Neuroendocrine activity and memory-related impairments in posttraumatic stress disorder

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Abstract
This article reviews memory-related impairments in trauma survivors with posttraumatic stress disorder and their possible association to neuroendocrine alterations seen in this disorder. The neuroendocrine profile in PTSD first described in chronically ill combat veterans is characterized by lower basal cortisol levels, higher glucocorticoid receptor number, enhanced sensitivity to exogenous steroids, and increased variation in basal cortisol levels over the diurnal cycle. The generalizability and time course of these neuroendocrine alterations are explored in longitudinal studies and studies in other traumatized populations. These studies suggest that at least some aspects of this neuroendocrine profile can also be seen in other populations, including women, children, and victims of childhood trauma. Additionally, the alterations may be present early in the course of illness, perhaps even in the immediate aftermath of trauma, and may continue to be manifest in elderly trauma survivors. The mechanisms by which these neuroendocrine alterations may influence the formation and processing of traumatic memories are discussed.

Introduction
The goal of this article is to evaluate memory-related impairments in trauma survivors and their possible association to neuroendocrine alterations observed in the aftermath of trauma. The phenomenology of posttraumatic stress disorder (PTSD) will be reviewed with an emphasis on symptoms that may reflect disturbances in memory. The neuroendocrine alterations associated with this disorder and their development over time will be described as well as their possible relevance to memory and memory-related symptoms.

PTSD was formally recognized as a psychiatric disorder in 1980 and included in the third edition of the Diagnostic and Statistical Manual (DSM-III) to describe the psychological consequences of exposure to extreme trauma. Prior to 1980, psychiatric syndromes precipitated by stressful events were generally thought to be transient as opposed to long lasting and were described and named according to the inciting event (e.g., the rape trauma syndrome, the concentration camp syndrome, combat neurosis). As similarities in these conditions became apparent and acceptance of the role of psychological trauma in mental illness grew, it became necessary to describe a condition with broader applicability. Furthermore, as the chronicity of these conditions became apparent, distinguishing between chronic stress reactions and adjustment disorders was necessary.

Although only recently recognized, PTSD is one of the most common psychiatric disorders, with an estimated lifetime prevalence of 8% in the United States (Kessler, Sonnega, Bromet & Nelson, 1995). Exposure to trauma is even more prevalent; 50% of women and 60% of men in the U.S. have experienced a significant trauma in their lives, most more than one. Although both PTSD and trauma exposure are much more prevalent than originally anticipated, PTSD only occurs in a minority of those exposed.

To meet criteria for PTSD, a person must have been exposed to a traumatic event. DSM-IV defines a traumatic event as one in
which the individual “experienced, witnessed or was confronted with an event or events that involved actual or threatened death or serious injury, or a threat to the physical integrity of self or others” and experienced “intense fear, helplessness, or horror” at the time. In children, the subjective response may be expressed instead as “disorganized or agitated behavior.” Additionally, the person must also have a specified number of symptoms from each of three clusters—reexperiencing, avoidance, and hyperarousal—for at least 1 month, which result in significant social and occupational impairment.

PTSD is only one of several possible psychiatric outcomes following traumatic stress exposure. For example, following the eruption of Mt. St. Helens there was an increased prevalence of new-onset depression and generalized anxiety disorder in the community, as well as PTSD (Shore, Tatum, & Vollmer, 1986). In a study of trauma survivors who presented to an emergency room, the prevalence of PTSD at 4 months was no greater than that of depression (14% and 17%, respectively) (Shalev et al., in press). In a longitudinal study of motor vehicle accident victims, new-onset psychiatric disorders included not only depression and PTSD, but also alcohol and substance abuse and dependence, eating disorders, and other anxiety disorders including obsessive compulsive disorder (A. C. McFarlane, M. Atchinson, & R. Yehuda, unpublished data). Given the differing phenomenologic responses to similar events, it is likely that there is considerable heterogeneity in trauma-related impairments in memory and neurobiology. Additionally this epidemiologic data highlights the fact that PTSD patients are not only a subset of those exposed to trauma, but also of those who develop psychiatric disorders afterwards. Nonetheless, this paper will primarily consider trauma-related impairments that are specific to PTSD.

PTSD Symptoms and Memory-Related Impairments

Memory-related impairments are prominent among the PTSD symptoms. Most characteristic of PTSD are the reexperiencing symptoms which include recurrent and intrusive distressing recollections or dreams of the trauma, acting or feeling as if the trauma were recurring, and intense distress or physiologic reactivity to reminders of the trauma. In children, the re-experiencing symptoms may include trauma-specific reenactment, repetitive play in which aspects of the trauma are expressed, and frightening dreams without recognizable content.

