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Neurobiological Perspectives on Trauma and Aging

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A growing body of clinical data indicates that psychological traumatization has harmful effects for a sizable subgroup of

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individuals exposed to extreme stress, and that these effects may be experienced intermittently or persistently throughout the life of the individual (Koranyi, 1969; Klonoff, McDougall, Clark, Kramer, and Horgan, 1976; Kilpatrick, Veronen, and Resick, 1979; Ellis, Atkeson, and Calhoun, 1981; Resick, Calhoun, Atkeson, and Ellis, 1981; Bowman, 1982; Eaton, Sigal, and Weinfeld, 1982; Nadelson, Notman, Zackson, and Gornick, 1982; Thienes-Hontos, Watson, and Kucala, 1982; Levav and Abramson, 1984; Carmil and Carel, 1986; Krystal, 1988; Miller, Martin, and Spiro, 1989; Solomon and Prager, 1992; Lima, et al., 1993; Resnick, Kilpatrick, Dansky, Saunders, and Best, 1993; Tennant, Goulston, and Dent, 1993; Robinson, Rapaport-Bar-Sever, and Rapaport, 1994). There currently exist identified populations with high rates of traumatized individuals for whom issues related to aging are quite important, including survivors of the Holocaust, World War II veterans, and Korean War veterans. There are also other, uncounted numbers of elderly survivors of natural disasters, sexual and physical assaults, political persecution, and other extreme stressors. In addition, there are younger populations, such as the 479,000 American Vietnam war veterans thought to suffer from posttraumatic stress disorder (PTSD) (Kulka, Schlenger, Fairbank, Hough, Jordan, Marmar, and Weiss, 1990), for whom issues related to aging are increasingly relevant. Although chronic PTSD is defined in DSM-IV by the persistence of symptoms for greater than three months, this time frame is not relevant to the aging survivor.

Neurobiological contributions related to the course and treatment of PTSD are unfolding as a consequence of a growing body of recent research. Growing from preclinical models

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of stress response, a relatively small number of studies now have been conducted in Vietnam combat veterans (reviewed in Krystal et al., 1989; Charney, Deutch, Krystal, Southwick, and Davis, 1993). The findings from these studies appear to apply to other traumatized populations (Yehuda, Kahana, Southwick, and Giller, 1994; Yehuda et al., 1995a), suggesting that components of the biological response may be consistent across traumas.

Because of the growing importance of addressing clinical issues related to the aging trauma survivor, all theoretical perspectives should be brought to bear on the convergent issues of trauma and aging. In particular, neurobiological perspectives may help to integrate a diversity of clinical findings, to inform considerations about the course of PTSD, and to suggest new avenues for treatment. This paper will begin with a review of epidemiological and clinical data regarding the long-term course of PTSD. We will then focus on two aspects of the emerging neurobiology of PTSD that appear to be relevant to the course of this disorder: alterations in the regulation of the hypothalamo-pituitary-adrenal axis (HPA) and in noradrenergic systems. In doing so, we will consider advances from neuroendocrinology, psychopharmacology, and brain imaging studies. Finally, we will consider prognostic and treatment issues raised in the process of integrating neurobiological and clinical findings.

DESCRIPTIVE STUDIES

PTSD Is a Chronic Disorder

PTSD symptoms persist indefinitely in an alarmingly high percentage of traumatized individuals. Several studies employing cross-sectional or retrospective designs have documented the persistence of the PTSD diagnosis in several traumatized populations. Sutker, Allain, and Winstead (1993) diagnosed PTSD in 70 percent of a sample of former World War II prisoners of

war (POWs) and in 29 percent of a sample of World War II combat veterans 40 years after the traumatic events occurred. Goldstein, van Kammen, Shelly, Miller, and van Kammen (1987) found that half of their sample of former World War II POWs met criteria for PTSD at a 40-year follow-up. Another study of World War II POWs found that 29 percent met DSM-III criteria for PTSD 40 years after the war (Speed, Engdahl, Schwartz, and Eberly, 1989). A study of Canadian POWs found 42.4 percent had the diagnosis in 1990, 50 years after exposure to the common traumatic event (Beal, 1995). Sutker, Winstead, Galina, and Allain (1990) reported that 90–100 percent of a sample of 20 POWs of the Korean War met DSM-III PTSD criteria 30 years after repatriation. In a study of noncombatants exposed to the trauma of war, Potts (1994) found that 15 percent of 200 civilian internees in Japanese camps during World War II met PTSD criteria in the 6-month period prior to follow-up. In another study, 46 percent of a sample of Holocaust survivors met PTSD criteria more than 40 years after their traumatic experiences occurred (Kuch and Cox, 1992).

Heterogeneity and Variability in the Course of PTSD

Several recent attempts to synthesize clinical and epidemiological data regarding the long-term course of PTSD highlighted the high degree of heterogeneity in the pattern of traumatic responses across individuals and the variability of symptom course within individuals (Krystal, 1988; McFarlane, 1988a,b; Op den Velde et al., 1993). According to these models, PTSD can have a rapid or delayed onset and a persistent or intermittent course, and it may be time-limited or irreversible.

