REVIEWS

The Body Keeps the Score: Memory and the Evolving Psychobiology of Posttraumatic Stress

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Ever since people's responses to overwhelming experiences have been systematically explored, researchers have noted that a trauma is stored in somatic memory and expressed as changes in the biological stress response. Intense emotions at the time of the trauma initiate the long-term conditional responses to reminders of the event, which are associated both with chronic alterations in the physiological stress response and with the amnesias and hypermnesias characteristic of posttraumatic stress disorder (PTSD). Continued physiological hyperarousal and altered stress hormone secretion affect the ongoing evaluation of sensory stimuli as well. Although memory is ordinarily an active and constructive process, in PTSD failure of declarative memory may lead to organization of the trauma on a somatosensory level (as visual images or physical sensations) that is relatively impervious to change. The inability of people with PTSD to integrate traumatic experiences and their tendency, instead, to continuously relive the past are mirrored physiologically and hormonally in the misinterpretation of innocuous stimuli as potential threats. Animal research suggests that intense emotional memories are processed outside of the hippocampally mediated memory system and are difficult to extinguish. Cortical activity can inhibit the expression of these subcortically based emotional memories. The effectiveness of this inhibition depends, in part, on physiological arousal and neurohormonal activity. These formulations have implications for both the psychotherapy and the pharmacotherapy of PTSD. (HARVARD REV PSYCHIATRY 1994;1:253–65.)

For more than a century, ever since people's responses to overwhelming experiences were first systematically explored, researchers have noted that the psychological effects of trauma are stored in somatic memory and expressed as changes in the biological stress response. In 1889 Pierre Janet[1] postulated that intense emotional reactions make events traumatic by interfering with the integration of the experience into existing memory schemes. Intense emotions, Janet thought, cause memories of particular events to be dissociated from consciousness and to be stored, instead, as visceral sensations (anxiety and panic) or visual images (nightmares and flashbacks). Janet also observed that traumatized patients seemed to react to reminders of the trauma with emergency responses that had been relevant to the original threat but had no bearing on current experience. He noted that, unable to put the trauma behind them, victims had trouble learning from experience: their energy was funneled toward keeping their emotions under control, at the expense of paying attention to current exigencies. They became fixated on the past, in some cases by being obsessed with the trauma, but more often by behaving and feeling as if they were traumatized over and over again without being able to locate the origins of these feelings.[2,3]

Freud[4] also considered the tendency to remain fixated on the trauma to be biologically based: "After severe shock . . . the dream life continually takes the patient back to the situation of his disaster from which he awakens with renewed terror. . . . The patient has undergone a physical fixation to the trauma." Pavlov's investigations[5] continued the tradition of explaining the effects of trauma as the

result of lasting physiological alterations. He, and others using his paradigm, coined the term *defensive reaction* for a cluster of innate reflexive responses to environmental threat. Many studies have shown how the response to potent environmental stimuli (unconditional stimuli) becomes a conditioned reaction. After repeated aversive stimulation, intrinsically nonthreatening cues associated with the trauma (conditional stimuli) can elicit the defensive reaction by themselves (conditional response). A rape victim may respond to conditioned stimuli, such as the approach of an unknown man, as if she were about to be raped again — and experience panic. Pavlov also pointed out that individual differences in temperament accounted for the diversity of long-term adaptations to trauma.

Abraham Kardiner,[6] who first systematically defined posttraumatic stress for American audiences, noted that sufferers of "traumatic neuroses" develop an enduring vigilance for and sensitivity to environmental threat. He stated:

> The nucleus of the neurosis is a physioneurosis. This is present on the battlefield and during the entire process of organization; it outlives every intermediary accommodative device, and persists in the chronic forms. The traumatic syndrome is ever present and unchanged.

In *Men Under Stress,* Grinker and Spiegel[7] cataloged the physical symptoms of soldiers in acute posttraumatic states: flexor changes in posture, hyperkinesis, "violently propulsive gait," tremor at rest, masklike facies, cogwheel rigidity, gastric distress, urinary incontinence, mutism, and a violent startle reflex. They noted the similarity between many of these symptoms and those of diseases of the extrapyramidal motor system. Today we understand them to result from stimulation of biological systems, particularly of ascending amine projections. Contemporary research on the biology of posttraumatic stress disorder (PTSD), generally uninformed by this earlier research, confirms that there are persistent and profound alterations in stress hormone secretion and memory processing in subjects with PTSD.