Intrusive symptoms are extremely common immediately following trauma exposure but fade over time for most survivors. For those with PTSD, the intrusive memories persist, are readily evoked, and are difficult to contain. These symptoms differ from the typical recall of traumatic experiences in several additional ways. The intrusive memories and especially dissociative flashbacks may be rich in perceptual detail and include not only visual images but also sounds or smells associated with the trauma. These intense sensory experiences contribute to a sense that the trauma is being relived rather than recalled. The vividness also contributes to the seeming accuracy of the memories even though they are often fragmented and distorted. Intrusive symptoms can be so distressing that patients frequently come to treatment wanting “to forget.”

The avoidance symptoms are also related to memory for the trauma and describe attempts to avoid conscious recollection of the trauma and the powerful feelings associated with it. The avoidance symptoms include efforts to avoid thoughts, feelings, or conversations related to the trauma and efforts to avoid activities, people, or places that are reminders of the trauma. Also included is an inability to recall aspects of the trauma, formerly called psychogenic amnesia. Often the avoidance extends beyond obvious traumatic reminders into a more generalized emotional withdrawal, characterized by the remaining symptoms in the cluster: diminished interest in significant activities, feelings of detachment or estrangement, a restricted range of affect, and a sense of a foreshortened future.

Additional memory-related impairments are present in the hyperarousal symptom cluster, including poor concentration and hyper-
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vigilance. Hyperarousal symptoms, such as hypervigilance, may reflect the ways in which the memory of having been traumatized continues to influence behavior, outside conscious awareness. As the symptoms in this cluster are defined independently of the traumatic event, it suggests cognitive impairments extend beyond those specific to the trauma.

Although there are memory-related symptoms in each of the three symptom clusters in PTSD, the disorder differs from typical memory disorders in many ways. Not only are most of these symptoms related to a specific incident, but unlike classic memory disorders such as amnesia and dementia, the symptoms include not only memory loss but excessive “remembering” as well. At first glance, it may seem contradictory that reexperiencing symptoms and psychogenic amnesia occur together, that both excessive “remembering” and “forgetting” aspects of the same trauma would be present and distressing. However, the symptoms not only coexist but fluctuate over time. The fact that oscillations occur suggests that the “amnesia” is not static and may be different from classic accounts associated with permanent neurologic damage. The oscillation between intrusive symptoms and avoidance symptoms suggests that memory-related impairments may be related to dynamic processes, such as a shifting neurochemical environment, rather than to a fixed lesion, such as structural brain damage. We will suggest that neurochemical fluctuations may help explain the bidirectional memory alterations in PTSD and their change over time.

Given the prominence of memory-related symptoms in PTSD, it is interesting to considering the effect of this disorder on recall for the traumatic event. A few studies have explored this relationship. In one, Australian firefighters’ recall of a traumatic event was recorded at 4 months and 11 months after exposure to devastating brush fires (McFarlane, 1988). All of the firefighters with PTSD who reported injuries at the first time point reported them again at the second. In contrast, only 43% of those who initially reported injuries but did not develop PTSD reported them again later. This significant difference in retrospective recall suggests that forgetting may be less likely to occur in trauma survivors who develop PTSD than those who do not. On the other hand, distortion of memory may be greater in those who develop the disorder. In one study, witnesses to a shooting were questioned at two points in time (Schwarz, Kowalski, & McNally, 1993). Although all witnesses changed their account in some ways, those who developed PTSD symptoms changed their accounts in ways that magnified their reactions to the shooting and its potential threat to their lives. Similarly, in a study of Desert Storm veterans, self-reported combat exposure increased over time in those with PTSD but was relatively constant in those without the disorder (Southwick, Morgan, Nicolaou, & Charney, 1997). Therefore it appears that the memory-related symptoms in PTSD may reflect abnormalities of the processing of traumatic memories including alterations in the consistency of recall for the inciting event and suggests that traumatic memories may not be as indelible and immutable as they seem.

The Normal Stress Response

The hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system (SNS) are the most intensively studied biologic systems in PTSD, owing to their critical role in the stress response and also the ease with which they can be studied. The SNS and HPA systems are also known to influence memory consolidation in animals and humans; therefore, it is likely that they play a pivotal role in the relationship between traumatic stress and memory.