A number of studies suggest that following an initial peak prevalence within the first few years after an extreme stress, the rates of PTSD decline over time to approximately one half of the peak prevalence. Analysis of data from the Epidemiologic Catchment Area (ECA) Survey (Helzer, Robins, and McEvoy, 1987) found a prevalence of PTSD of 1 percent in the general

population, 3.5 percent in civilians exposed to physical attacks and in Vietnam veterans who had not been wounded, and 20 percent in Vietnam veterans who had been wounded. Symptoms of PTSD in those who do not meet the full criteria for PTSD were even more common after a traumatic event. However, these symptoms resolved in 49 percent of individuals who experienced them within 6 months. Importantly, one third of symptomatic individuals continued to experience symptoms for more than 3 years. Combat-related PTSD seemed more enduring. Symptoms that appeared more specific to combat-related PTSD were delayed onset, guilt, belief that the combat experience was recurring, and emotional numbing. Approximately 56 percent of a sample of former POWs of World War II reported PTSD symptoms of a severity sufficient to diagnose PTSD by DSM-III criteria (Zeiss and Dickman, 1989). Further, 60.7 percent of this sample reported being "seriously troubled" by PTSD symptoms during the first year after returning from the war, and 60.0 percent reported being "seriously troubled" by such symptoms between 1946 and 1950. Between 1950 and 1980, this percentage fell to 49.2, and between 1980 and 1983, the percentage who complained of serious symptoms was 48.0 percent. Another study of World War II POWs found that 50 percent of the men would have met criteria for PTSD by DSM-III during the year following repatriation, and 29 percent continued to meet criteria for PTSD 40 years after the war (Speed et al., 1989). A study of Canadian POWs found that 47.5 percent met criteria for PTSD in 1946 and 42.4 percent had the diagnosis in 1990, 50 years after exposure to the common traumatic event (Beal, 1995). In a study of noncombatants exposed to the trauma of war, Potts (1994) found that 36.7 percent of 200 civilian internees in Japanese camps during World War II met criteria for PTSD during the 6-month period following the war. Approximately half of these individuals (15%) continued to meet PTSD criteria in the 6-month period prior to follow-up. A study of the effects of trauma in refugees found that 9 percent of a sample of 145 Vietnamese refugees

living in Norway met criteria for PTSD 3 months after their arrival, and 24 percent met criteria for partial PTSD (Hauff and Vaglum, 1994). At the time of follow-up 3 years later, 4 percent met criteria for PTSD and 10 percent had partial PTSD. Green and colleagues (1990) found a decrease in PTSD from 44 percent in 1974 to 28 percent in 1986 for survivors of the Buffalo Creek disaster.

Several studies document a fluctuating course of PTSD symptoms in individuals with this diagnosis (Zeiss and Dickman, 1989). For example, Kluznick, Speed, Van Valenbury, and Magraw (1986) found that 67 percent of 188 former POWs met criteria for lifetime diagnoses of PTSD. However, 40 years after the trauma, 8 percent of the affected individuals had marked and persistent symptoms, 24 percent had moderate symptoms, 39 percent reported mild symptoms, and 29 percent reported full recovery. In the Buffalo Creek study (Green et al., 1990), 44 percent of subjects initially met PTSD criteria, and 28 percent of subjects met criteria at follow-up, but a lower rate (17%) met PTSD criteria at both timepoints. Op den Velde et al. (1993) found that in 123 individuals who met criteria for lifetime diagnosis of PTSD, 9.7 percent reported a chronic progressive course following an acute onset of the illness, and 12.2 percent reported a chronic progressive course after a delayed onset of the illness. These values correspond to 8 percent and 10 percent of the total sample, respectively.

One corollary of the variability in posttraumatic response has been the growing focus on factors influencing the resiliency of traumatized individuals (Antonovsky, Maoz, Dowty, and Wijsenbeek, 1971; Dimsdale, 1974; Harel, Kahana, and Kahana, 1993). These data draw attention to the effects of subsequent stressful events in the lives of survivors, such as exposure to reminders of the trauma, that might lead to prolongation or exacerbation of symptoms. For example, events such as desecration of a synagogue or public displays by neo-Nazi groups have been noted to cause distress and to exacerbate symptoms in survivors of the Holocaust (Christenson, Walker, Ross, and

Maltbie, 1981; Lipton and Schaffer, 1986; Solomon and Prager, 1992; Wolfe, Brown, and Buscela, 1992; Macleod, 1994). The focus on resiliency and the possibility that treatment might alter the persistence of PTSD-related distress stimulate interest in predictors of chronicity in PTSD patients.

Undoubtedly, there are genetic and early life factors that influence the persistence of PTSD symptoms (Krystal, Nagy, Southwick, and Charney, in press). These issues would be addressed most clearly by large-scale prospective studies of individuals beginning prior to traumatization and including long-term follow-up. However, to our knowledge, no such studies exist. One interesting study that documented long-term difficulties in a small subsample of 152 Harvard students who served in World War II had significant limitations to its generalizability due to its small sample of individuals meeting PTSD diagnostic criteria at follow-up (Lee, Vaillant, Torrey, and Elder, 1995).

Predictors of Chronicity in PTSD

Despite numerous reports of chronic PTSD lasting even decades after traumatization, there remains little clarity regarding the long-term course of subgroups of PTSD symptoms, as outlined in Table 1.