SYMPTOMATOLOGY

Starting with Kardiner[6] and closely followed by Lindemann,[8] a vast literature on combat trauma, crimes, rape, kidnapping, natural disasters, accidents, and imprisonment[9–12] has shown that the trauma response is bimodal: hypermnesia, hyperreactivity to stimuli, and traumatic re-experiencing coexist with psychic numbing, avoidance, amnesia, and anhedonia. These responses to extreme experiences are so consistent across the different forms of traumatic stimuli that this bimodal reaction appears to be the

normative response to any overwhelming and uncontrollable experience. In many persons who have undergone severe stress, the posttraumatic response fades over time, whereas in others it persists. Much work remains to be done to spell out issues of resilience and vulnerability, but magnitude of exposure, previous trauma, and social support appear to be the three most significant predictors for development of chronic PTSD.[13,14]

In an apparent attempt to compensate for chronic hyperarousal, traumatized people seem to shut down: on a behavioral level by avoiding stimuli reminiscent of the trauma, and on a psychobiological level by emotional numbing, which extends to both trauma-related and everyday experience.[15] Thus subjects with chronic PTSD tend to suffer from a numbed responsiveness to the environment, punctuated by intermittent hyperarousal in reaction to conditional traumatic stimuli. However, as Pitman and colleagues[16,17] have pointed out, in PTSD the stimuli that precipitate emergency responses may not be conditional enough: many triggers not directly related to the traumatic experience may precipitate extreme reactions. Subjects with PTSD suffer both from generalized hyperarousal and from physiological emergency reactions to specific reminders.[9,10]

The loss of affective modulation that is so central in PTSD may help to explain the observation that traumatized persons lose the capacity to use affect states as signals.[18] In subjects with PTSD, feelings are not used as cues to attend to incoming information and arousal is likely to precipitate flight-or-fight reactions.[19] Thus they often go immediately from stimulus to response without psychologically assessing the meaning of an event. This makes them prone to freeze or, alternatively, to overreact and intimidate others in response to minor provocations.[12,20]

PSYCHOPHYSIOLOGY

Abnormal psychophysiological responses in PTSD have been observed at two different levels: (1) in response to specific reminders of the trauma and (2) in response to intense but neutral stimuli, such as unexpected noises. The first paradigm implies heightened physiological arousal to sounds, images, and thoughts related to specific traumatic incidents. Many studies [20–25] have confirmed that traumatized individuals respond to such stimuli with significant conditioned autonomic reactions — for example, increases in heart rate, skin conductance, and blood pressure. The highly elevated physiological responses accompanying the recall of traumatic experiences that happened years, and sometimes decades, before illustrate the intensity and timelessness with which traumatic memories continue to affect current experience.[3,16] This phenomenon has been understood in the

light of Lang's work,[26] which shows that emotionally laden imagery correlates with measurable autonomic responses. Lang has proposed that emotional memories are stored as "associative networks" that are activated when a person is confronted with situations that stimulate a sufficient number of elements within such networks. One significant measure of treatment outcome that has become widely accepted in recent years is a decrease in physiological arousal in response to imagery related to the trauma.[27] However, Shalev and coworkers[28] have shown that desensitization to specific trauma-related mental images does not necessarily generalize to recollections of other traumatic events as well.

Kolb[29] was the first to propose that excessive stimulation of the central nervous system (CNS) at the time of the trauma may result in permanent neuronal changes that have a negative effect on learning, habituation, and stimulus discrimination. These neuronal changes would not depend on actual exposure to reminders of the trauma for expression. The abnormal startle response characteristic of PTSD[10] exemplifies such neuronal changes.

Although abnormal acoustic startle response (ASR) has been seen as a cardinal feature of the trauma response for more than half a century, systematic explorations of the ASR in PTSD have just begun. The ASR is a characteristic sequence of muscular and autonomic responses elicited by sudden and intense stimuli.[30,31] The neuronal pathways involved consist of only a small number of mediating synapses between the receptor and effector and a large projection to brain areas responsible for CNS activation and stimulus evaluation.[31] The ASR is mediated by excitatory amino acids such as glutamate and aspartate and is modulated by a variety of neurotransmitters and second messengers at both the spinal and the supraspinal levels.[32] Habituation to the ASR in normal human subjects occurs after three to five presentations.[30]

Several studies [33-36] have shown abnormalities in habituation to the ASR in PTSD. Shalev and coworkers[33] found a failure to habituate to both CNS- and autonomic nervous system–mediated responses to ASR in 93% of subjects in the PTSD group, compared with 22% of the control subjects. Interestingly, persons who previously met criteria for PTSD but no longer do so continue to show failure of habituation to the ASR (van der Kolk BA, et al., unpublished data, 1991–1992; Pitman RK, et al., unpublished data, 1991–1992), which raises the question of whether abnormal habituation to acoustic startle may be a marker or a vulnerability factor for development of PTSD.