Acute stress results in activation of the HPA axis and SNS. In response to stress, neuropeptides in the brain stimulate the release of corticotropin releasing factor (CRF) and other secretagogues from the hypothalamus, which in turn activate the release of adrenocorticotropic hormone (ACTH) from the pituitary and the release of cortisol from the adrenals (Chrousos & Gold, 1992; Munck, Guyre, & Holbrook, 1984). In response to stress, SNS activation also results in the release of catecholamines, primarily norepinephrine (NE) and epinephrine (EPI). Coordinated sympa-
thetic discharge causes increases in heart rate and blood pressure, which allow for increased perfusion of muscles and vital organs, and mobilizes blood glucose which increases energy available to skeletal muscles (Mountcastle, 1973). After mobilizing the body’s stress responses, cortisol then shuts down the neural defensive reactions activated. The negative feedback inhibition exerted by cortisol on the pituitary, hypothalamus, and other sites serves ultimately to contain the stress response.

**Neuroendocrine Studies of PTSD in Adults**

It was initially assumed that cortisol levels would be elevated in PTSD, as they are in the typical response to stress. However it is now well established that cortisol levels are lower than normal. The earliest studies were conducted on male combat veterans with chronic PTSD. Veterans with PTSD were shown to have lower 24-hr urinary cortisol excretion than other psychiatric patients (Mason, Giller, Kosten, Ostroff, & Podd, 1986; Yehuda, Boisoneau, Mason, & Giller 1993) and normal comparison subjects (Yehuda et al., 1990), although one study found the opposite (Pitman & Orr, 1990).

This finding of lower cortisol level was confirmed in a large sample of more than 2,000 Vietnam theater and Vietnam era veterans using a single measurement of morning cortisol. Vietnam theater veterans with current PTSD had lower plasma cortisol levels than those without the disorder (Boscarino, 1996). Additionally, cortisol levels were associated with combat exposure; those with the heaviest exposure had the lowest cortisol levels. In another study, basal plasma cortisol was measured using repeated sampling in a controlled setting, a method that is more reliable than a single measurement as venipuncture and other stressors can result in transient fluctuations of hormones and obscure basal activity. Using this method, cortisol was measured in PTSD patients and comparison subjects at rest, at half-hour intervals over a diurnal cycle (Yehuda, Teichner, Trestman, Levengood, & Siever, 1996). PTSD subjects had cortisol levels that were lower on average than either normal subjects or depressed patients. The differences were not evident at all time points during the day. Rather, they were significantly lower primarily in the late evening and very early morning. Further chronobiological analysis revealed that PTSD patients showed a greater degree of circadian rhythm with greater variation in cortisol levels. This greater variation is characterized by lower trough levels of cortisol, but comparable circadian peaks.

Trying to understand this seemingly paradoxical finding of low cortisol in a stress disorder has been an important impetus for advances in the neuroendocrinology of PTSD. A fuller understanding of the significance of cortisol levels requires measurement of the steroid receptors to which they bind. In PTSD, glucocorticoid receptors (GRs) are greater in number. The number of lymphocyte GRs has been found to be higher in male combat veterans with PTSD than in other psychiatric patients and non combat-exposed normal controls (Yehuda, Boisoneau, Lowy, & Giller, 1995; Yehuda, Boisoneau, Mason, & Giller, 1993; Yehuda, Lowy, Southwick, Shaffer, & Giller, 1991). This alteration in GR is in the opposite direction from the "downregulation" of GRs in response to stress (Sapolsky, Krey, & McEwen, 1984) or the smaller number of GRs seen in major depressive disorder (Gormley et al., 1985; Whalley, Borthwick, & Copolov, 1986). This finding suggests that the HPA axis might be differentially regulated in PTSD. Neuroendocrine challenge studies have been used to explore the significance of these receptor differences.

The dexamethasone suppression test (DST) has been used to explore the sensitivity of the HPA axis in PTSD. Dexamethasone (DEX) is a synthetic steroid that mimics the actions of cortisol and therefore can be used to assess the strength of cortisol negative feedback inhibition. Morning cortisol levels are typically decreased following DEX administration at night. Nonsuppression of cortisol following DEX (8:00 a.m. levels at or above 5.0 µg/dL) is seen in about half of patients with major depression (Arana, Baldessarini, & Ornsteen, 1985; Carol, 1982) and is thought to reflect diminished negative feedback inhibition. In
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PTSD, given the increased number of GRs it is of interest to study the strength of negative feedback inhibition. To do so, the response to DEX has been tested using a dose lower (0.5 mg) than the standard dose (1.0 mg) in order to avoid the floor effect associated with the higher dose. Using the low dose DST, cortisol suppression was greater in combat veterans with PTSD than normals (Yehuda, Southwick, Krystal, Charney, & Mason, 1993) and than nonexposed men or combat veterans without PTSD (Yehuda et al., 1995). As cortisol hypersuppression was not present in combat veterans without PTSD, it suggests this alteration is associated with the disorder rather than traumatic stress exposure per se. Lymphocyte GR number was also measured before and after DEX administration. A decline in lymphocyte GR number following DEX administration was seen in PTSD subjects but not controls. A decrease in GR reflects translocation of the bound steroid-complex into the nucleus (Svec, 1985). Therefore, this decrease suggests the receptors may be more sensitive to the administration of exogenous steroids (Gormley et al., 1985; Yehuda et al., 1995) and is consistent with the idea that there is increased functional sensitivity of the GRs in this disorder.