Hyperarousal. Op den Velde et al. (1993) suggested that, in the elderly, hyperarousal symptoms persisted more than avoidance or reexperiencing symptoms. In contrast, several groups (Sutker et al., 1990; Robinson et al., 1994; Yehuda et al., 1995a) found that, while present, arousal symptoms were not clearly elevated above avoidance and reexperiencing symptoms in Holocaust survivor and POW populations. One study suggested that advanced age was associated with more arousal symptoms following traumatic stress exposure (Goenjian et al., 1994). However, hyperarousal symptoms are a persistent component

TABLE 1
Categories of DSM-IV PTSD Symptoms

Hyper-arousal
Sleep disturbance
Irritability
Impaired concentration
Hypervigilance
Increased startle
Avoidance
Avoids thoughts, feelings, activities, people, or places associated with the trauma
Inability to recall aspects of the trauma
Diminished interest/participation in activities
Feelings of detachment
Restricted affect range
Sense of foreshortened future
Reexperiencing
Recurrent, intrusive traumatic memories or dreams
Flashbacks
Emotional distress and physiological arousal upon exposure to traumatic reminders

of traumatic stress response in younger individuals as well (Southwick et al., 1995).

Avoidance. Avoidance symptoms are commonly seen in elderly survivors of severe trauma. Sutker et al. (1990) and Beal (1995) found that inability to express emotional feelings was a persistent consequence of the POW experience and of combat. While avoidance symptoms are prevalent in both POWs and combat veterans, these symptoms, such as feelings of detachment or estrangement, loss of interest in usual activities, restricted range of affect, and a foreshortened sense of the future, appear to be more problematic in POWs (Sutker et al., 1993), and are likely due to the higher rates of PTSD in this population. The importance of avoidance symptoms in individuals with chronic PTSD has also been noted by the ECA study (Helzer et al., 1987). Finally, two recent studies also report persistent avoidance symptoms among Holocaust survivors with PTSD relative

to survivors without PTSD or noninterned refugees (Kuch and Cox, 1992; Yehuda et al., 1995a).

Reexperiencing Trauma. Two studies of aging populations, one conducted with Holocaust survivors (Kuch and Cox, 1992) and one with World War II POWs (Sutker et al., 1993), reported that intrusive symptoms, such as traumatic memories, flashbacks, and nightmares, discriminated survivors of extreme stress who developed PTSD from those who did not develop this disorder. In contrast, Op den Velde et al. (1993) reported a decrease in intrusive symptoms over time, perhaps related to coping or resiliency factors.

NEUROBIOLOGICAL STUDIES

Hypothalamo-Pituitary-Adrenal Axis Regulation, Avoidance, and Chronicity

Acute psychological traumatization (Resnick, Yehuda, Pitman, and Foy, 1995), like acute overwhelming stress in animals (Selye, 1956), is associated with activation of the hypothalamo-pituitary-adrenal axis (HPA). However, over time PTSD becomes associated with the opposite finding, reduced cortisol production under resting conditions. Studies of 24-hour urinary cortisol levels in Vietnam War combat veterans with chronic PTSD found lower levels relative to depressed and healthy control groups (Mason, Giller, Kosten, Ostroff, and Podd, 1986; Yehuda et al., 1990).

Subsequently, studies of HPA function in PTSD patients have described a growing number of alterations within the HPA that are consistent with reduced cortisol levels in these patients. Several findings suggest that PTSD is associated with increased HPA sensitivity to feedback suppression by cortisol. Two studies found that PTSD patients show increased sensitivity to the cortisol-suppressing effects of low dexamethasone doses (0.25-0.5 mg) compared to control groups (Yehuda et

al., 1993, in press). These findings are consistent with those of other studies of PTSD patients, which found increased lymphocyte glucocorticoid receptor numbers (Yehuda, Lowy, Southwick, Shaffer, and Giller, 1991) and reduced corticotrophin releasing factor (CRF)-stimulated increases in plasma cortisol (Smith et al., 1989). Reduced CRF effects on plasma cortisol in PTSD patients could reflect increased feedback inhibition both of the HPA and for reduced sensitivity to CRF. The latter finding may have developed as a consequence of increased CRF release, consistent with a report of increased cerebrospinal fluid CRF levels in PTSD patients (Bremner et al., in press).

Studies by Yehuda and her colleagues suggest that the reduced 24-hour urinary cortisol levels and increased sensitivity to cortisol feedback in PTSD patients reflect increased dynamic regulation of HPA function associated with this disorder. For example, Yehuda et al. (1991) found that the numbers of lymphocyte glucocorticoid receptors showed significant diurnal variation between 8 A.M. and 4 P.M. Also, a chronobiological study (Yehuda et al. 1996) indicates that relative to healthy subjects and depressed patients, PTSD patients exhibit greater peak-to-trough variability. As a result, plasma cortisol levels in PTSD patients vary from very low levels to within the normal peak range.

The increased dynamism of HPA regulation in PTSD patients may contribute to the failure of two studies (Pitman and Orr, 1990; Bauer, Priebe, Kurten, Graf, and Baumgartner, 1994) to replicate the reduction in cortisol levels. Pitman and Orr (1990), for example, based their evaluation of HPA axis function on a single plasma cortisol determination. The investigation by Bauer et al. (1994) studied an acutely traumatized population, raising the possibility that the reduction in 24-hour urinary cortisol levels accompanies chronic but not acute PTSD. Factors such as comorbid depression influence HPA regulation in PTSD patients but do not alter the fundamental pattern of increased feedback inhibition (Yehuda et al., 1993).

