, such as problems concentrating, hyperarousal, and an impairment in the ability to socialize with others and develop feelings of trust and attachment, will further complicate the child's development (Cicchetti & Toth, 1995). The best cure for these problems is prevention (Toth & Cicchetti, 1993). There is a need for greater awareness of the magnitude of the problem, and intervention at early stages to prevent the complications of abuse (Cicchetti, Toth, & Hennessy, 1993).

Studies in aging are also currently being stimulated by another type of invisible epidemic. The proportion of the American population that is greater than age 65 years is progressively increasing secondary to medical progress and an increase in life expectancy. Increasingly, the disorders that will come to medical attention will be disorders of chronicity, such as age-related memory impairment. One question which underlies research in aging and memory is whether there is any way to slow or prevent the decline in memory function associated with aging. The studies reviewed above suggest that stress may have an interactive effect with normal aging resulting in the acceleration of hippocampal atrophy and memory dysfunction. Decreasing stress should have a beneficial effect, especially at later stages of life when the hippocampus may be more vulnerable.

Conclusions

Traumatic stress has far reaching effects on memory and the brain that need to be understood in relation to development throughout the life cycle. Studies in animals are consistent with stress resulting in atrophy of the hippocampus, a brain area that plays an important role in learning and memory. There is evidence supporting a role for glucocorticoids released during stress resulting in damage to the hippocampus. Clinical studies in traumatized human populations with posttraumatic stress disorder (PTSD) have replicated studies in animals by finding a reduction in hippocampal volume with associated memory deficits. Trauma at different stages of development (early childhood abuse versus trauma in later life due to combat) may influence the nature of memory deficits and hippocampal atrophy. Studies in aging human subjects appear to replicate animal studies, although future research is needed in this area. The similarities between biological findings related to cortisol and the hippocampus in stress and aging in both animal and human studies raises the question of whether PTSD can be seen as a form of accelerated aging.

Findings of hippocampal atrophy and memory deficits in stress have broad implications for public policy. With recent data showing that 16% of women have a history of childhood sexual abuse, it is clear that childhood trauma is a major public health problem. If stress results in damage to the hippocampus, this could have far reaching effects on childhood development. Given the important role that the hippocampus plays in learn-

ing and memory, victimized children may suffer in terms of academic achievement. These deficits in academic achievement may plague them throughout the rest of their lives. An increased emphasis is needed to direct resources and attention to the prevention and treatment of childhood victimization as well as stress at other stages of development.

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