The model of enhanced cortisol negative feedback inhibition has also been demonstrated using the metyrapone stimulation test (Yehuda, Levengood et al., 1996). The metyrapone stimulation test allows for measurement of pituitary activity in the absence of cortisol feedback inhibition. Metyrapone temporarily inhibits cortisol by blocking the conversion of 11-deoxycortisol to cortisol, thereby removing cortisol feedback inhibition on the pituitary. The pituitary release of ACTH is influenced by both negative feedback inhibition from cortisol and CRF stimulation from the hypothalamus. Therefore, removing cortisol feedback inhibition allows for an assessment of basal pituitary release of ACTH. Metyrapone stimulation typically results in increased pituitary release of ACTH. In a study of metyrapone stimulation in PTSD, both patients and normal comparison subjects showed postmetyrapone increases in ACTH levels. However, in PTSD the percent increase in ACTH was more than 4 times greater than that of controls (Yehuda, Levengood, et al., 1996). This greater increase in ACTH in the absence of cortisol negative feedback inhibition suggests that pituitary activation is a feature of PTSD, perhaps due to CRF hypersecretion, and that the lower cortisol levels are not the result of global hypoactivity of the HPA axis. Rather the lower cortisol levels and pituitary activation occur concurrently, which is compatible with enhanced negative feedback inhibition of cortisol.

In summary, the neuroendocrine profile of combat-related PTSD best fits a model of enhanced negative feedback, in which the primary deficit is an increased responsiveness of glucocorticoid receptors at several sites along the HPA axis. This increased responsiveness results in a stronger negative feedback, attenuated basal cortisol levels, and enhanced responsiveness to exogenous steroids (i.e., DEX) (Yehuda, Giller, Levengood, Southwick, & Siever, 1995; Yehuda, Giller, & Mason, 1993). Importantly, this model differs from the neuroendocrine profile typically associated with stress, or with other psychiatric disorders such as major depression (Yehuda, Giller, Southwick, Lowy, & Mason, 1991). Whereas chronic stress and depression are associated with a reduced negative feedback inhibition of the HPA axis and a resultant decrease in stress responsiveness, the biological alterations in PTSD appear to reflect a neuroendocrine system that may be highly responsive to environmental challenge. As chronic PTSD is characterized by a unique neuroendocrine profile that is not simply an exaggeration of the typical biological stress response, the question arises about when this profile first becomes manifest, what factors influence its development, and how it may affect other biological and psychological measures.

The Acute Stress Response and PTSD

The longitudinal course of HPA axis functioning in trauma survivors is of considerable interest as it is not yet known whether the neuroendocrine profile in PTSD represents a posttraumatic alteration in functioning or represents a risk factor. Recent studies suggest
that one aspect of the neuroendocrine profile in PTSD, low cortisol levels, may be evident in the immediate aftermath of trauma. In a study of rape victims, blood samples were obtained from among those drawn in the emergency room as part of the medical assessment (Resnick, Yehuda, Pitman, & Foy, 1995). Among women without a prior history of assault, the typical relationship between stressor magnitude and cortisol level was observed; cortisol levels correlated with the severity of assault. However, this association was not observed in the rape victims who had a prior history of assault. Women with a prior history of assault had lower cortisol levels and were more likely to develop PTSD. A similar study was done in survivors of motor vehicle accidents. Cortisol levels in the traumatic aftermath were lowest in those who later developed PTSD and highest among those who developed depression (McFarlane, Atchinson, & Yehuda, 1997). These preliminary findings suggest that differences in the consolidation of traumatic memories in trauma survivors may be attributable to the differential cortisol response at the time of trauma.