A recent study involving Holocaust survivors, ranging in age from 56 to 75 years, approximately 5 decades after their traumatization (Yehuda et al., 1995a) provided initial insights into the interaction of aging and trauma in HPA regulation. Holocaust survivors with PTSD (n = 22, 32.6 μg/day 17.0 μg/day cortisol) had lower 24-hour urinary cortisol levels than Holocaust survivors without PTSD (n = 25, 62.7μg/day 23.7 μg/day cortisol) or healthy age-matched controls (n = 15, 51.9 μg/day 23.7 μg/day cortisol). In this study, hypocortisolism in the Holocaust survivors with and without PTSD was highly correlated with avoidance symptoms ($r = -.49$, $p = .0005$) and not significantly correlated with hyperarousal ($r = -.40$) or intrusive symptoms ($r = -.29$). These findings are consistent with those from younger traumatized populations and support the contention by Yehuda et al. (1995a) that age-related changes in HPA regulation did not influence their findings.

In summary, data collected to date suggest that altered HPA regulation is a long-lasting consequence of traumatization. Reduced cortisol output correlates with the persistence of avoidance symptoms, raising the possibility that these two correlates of chronic PTSD are pathophysiologically related. However, neither stress exposure independent of traumatization nor process related to aging per se appear to lower cortisol in the way observed in PTSD. Current studies, however, do not rule out a within-individual adaptive reduction in feedback inhibition of the HPA, as previously described in association with hippocampal neuron losses associated with advanced age (Sapolsky, 1992).

Stress, HPA Dysregulation, and Neurotoxicity

A growing body of preclinical research indicates that HPA activation associated with severe stress promotes the excitotoxic death of pyramidal neurons in the CA3 region of the hippocampus, a brain region implicated in the encoding of memory (Zola-Morgan, Squire, and Mishkin, 1982; Squire, 1986). The

hippocampus has the highest density of type II glucocorticoid receptors in the brain (van Eekelen, Kiss, Westphal, and de Kloet, 1987; Herman, Patel, Akil, and Watson, 1989; Herman, 1993). In situations of acute stress, the hippocampus contributes to the termination of HPA activation (Jacobson and Sapolsky, 1991). Similarly, hippocampal stimulation inhibits HPA activation (Slusher and Hyde, 1961; Dupont, Bastarache, Endroczi, and Fortier, 1972), while hippocampal lesion prolongs the elevation in plasma cortisol produced by stress (for a review, see McEwen et al., 1992). Glucocorticoids promote neuronal death by increasing the toxicity associated with exposure to the excitatory neurotransmitter glutamate, acting via N-methyl-D-aspartate (NMDA) and AMPA/kainate receptors (see Sapolsky, 1992, for a review). *In vitro* models demonstrating the relationship between glucocorticoids and excitotoxicity have been supported by growing numbers of preclinical studies suggesting that HPA activation associated with naturalistic and nonnaturalistic stressors contributes to the loss of hippocampal pyramidal neurons in rodents and nonhuman primates (Meaney, Aitken, Bhatnagar, and Sapolsky, 1991; Angelucci, 1994; Luine, Villegas, Martinez, and McEwen, 1994; Uno et al., 1994).

In humans, aging is associated with greater stress-induced HPA activation and reduced feedback inhibition (Heuser et al., 1994; Gotthardt et al., 1995). A 4-year prospective study (Lupien et al., 1994) indicated that elderly individuals with elevated baseline cortisol levels or who had increases in basal cortisol levels over the 4-year evaluation period had poorer attention and memory function relative to a lower cortisol group of elderly people and a younger comparison group. These data suggest that elevated glucocorticoids may impair cognitive functions associated with the hippocampus, raising questions regarding the implications of these data for studies linking elevated glucocorticoid levels and hippocampal neurotoxicity.

There is growing evidence of hippocampal volume loss associated with chronic PTSD. Reported abnormalities in brain structure would not be surprising among POWs, given the possible exposure to head trauma or severe nutritional deprivation (Skelton, 1990). For example, subgroups of Holocaust survivors showed abnormalities on neurological examination, tests of attention and memory, spinal fluid analyses, and pneumoencephalography (Eitinger, 1971). Further, two computed axial tomography (CAT) scan studies reported evidence of cortical atrophy or increased ventricle-to-brain ratios among former POWs and torture victims (Jensen et al., 1982; Peters, van Kammen, van Kammen, and Neylan, 1990). However, more recent magnetic resonance imaging (MRI) studies have documented structural brain changes in other traumatized populations where nutritional deprivation and head trauma did not confound data interpretation. Bremner et al. (1995), reported a reduction in right hippocampal volume from PTSD patients (n = 26, 1184 mm^3 142 mm^3) relative to a matched control group (n = 22, 1286 mm^3 175 mm^3) and a similar trend for the left hippocampus. No other brain region studied showed this difference between groups, and the findings could not be accounted for by comorbid conditions. In this population, reductions in right hippocampal volume correlated with verbal memory deficits on the Wechsler scale.

The finding of reduced hippocampal volume in PTSD patients has been replicated in three subsequent studies. Bremner replicated the initial study in a population of adult survivors of severe physical and sexual abuse. This finding raises the possibility that premilitary traumas may have contributed to the earlier finding from Bremner and colleagues. Stein (1995) also reported reduced hippocampal volume in adult women with a history of sexual abuse. Lastly, Pitman (personal communication, 1995) reported a decrease in hippocampal volume bilaterally in a sample of combat veterans with PTSD.

The association of PTSD with reduced hippocampal volumes, learning and memory deficits, and hypocortisolemia is disturbing and perplexing. The association between memory deficits and hippocampal volumes suggests that the hippocampal volume loss associated with PTSD may have functional significance. These data suggest, but do not prove, that one long-term consequence of traumatization is hippocampal neuronal loss. This possibility is consistent with preclinical studies cited earlier. If this interpretation is correct, then one treatment imperative will be to identify traumatized individuals, both children and adults, as early as possible and to evaluate the utility of neuroprotective agents in preventing hippocampal volume loss.

However, many questions remain regarding hippocampal volume changes and PTSD. First, it has not been demonstrated that the hippocampal volume changes associated with PTSD reflect neuronal loss. Alternative explanations could include reductions in neuronal volume, extracellular space, or less likely, glial loss. In order to be consistent with the preclinical literature, a selective loss of pyramidal neurons, most likely in CA3, would need to be found in PTSD patients. Thus, quantitative postmortem studies from PTSD patients are needed to fully interpret the clinical imaging studies.

A second issue regarding the MRI data is that the literature regarding hippocampal-HPA interactions suggests that hippocampal lesions produced by stress are associated with loss of feedback inhibition of the HPA during stress. In contrast, PTSD patients showed enhanced feedback inhibition of the HPA. Thus, the HPA studies in PTSD suggest that hippocampal alterations associated with this disorder are in some way different from those observed in the preclinical studies.

A third question raised by the current MRI studies pertains to the relationship between hippocampal volumetric changes and cognitive functions. Bremner et al. (1995) found that performance on the percent retention subscale of the logical component of the Wechsler Memory Scale correlated with small

right hippocampal volume. However, memory retention is built on several cognitive processes that functionally precede retention, including vigilance, divided attention (distractibility), working memory, and memory encoding. Attention and working memory disturbances have been described in PTSD patients (reviewed in Krystal, Bennett, Bremner, Southwick, and Charney, 1995). Thus, the functional correlates of reduced hippocampal volume should be reevaluated in future studies, controlling for changes in other cognitive functions.

Finally, the current studies were not designed to rule out altered hippocampal volume as a predisposing factor for traumatization. Behavioral traits such as sociopathy, substance abuse, and preexisting psychiatric illness have been identified as risk factors for traumatization in both men (Kulka et al., 1990) and women (Burnam et al., 1988). Because reduced hippocampal volumes could contribute to the relationship between pretrauma clinical variables and subsequent PTSD, future studies will be needed to rule out contributions of pretrauma reductions in the volume of the hippocampus.

Hyperarousal and Noradrenergic Systems

A growing body of data also implicate noradrenergic systems in the pathophysiology of PTSD. PTSD patients exhibit increased 24-hour urinary norepinephrine levels (Kosten, Mason, Giller, Ostroff, and Harkness, 1987), down-regulation of platelet α_2 receptors and lymphocyte β-receptors (Lerer, Bleich et al., 1987; Lerer, Ebstein, Shestatzky, Shemesh, and Greenberg, 1987; Perry, Giller, and Southwick, 1987); reductions in symptoms with acute administration of the α_2 receptor agonist clonidine (Kolb, Burris, and Griffiths, 1984; Kinzie and Leung, 1989), and increased symptoms with the administration of the α_2 receptor antagonist, yohimbine (Southwick et al., 1993). PTSD patients also exhibit increased acoustic startle amplitude relative to matched controls, a function that is enhanced by yohimbine administration (Morgan et al., 1993; 1995). The

increased 24-hour urinary catecholamine excretion in patients with PTSD is enhanced under stressful conditions, occurs in elderly Holocaust survivors with PTSD as well as in combat veterans with PTSD, and has not been shown to occur in Holocaust survivors with a history of trauma but no diagnosis of PTSD (Yehuda et al., 1994).

Preclinical research also suggests that uncontrollable or inescapable stress exposure produces long-lasting alterations in noradrenergic regulation in animals. Inescapable stress downregulates the presynaptic α_2 receptors located on locus coeruleus neurons, the primary source of noradrenergic innervation for the limbic system and cerebral cortex (Glavin, 1985; Tsuda and Tanaka, 1985). These alterations are associated with increased locus coeruleus neuronal activation in response to stress (Abercrombie and Jacobs, 1987) and yohimbine exposure (Simson and Weiss, 1987). Preclinical data also suggest that inescapable stress exposure produces conditioned noradrenergic activation. Following inescapable stress exposure, reexposure to reminders of the stress exposure result in the display of fear behaviors and increased norepinephrine turnover (Cassens, Kuruc, Roffman, Orsulak, and Schildkraut, 1981). Similarly, even relatively mild stressors may support conditioned activation of locus coeruleus neurons (Rasmussen, Marilak, and Jacobs, 1986).

The potential overlap of panic disorder and PTSD has been of interest in light of evidence that panic disorder rates are elevated in PTSD populations (Kulka et al., 1990; Breslau, Davis, Andreski, and Petersen, 1991). This overlap is also suggested by the phenomenological similarity between naturally occurring (Mellman and Davis, 1985) and lactate-induced (Rainey et al., 1987) flashbacks and panic attacks in PTSD patients. Further, yohimbine provoked panic attacks and flashbacks in a subgroup of PTSD patients (Southwick et al., 1993) and panic disorder patients (Charney, Woods, Krystal, Nagy, and Heninger, 1992) even though it failed to have this effect

in many other diagnostic groups, including alcoholics, schizophrenics, depressed patients, generalized anxiety disorder patients, obsessive-compulsive disorder patients, and healthy subjects.