Neuroendocrine Studies of Trauma in Childhood and Adolescence

The neuroendocrine profile of chronic PTSD in adulthood as described above has been based largely on the study of male veterans, who were studied in middle age approximately two decades after exposure to war zone stress. Therefore, it is not yet clear the extent to which the model of enhanced negative feedback is generalizable to other populations of trauma survivors. Age or developmental stage at the time of traumatization may influence the neurobiology of traumatic stress, as may gender, the nature of the trauma, the duration since traumatization, and the chronicity or type of posttraumatic symptoms. The studies that could examine the effects of these factors are just beginning to be done but may ultimately help to delineate the time course of the neurobiological consequences of traumatic stress and their interaction with development. To date, several neuroendocrine studies have been done in female victims of childhood sexual abuse (CSA), both in girls, soon after they were abused, and in women, decades later.

In one study, girls referred to child protective services after having been sexually abused were followed longitudinally to assess the social, psychological, and biological consequences of this type of abuse. The average age of the onset of abuse was 6 ± 2 years and average age at study entry was 11 ± 3 years. When studied initially, within a year of disclosure of the abuse, the girls had higher morning and lower afternoon cortisol levels than control girls, and a higher time-integrated cortisol level (Putnam, Trickett, Helmers, Dorn, & Everett, 1991). Girls from the same cohort were studied again, about 5 years after the abuse had been reported (De Bellis et al., 1994). More than half were suffering from Dysthymia and had attempted suicide, but did not meet criteria for Major Depressive Disorder or PTSD. The cortisol levels (24-hr urinary cortisol, basal plasma cortisol, and cortisol response to ovine corticotropin releasing hormone [o-CRH]) did not differ between the abused and control girls, but the abused girls had lower basal plasma ACTH and a blunted ACTH response to o-CRH. At 7-year follow-up, the girls have been found to have lower cortisol levels than controls (Putnam, 1998). This longitudinal study suggests that the effects of trauma on the HPA axis may change over time, although the factors mediating these changes are not yet clear. The development of lower cortisol levels over time in these girls, together with the finding of lower cortisol levels in the immediate aftermath of rape in women with a prior history of assault compared to those without a prior history (Resnick, Yehuda, Pitman, & Foy, 1995) raises the possibility that an early or initial trauma modifies the neurobiologic response to stress and perhaps the risk for developing PTSD following subsequent exposures.

A study of survivors of the Armenian earthquake provides further support to the idea that neuroendocrine alterations associated with PTSD are demonstrable as early as adolescence. A study was done in children who survived the devastating Armenian earth-
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Quake of 1988 that destroyed four cities and hundreds of villages and killed 25,000 people (Pynoos, Steinberg, Ornitz, & Goenjian, 1997). During the implementation of mental health services, studies were conducted on children in two cities, Spitak and Gumri. Spitak is close to the epicenter and residents who survived witnessed scenes of death, mutilation, and horrific destruction. Gumri is 20 miles from the epicenter, its residents experienced earthquake-related trauma, which was less severe. Five years after the earthquake 12–15-year-old adolescents were studied. The adolescents from Spitak experienced more severe posttraumatic stress reactions than those from Gumri. Basal salivary cortisol level was measured in the adolescents before and after administration of low-dose DEX (Goenjian et al., 1996). The basal cortisol levels were lower in the morning in the adolescents from Spitak than from Gumri and were negatively associated with intrusive symptoms of PTSD. In response to DEX, both groups showed considerable cortisol suppression. In the afternoon, the group from Spitak showed significantly greater cortisol suppression. These differences in neuroendocrine activity are particularly remarkable as both groups were symptomatic and trauma exposed to some degree, but those with greater symptoms and exposure showed HPA axis alterations similar to those described in adults with PTSD. As biological data was not available earlier than 5 years later, it is not known whether these adolescents, like the girls who suffered sexual abuse, had elevated cortisol responses in the immediate aftermath of the earthquake.