The reduction in the dynamic range of the noradrenergic system in the elderly may be adaptive for traumatized individuals with hyperarousal symptoms. Preclinical studies suggest that noradrenergic systems change with age. There is a loss of cells in the locus coeruleus as humans age, increased levels of monoamine oxidase levels, decreased levels of norepinephrine and 3-methoxy-4-hydroxyphenylglycol (MHPG), and a decreased response to noradrenergic agonists (Lohr and Jeste, 1988; reviewed in Krystal, Leaf, Bruce, and Charney, 1992).

Panic disorder, noted earlier to have some similarity to PTSD, shows clear age-related changes in prevalence. Data from the Epidemiologic Catchment Area study indicate that the prevalence of panic disorder peaks in the third decade of life and then declines in prevalence in the elderly, with the changes in men occurring a decade earlier than in women (Krystal et al., 1992). In light of the other age-related findings, these clinical data suggest that down-regulation of noradrenergic function with age may contribute to reductions in panic attack prevalence with age (Krystal et al., 1992). If the data from the panic disorder literature is applicable to the PTSD literature, then panic attacks associated with PTSD may also decline with advanced age. Unfortunately, no current data set has addressed this issue directly.

There are several limitations to the capacity to draw direct parallels between panic disorder and PTSD in relation to aging. First, panic disorder and PTSD do not appear to be clearly genetically associated in family history studies (reviewed in Krystal et al., in press). Also, yohimbine response in probands does not influence the familial association of PTSD and panic disorder (Nagy et al., in press). Second, the time between onset of panic disorder, generally in the second to third decade, and

"maturing out" of panic disorder, in the sixth to eighth decade, is a fairly consistent interval. In contrast, individuals may be traumatized at any stage in their life. It is not clear, for example, that patterns of maturing out of childhood and adult traumas would be similar. Also, individuals traumatized as adults may not live sufficiently long for processes related to maturation to have a significant influence on the neurobiological functions that influence their panic attacks. These questions suggest a need for more prospective longitudinal data on the course of PTSD in the elderly.

TREATMENT IMPLICATIONS

Posttraumatic Neurobiological Response and Health

Health status appears to be compromised in individuals with PTSD. However, there is very little data from groups of sufficient size, followed for sufficiently long periods of time, using appropriate methods for assessing health status and psychiatric diagnoses in order to provide definitive information regarding the relationship between PTSD and health (Friedman and Schnurr, 1995). Given the physical torture and nutritional deprivation associated with traumatic experiences such as concentration camp internment or POW status (Eitinger, 1971; Skelton, 1990), reports describing impaired health and increased mortality in survivors with short- and long-term follow-up were not surprising (Morgan, Wright, and van Ravensway, 1946; Antonovsky et al., 1971; Eitinger, 1980). Health complaints in Holocaust survivors and POWs have been diverse in nature. Somatic complaints involving neurological, reproductive, dermatological, rheumatological, immunological, gastrointestinal, cardiology, and pulmonary systems have been reported in increased rates (Krystal and Neiderland, 1968; Eitinger, 1971, 1973, 1980; Tennant, Goulston, and Dent, 1986, 1993; Skelton, 1990; Stermer, Bar, and Levy, 1991; Venn and Guest, 1991; Ohry et al., 1994). However, other studies suggest

that there is gradual recovery in many survivors in many physical domains over several decades after liberation, such that their long-term physical health and age-adjusted mortality was similar to control subjects (Aviram, Silverberg, and Carel, 1987; Guest and Venn, 1992; Williams et al., 1993).

The reliance on cross-sectional and retrospective data and evolving diagnostic criteria since World War II suggests that the exploration of the long-term health consequences of trauma is an urgent problem, but makes difficult the determination of the actual course of physical health following psychological traumatization in survivors of the Holocaust. Further, given the breadth of physical health problems described in the published studies, it is difficult to determine the relative vulnerability to specific health problems, that is, the earliest health problems to emerge, the most severe health problems, and the most protracted health problems among survivors.

Several descriptions of traumatized populations that did not undergo physical trauma or nutritional deprivation also suggest that psychological traumatization has important health consequences. Illustrating this point, female army nurses who served in Vietnam report often experiencing recurrent headaches and skin problems since returning from Vietnam (Baker, Menard, and Johns, 1989). Further, triage/operating room (OR) nurses reported a significantly higher frequency of amenorrhea, nausea, vomiting, or diarrhea within the year prior to follow-up as compared with other nurses. This suggests that the level of psychological traumatization they endured is responsible for the higher frequency of symptoms reported by the triage/OR nurses. Among a population of women being treated at a gastrointestinal (GI) clinic, a history of sexual abuse predicted complaints of greater GI pain levels, more non-GI somatic symptoms, more bed disability days, more lifetime surgeries, more psychological distress, and worse overall health quality (Lesserman, et al. 1996). In a large twin study conducted in veterans, the degree of combat exposure was related to increased reports of GI and dermatological disorders (Eisen,

Goldberg, True, and Henderson, 1991). Similarly, the Vietnam Veterans Readjustment Study found that degree of combat exposure, the development of PTSD, the development of service-connected disabilities, and subsequent substance abuse predicted the severity of subsequent physical health problems among male and female Vietnam theater veterans (Kulka et al., 1990). Most importantly, PTSD was a mediating factor influencing the relationship of war zone stress and subsequent reports of poor health in female Vietnam veterans (Wolfe, Schnurr, Brown, and Furey, 1994), male Vietnam veterans (Long, Chamberlain, and Vincent, 1992) and Israeli combat veterans of the Lebanon War (Solomon, 1988).