Neuroendocrine measures have also been studied in women who were abused as children. Women with a history of CSA were compared with women without such a history on the low-dose DST and measurement of lymphocyte GRs. Like combat veterans with PTSD, the women with CSA showed enhanced suppression of cortisol in response to dexamethasone (Stein, Yehuda, Koverola, & Hanna, 1997). The subset of women with a history of CSA and PTSD also showed a significantly enhanced cortisol suppression and a trend toward an increased number of lymphocyte glucocorticoid receptors. Given that most of the women with CSA were psychiatrically impaired, it was not possible to assess the extent to which the alterations were related to sexual abuse or to having PTSD or other abuse-related psychopathology. A study of urinary neuroendocrine measures done in women with a history of CSA does not support the finding of lower urinary cortisol in PTSD. After controlling for weight and creatinine, the women with PTSD, as compared with abused women without PTSD and non-abused women, had elevations in 24-hr urinary cortisol, norepinephrine, and epinephrine (Lemieux & Coe, 1995) and did not show the increased norepinephrine/cortisol ratio initially described in combat-related PTSD (Mason, Giller, Kosten, & Harkness, 1988). Although this may reflect differences in neurobiology related to gender or type of trauma, methodologic questions have been raised about this study as the mean cortisol level in the PTSD group (112 ± 56 µg/mL) is rather high (Yehuda, 1997). Nonetheless, this study suggests further study in this population is needed.

These findings suggest that the model of enhanced negative feedback may apply to women and men, to those exposed to sexual abuse/assault as well as to combat, and to those traumatized in childhood as well as in adulthood. To date, neuroendocrine studies of childhood trauma suggest that neuroendocrine activation is seen in early adolescence following sexual trauma, and that lower cortisol levels and enhanced cortisol negative feedback can be seen in adolescents with PTSD symptoms as early as 5 years after trauma exposure, and may persist into adulthood. The magnitude of this effect on development and its interactions with a range of behavioral and cognitive symptoms is yet to be defined. As sampling in the studies of childhood trauma has been largely based on exposure to a particular type of trauma, rather than on a particular psychiatric sequelae, the specificity of these findings to PTSD is unclear. However, as trauma exposure may have wide ranging effects, longitudinal follow-up of child abuse victims may ultimately elucidate the relationship between trauma, neurobiologic alter-
ations and a number of psychiatric disturbances, including substance abuse, eating disorders, personality disorders, and attention deficit disorder.

PTSD and aging

Developmental changes in the phenomenology or neurobiology of traumatic stress may be expected to be manifest not only in the very young but also in the very old. However, even less is known about development and the interaction of aging with posttraumatic stress symptoms and biological alterations in the elderly than is known in children.

PTSD is a chronic condition, marked by recurrences and exacerbations. Reactivation of PTSD, or even a delayed onset of PTSD, is not uncommon in elderly trauma survivors even after decades of few or no symptoms and good social and occupational functioning. For example, recurrence of symptoms in elderly combat veterans has been associated with typical age-associated stressors, such as retirement or the death of loved ones, as well as with trauma-specific reminders (e.g., military reunions and the emergence of military conflicts, such as the Gulf War) (Hierholzer, Munson, Peabody, & Rosenberg, 1992). Medical illnesses have also been associated with exacerbation or reactivation of symptoms (Hamner, 1994; Herrman & Eryavec, 1994). Among Holocaust survivors, the persistence of PTSD symptoms into old age was associated with cumulative lifetime trauma and recent stress exposure (Yehuda, Kahana, Schmeidler et al., 1995). These findings suggest that stressors other than the focal traumatic stressor contribute to the persistence of PTSD symptoms, although the mechanism is unclear.

The only neuroendocrine study of PTSD in the elderly to date, found that cortisol levels are lower in symptomatic trauma survivors (Yehuda, Kahana, Binder–Brynes et al., 1995). Men and women who survived the Holocaust and had current PTSD were compared with survivors without PTSD and demographically matched controls. The survivors with PTSD had significantly lower 24-hr urinary cortisol secretion than nonexposed controls. Additionally, they had lower cortisol levels than survivors without PTSD, who did not differ from nonexposed controls, suggesting the differences were not simply the result of exposure to the Holocaust. Additionally, when the survivor group without current PTSD was subdivided into those with and without a past history of PTSD, no significant differences were observed. It appears then that at least one of the neurobiological alterations described in PTSD is also present in survivors more than 50 years after the Holocaust and is associated with current symptoms.

The fact that the elderly survivors without current PTSD but with a past history of it, a subgroup that consisted of half of the non-PTSD group, did not have lower cortisol levels, suggests that the neuroendocrine alterations are not inevitable, and raises the question of what factors may mediate the persistence or resurgence of alterations and how they are affected by the aging process. Much work is needed in this area to explain why some experience a recrudescence of symptoms with age while others do not. A greater understanding of the factors responsible for the varied clinical outcome in the elderly may help us to understand symptom reactivation better and how to prevent it.

The HPA Axis Alterations and Memory Disturbance in PTSD

The relationship between arousal and memory has been described as an inverted U-shaped curve where stress hormones enhance memory, but have a deleterious effect at higher levels (McGaugh, Liang, & Bennett, 1984). Although a number of neuropeptides and neuromodulators are involved in facilitating memory consolidation, there has been a considerable focus on the role of catecholamines and glucocorticoids in mediating the effect of emotional arousal on memory (for a review, see McEwen and Sapolsky, 1995). In humans, the administration of catecholamines, such as low to moderate doses of epinephrine, has been shown to enhance memory in some (Walker, 1958, 1967) but not all studies (Christianson & Mjorndal, 1985; Eysenck,
The importance of catecholamines in emotional memory was demonstrated in a study in which memory for an emotional version of a story was compared to memory for a neutral version. Subjects were presented with a neutral version in which a boy is shown around a hospital and an emotional one in which he is injured and rushed to the hospital (Cahill, Prins, Weber, & McGaugh, 1994). The stories were otherwise identical in content, length, and complexity. A marked enhancement of memory for the emotionally laden details of the emotional story was found. Pretreatment of subjects with propranolol, a β-adrenergic receptor blocker, abolished the enhancement of memory for the emotional aspects of the story, but did not interfere with memory for either the neutral story or neutral aspects of the emotional story. This study suggests that sympathetic activation mediates and is necessary for the enhancing effect of emotional arousal on memory.

Many of the studies of the effects of chronic stress on memory have focused on glucocorticoids. One approach has been to study cognition in diseases associated with hypercortisolism (e.g., Cushing’s disease, Major Depressive Disorder) and another has been through the study of exogenous corticosteroid administration. In Cushing’s disease, most patients show evidence of cognitive impairment which correlates with the level of cortisol and diminishes in response to successful treatment (Starkman, Gebarski, Berent, & Schteingart, 1992). In major depression a relationship has been found between cognitive impairment and hypercortisolism (Rubinow, Post, Savard, & Gold, 1984) and DST nonsuppression (Reus, 1984; Wolkowitz et al., 1990). Additionally, among depressed patients, mood and neuropsychological functioning vary across the diurnal cycle in relation to fluctuations in neuroendocrine activity (Moffoot et al., 1994).

A relationship between elevated glucocorticoids and cognition has also been demonstrated in healthy subjects, suggesting the relationship is independent of disease effects. In one series, cognitive performance was adversely affected by both a single dose (1 mg dexamethasone) and chronic administration (80 mg/day prednisone for 5 days) of cortico-steroids (Wolkowitz et al., 1990). Even within the physiologic range of glucocorticoids, an inverse relationship between good performance and cortisol levels was evident in a study of circadian rhythms (Monk et al., 1997). Therefore, a relationship between glucocorticoid concentration and memory function is apparent within normal and supraphysiologic dose ranges and in states of health and disease.

Given the known effects of arousal on memory, it has been hypothesized that in PTSD an increase in stress responsive hormones and neuromodulators at the time of trauma exposure leads to enhanced memory consolidation for the traumatic event in PTSD. The intrusive recollections of the trauma, a hallmark symptom of PTSD, are thought to be manifestations of these enduring, seemingly indelible, traumatic memories (Pitman, 1989). However, as the processing of traumatic memories may be quite different in PTSD patients than other trauma survivors, it is important to consider these differences when extrapolating from the neurobiology of stress. It is interesting to speculate on the mechanism by which neuroendocrine alterations that are associated with PTSD but not with the general traumatic stress response, such as lower basal cortisol, might influence the encoding and retrieval of traumatic memories. Cortisol is typically released in response to traumatic stress and its role in constraining the release of neuromodulators involved in memory consolidation is well established. A cortisol response that is insufficient in magnitude or duration following trauma exposure may lead to a failure to terminate other neuromodulators released by stress, such as catecholamines, vasopressin, and ACTH. If so, differences in cortisol levels in the acute aftermath of trauma may be one explanation for the variation in the encoding of traumatic memories and the overconsolidation that occurs in PTSD (Yehuda & Harvey, 1997).

As the symptoms in PTSD are not constant but fluctuate over time it is likely that the neurobiological alterations that account for these changes extend beyond the period of encoding of traumatic memories. One possible explanation for these fluctuations is that different
symptoms become manifest depending on the neuroendocrinologic milieu. A diurnal study has shown that while the average level of cortisol is lower in PTSD subjects, the range of values is greater. Therefore, PTSD subjects have cortisol peaks that are high relative to the trough levels (Yehuda, Levingood et al., 1996). It is possible that this greater variation in glucocorticoid levels accounts for symptom fluctuations and the bidirectional nature of the memory impairments. During the relatively high peaks, and in the presence of increased glucocorticoid receptor number or sensitivity, cortisol could have deleterious effects on memory, which may account for the cognitive impairments that are present in, but not unique to, PTSD.