The evidence for long-term physical health consequences of extreme stress or traumatization is less clear when objective measures of health are employed. Combat veterans with chronic PTSD have been found to have lower effort tolerance on a multistage, incremental-load ergometric test reaching 85 percent of the maximal heart rate, a test that is purported to reflect effort tolerance, cardiac reserve, and physical fitness (Shalev, Bleich, and Ursano, 1990). White and Faustman (1989) reported that 60 percent of a sample of 543 veterans with PTSD who were inpatients over a 4-year period had a physician-identified medical problem. Unfortunately, this study is difficult to interpret due to the absence of an age-matched comparison group. Another study that relied on physician diagnosis failed to find an increased rate of hypertension, diabetes, myocardial infarction, cerebrovascular accidents, and intermittent claudication in former POWs, compared with the rates of these illnesses found in general population groups of similar age (Eberly and Engdahl, 1991).

The effects of extreme stress exposure and traumatization upon health appear more pronounced when subjective, rather than objective, measures are employed. For example, Litz, Keane, Fisher, Marx, and Monaco (1992) found that combat veterans with PTSD reported more current health problems but did not have more physician-diagnosed disorders than the

non-PTSD comparison group. The Centers for Disease Control Vietnam Experience Study (1988) found that when interviewed before age 40, on average, a higher percentage of Vietnam veterans (n = 7924, 19.6%) viewed their health as poor-to-fair than did non-Vietnam veterans from the same era (n = 7364, 11.1%). However, medical examinations did not reveal higher rates of skin conditions, including chloracnelike lesions associated with Agent Orange exposure, cardiovascular abnormalities including hypertension, abnormal immune function tests, or other illnesses.

The distinction between objective and subjective assessments of health among traumatized populations may reflect clinically important processes. First, it is possible that some physical diagnoses are underdiagnosed in traumatized populations. Second, several aspects of the psychological response to psychological traumatization may increase the likelihood that psychological distress would be perceived by victims and expressed to clinicians and researchers as somatic illness, including increases in somatic symptoms of anxiety, increased somatic preoccupation, and a tendency to express emotional states in terms of bodily feelings (alexithymia) (Hyer, Fallon, Harrison, and Boudewyns, 1987; Krystal, 1988). Thus, Lipton and Schaffer (1988) note that aged veterans with PTSD reported more physical complaints during periods when their PTSD symptoms were more severe. Group therapy was reported to be effective in decreasing complaints of physical symptoms, and in some cases medications were used to treat angina, chronic back pain, stomach problems, and other physical problems.

The association of neuroendocrine dysregulation with indices of poorer health in Vietnam veterans raises the possibility of a functional relationship between posttraumatic neurobiological response and health. One candidate for study is the relationship between posttraumatic HPA function and health. Glucocorticoids are implicated in glucose metabolism, inflammatory response, immune function, and other processes

that directly influence health. Second, HPA regulation is often a marker of changes in other stress-responsive systems, such as several of the interleukins, that may independently influence immune function (Harbuz and Lightman, 1992). Central noradrenergic systems have been implicated in cardiac regulation and may contribute to the reported increase in hypertension among Vietnam veterans (Centers for Disease Control Vietnam Experience Study, 1988). The association between stress and immune function is already well established. For example, uncontrollable stress exposure in animals produces alterations such as immune dysfunction and poorer tumor rejection (Krystal et al., 1989). Thus, although relationships between the neurobiology of PTSD and the health status of traumatized individuals are currently speculative, they are an important area for future study.

Neurobiology, Course, and Treatment

Because of the small number of studies currently published, there are no clear data-based treatment implications based on the interactive neurobiologies of PTSD and aging. It is likely that further research in this area will be aided by better characterization of the long-term course of PTSD symptoms. Unfortunately, the pharmacological treatment of even younger traumatized populations has been a focus of relatively little research. However, this review would be remiss if it failed to provide a framework for the next generation of neurobiological studies that will provide a foundation for substantive integration with the treatment literature.

First, the current data suggest that there will be a diverse array of changes in neurobiological systems contributing to PTSD symptoms with age. Two aspects of posttraumatic neurobiology were considered in relation to aging in this review. One focus, HPA alterations, did not show evidence of age-related modifications. Essentially, the findings regarding HPA dysregulation in Holocaust survivors 50 years following their trauma

appear to be similar to those for younger PTSD populations. The other focus of this review, noradrenergic responses, has received limited study in elderly PTSD populations. However, noradrenergic systems undergo changes with age that appear to influence the course of other disorders, such as panic disorder. Based on the analogy to panic disorder, noradrenergic contributions to hyperarousal symptoms of PTSD would be expected to diminish with age. For those patients who experience persistent arousal symptoms, it is unclear whether they have not down-regulated their noradrenergic systems with age sufficiently to reduce symptoms or whether other systems, such as the serotonin system, might play a greater role with advanced age.

Changes in the regulation of particular systems with age may influence pharmacotherapeutic strategies. Initial reviews (van der Kolk, Greenberg, Boyd, and Krystal, 1985; Krystal et al., 1989), noted the presence of noradrenergic hyperreactivity associated with PTSD and suggested that pharmacological strategies aimed at reducing the dynamic range of noradrenergic activity might reduce hyperarousal symptoms. As a result, these reviews focused on treatments such as clonidine and norepinephrine reuptake blockers, pharmacological agents shown to reduce locus coeruleus activation in preclinical systems. If the dynamic range of noradrenergic response is reduced in aged populations, then the utility of treatments acting on noradrenergic systems might decrease as well. Alternative treatments, such as serotonin reuptake blockers, might be focused at other systems that might contribute to symptoms in PTSD patients.

Alternatively, the noradrenergic contributions to PTSD symptoms in the elderly may shift from the hyperarousal spectrum to the "negative" symptoms associated with PTSD, including numbing, anhedonia, poor concentration, and psychomotor retardation. Behaviors in this spectrum are produced in healthy humans by agents that deplete catecholamine systems. Similarly, catecholamine depletion has been shown to reverse the antidepressant effects of noradrenergic reuptake

(reviewed in Berman, Krystal, and Charney, 1996). Preclinical studies of inescapable and uncontrollable stress previously linked stress-induced depletion of noradrenergic systems in animals to motor retardation, learning deficits, and use of passive rather than active avoidance strategies (reviewed in van der Kolk et al., 1985, and Krystal et al., 1989). The behavioral inhibition observed in these animal studies following inescapable stress exposure was prevented and reversed by pharmacological strategies including administration of noradrenergic agonists, norepinephrine reuptake blockers, and catecholamine releasing agents. These agents also reduce the dynamic range of noradrenergic neuronal activity, making it difficult to discriminate pharmacological effects on arousal- and inhibition-related mechanisms. Thus, if noradrenergic systems increasingly contribute to negative symptoms of PTSD with advanced age, then pharmacotherapies addressing this deficit might focus on "catecholamine replacement strategies" like those applied in the treatment of Parkinsonism, where there are clear deficits in dopamine systems. Based on this model, agents such as clonidine, amphetamine, or desipramine may be more useful in elderly populations than in younger populations, much as amphetamine appears to be more useful as an antidepressant in elderly medical populations (Woods et al. 1986).

Neuroendocrine consequences of PTSD may have consequences for the nonpsychiatric health of elderly trauma survivors, potentially informing the medical management of these patients. The association of HPA dysregulation with PTSD also raises treatment issues for the elderly. As noted earlier, it is not clear whether the HPA disturbances have direct health consequences for PTSD patients. These concerns are more pronounced in the elderly, who might have primary pathology related to glucose metabolism, inflammatory response, or immune regulation. Because of the potential clinical importance of this possibility, future research should examine whether HPA dysregulations contribute to existing pathology. Unfortunately, it is not yet clear whether any treatment for PTSD normalizes the pattern of HPA regulation in these individuals.

Until such treatments are identified, characterization of HPA dysfunction within individual PTSD patients may have little direct clinical utility.

The controversy regarding stress-related neurotoxicity also may have implications for the treatment of memory dysfunction in PTSD patients. Hippocampal pathology has generally been associated with memory encoding deficits and not with psychogenic amnesia or repression mechanisms that contribute to the inability of many individuals to recall significant aspects of the trauma (Krystal et al., in press). Thus, stress-related hippocampal neurotoxicity might be predicted to contribute to memory encoding deficits that have been described in traumatized populations (reviewed in Krystal et al., in press). Also, in the elderly population, decades following traumatization, it is unlikely that prevention of neurotoxicity will be a relevant focus of treatment.

In contrast, agents designed to enhance memory encoding may be helpful for reducing cognitive deficits in elderly PTSD patients. Because stress-related neurotoxicity involves NMDA receptor mechanisms, it may result in a loss of NMDA receptor function in the hippocampus (Sapolsky, 1992). NMDA receptors have been implicated in human memory encoding (Krystal et al., 1994); thus, deficits in NMDA receptor function could directly contribute to memory deficits in PTSD patients. One pharmacological strategy would be to enhance NMDA receptor function. However, agents directly acting at the glutamate binding site of the NMDA receptor complex might be neurotoxic (Sapolsky, 1992). Alternatively, agonists of the strychnine-insensitive glycine modulatory site of the NMDA receptor do not appear to be neurotoxic at therapeutic doses. These agents, including glycine, D-cycloserine, and milacemide have been modestly effective memory-enhancing agents in humans, but may be particularly useful for memory encoding deficits in PTSD patients (D'Souza, Charney, and Krystal, 1995). In contrast, there is no data yet to suggest that 1,2,3,4-tetrahydro-9-acridinamine monohydrochloride monohydrate (THA) or

other drugs enhancing cholinergic transmission would be helpful in this population. This discussion suggests that the evaluation of neurotropic agents in aging trauma survivors will be an emerging area of clinical research.

Call for Future Research

Surviving massive psychic trauma is an achievement for the victim survivor, but one that is burdened by chronic PTSD symptoms in too many cases. Other papers in this special issue (H. Krystal, Y. Danieli) focused on changes in psychosocial processes in the aging survivor, many of which are associated with the long-term course of PTSD. Neurobiological processes also appear to contribute to PTSD symptoms, yet there is very little available information regarding the impact of aging on the neurobiology of this disorder. Processes related to aging may influence the association between particular neurotransmitters and PTSD symptoms, altering pharmacotherapeutic objectives. Further, alterations in systems, such as the HPA, could have secondary neurotoxic and medical consequences influencing the quality of life of aging survivors. The paucity of current research on the neurobiology of the aging survivors contrasts with its potential clinical importance. This paper has highlighted the limited relevant current data in hopes of stimulating greater interest in this research topic.

Authors' note: Dr. Yehuda (personal communication) subsequently found no difference in the 24-hour urinary norepinephrine of elderly Holocaust survivors with PTSD compared with non-PTSD controls.

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