Although there is evidence that cortisol levels are inversely associated with overall PTSD symptoms, to date there are few studies that have examined the relationship between cortisol and specific memory-related symptoms. In one, an inverse relationship was found between cortisol level and the reexperiencing/reliving symptoms in adolescents (Goenjian et al., 1996). However, in the elderly with PTSD, an inverse relationship was found with avoidance symptoms, which includes psychogenic amnesia (Yehuda, Kahana, Binder–Byrnes et al., 1995). To further test the hypotheses presented here studies are needed which simultaneously measure neuroendocrine activity, cognition, and symptoms in trauma survivors, ideally over a diurnal cycle and longitudinally.

**Hippocampal Size and Memory in PTSD**

The hippocampus, a structure implicated in memory and learning, is a target for glucocorticoids, which are typically released from the adrenal gland in response to stress. The hippocampus is rich in glucocorticoid receptors, and therefore sensitive to these hormones. Animal studies have shown that stress and corticosteroids can induce hippocampal atrophy and, if the exposure is prolonged, hippocampal neuron loss (for a review, McEwen & Sapolsky, 1995). Therefore, the hippocampus may provide a link between traumatic stress and memory impairments. As a result, there has been increasing interest in evaluating the hippocampus in PTSD. To date four studies have demonstrated smaller hippocampal volumes in PTSD subjects. Symptomatic survivors of childhood abuse have been found to have smaller hippocampal volume on MRI than nontrauma exposed controls (Bremner et al., 1997; Stein, Koverola, Hanna, & Torchia, 1997). Combat veterans with PTSD have been found to have reduced hippocampal volumes compared to a noncombat comparison group (Bremner et al., 1995) and to combat-exposed controls (Gurvits et al., 1996). There are some methodologic problems with the studies to date. For example, in all of them the subjects had considerable psychiatric comorbidity and the majority had a lifetime history of alcohol or drug abuse. Additionally, two (Bremner et al., 1995; Bremner et al., 1997) did not control for variations in head size or brain volume, making it difficult to appreciate the significance of the observed volume differences. However, the confluence of results suggests that the hippocampus may play a role in the memory-related impairments in PTSD.

To the extent that trauma exposure is hypothesized to be etiologically related to smaller hippocampal volume in PTSD, glucocorticoid toxicity at the time of trauma exposure has been posited as one mechanism (Bremner et al., 1995). However, if hippocampal damage results directly from traumatic stress, smaller hippocampi would be expected in individuals with comparable levels of trauma exposure irrespective of a PTSD diagnosis. The imaging study that compared trauma exposed subjects with and without PTSD and healthy nonexposed comparison subjects, found no volume differences between combat exposed veterans without PTSD and the comparison subjects, suggesting that trauma per se may not be an explanation for the findings (Gurvits et al., 1997). Although traumatic stress induced glucocorticoid toxicity has been suggested as an explanation, there is no substantial evidence for high cortisol levels in PTSD. Therefore, alterations other than those specifically associated with traumatic stress exposure need to be considered.
One plausible explanation is that the hippocampal damage is mediated by glucocorticoids but is related to glucocorticoid receptor responsiveness rather than glucocorticoid concentration. As described in this article, trauma survivors with PTSD show enhanced cortisol negative feedback with increased glucocorticoid receptor sensitivity, which may render the hippocampus more vulnerable to atrophy (Yehuda, 1997). Additionally, fluctuations in memory related symptoms may be better accounted for in this model, which posits that the neuropathologic processes are related to dynamic processes rather than permanent ones, to atrophy rather than neuronal loss. The linking of memory symptoms to dynamic neuroendocrinologic processes rather than to a fixed structural lesion also allows for an explanation of why recovery can occur in even the most chronic cases with successful treatment.

In summary, trauma survivors with PTSD, show a range of psychological and biological alterations that are different from those seen as part of the typical response to traumatic stress. The unusual neuroendocrine response has been seen in survivors of trauma in childhood as well as adulthood. Evidence for this response has been detected as early as adolescence and as late as the seventh decade of life, although there are likely variations related to development and symptom severity. The neuroendocrine abnormalities described in PTSD appear not to be an amplification of the typical stress response but a distinctly different response. Further work is needed to understand the functional significance of this unique neuroendocrine profile and its relationship to the longitudinal course of posttraumatic stress symptoms and memory-related impairments.

References


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