The failure to habituate to acoustic startle suggests that traumatized people have difficulty evaluating sensory stimuli and mobilizing appropriate levels of physiological arousal.[30] Thus the inability of people with PTSD properly to integrate memories of the trauma and the tendency they have to get mired in a continuous reliving of the past are mirrored physiologically by the misinterpretation of innocuous stimuli, such as unexpected noises, as potential threats.

HORMONAL STRESS RESPONSE AND PSYCHOBIOLOGY

PTSD develops after exposure to events that are intensely distressing. Extreme stress is accompanied by the release of endogenous neurohormones, such as cortisol, epinephrine and norepinephrine, vasopressin, oxytocin, and endogenous opioids. These hormones help the organism to mobilize the energy required to deal with the stress; they induce reactions ranging from increased glucose release to enhanced immune function. In a well-functioning organism, stress produces rapid and pronounced hormonal responses. However, chronic and persistent stress inhibits the effectiveness of the stress response and induces desensitization.[37]

Much still remains to be learned about the specific roles of the different neurohormones in the stress response. Norepinephrine is secreted by the locus ceruleus and distributed through much of the CNS, particularly the neocortex and the limbic system, where it plays a role in memory consolidation and helps to initiate fight-or-flight behaviors. Corticotropin is released from the anterior pituitary and activates a cascade of reactions, eventuating in release of glucocorticoids from the adrenal glands. The precise interrelation between hypothalamic-pituitary-adrenal (HPA) axis hormones and the catecholamines in the stress response is not entirely clear, but it is known that stressors that activate norepinephrine neurons also increase the concentration of corticotropin-releasing factor in the locus ceruleus,[38] and intracerebral ventricular infusion of corticotropin-releasing factor increases norepinephrine in the forebrain.[39] Glucocorticoids and catecholamines may modulate each other's effects: in acute stress, cortisol helps to regulate the release of stress hormones via a negative feedback loop to the hippocampus, hypothalamus, and pituitary,[40] and there is evidence that corticosteroids normalize catecholamine-induced arousal in limbic midbrain structures in response to stress.[41] Thus the simultaneous activation of corticosteroids and catecholamines could stimulate active coping behaviors, whereas increased arousal in the presence of low glucocorticoid levels may promote undifferentiated fight-or-flight reactions.[42]

Although acute stress mobilizes the HPA axis and increases glucocorticoid levels, organisms adapt to chronic stress by activating a negative feedback loop that results in (1) decreased resting glucocorticoid levels,[43] (2) decreased glucocorticoid secretion in response to subsequent stress,[42]

TABLE 1. Biological Abnormalities in PTSD

A. Psychophysiological
1. Extreme autonomic responses to stimuli reminiscent of the trauma
2. Nonhabituation to startle stimuli
B. Neurotransmitter
1. Noradrenergic
a. Elevated urinary catecholamines
b. Increased MHPG to yohimbine challenge
c. Reduced platelet MAO activity
d. Down-regulation of adrenergic receptors
2. Serotonergic
a. Decreased serotonin activity in traumatized animals
b. Best pharmacological responses to serotonin uptake inhibitors
3. Endogenous opioids: increased opioid response to stimuli reminiscent of trauma
C. HPA axis
1. Decreased resting glucocorticoid levels
2. Decreased glucocorticoid response to stress
3. Down-regulation of glucocorticoid receptors
4. Hyperresponsiveness to low-dose dexamethasone
D. Memory
1. Amnesias and hypermnesias
2. Traumatic memories precipitated by noradrenergic stimulation, physiological arousal
3. Memories generally sensorimotor rather than semantic
E. Miscellaneous
1. Traumatic nightmares often not oneiric but exact replicas of visual elements of trauma; may occur in stage II or III sleep
2. Decreased hippocampal volume (?)
3. Impaired psychoimmunologic functioning (?)

and (3) increased concentration of glucocorticoid receptors in the hippocampus.[44] Yehuda et al.[45] suggested that increased concentration of glucocorticoid receptors could facilitate a stronger negative glucocorticoid feedback, resulting in a more sensitive HPA axis and a faster recovery from acute stress.

Chronic exposure to stress affects both acute and chronic adaptation: it permanently alters how an organism deals with its environment on a day-to-day basis and interferes with how it copes with subsequent acute stress.[45]

NEUROENDOCRINE ABNORMALITIES

Because there is an extensive literature on the effects of inescapable stress on the biological stress response of animal species such as monkeys and rats, much of the biological research on people with PTSD has focused on testing the applicability of those research findings to human subjects with PTSD.[46,47] Subjects with PTSD, like chronically and inescapably shocked animals, seem to have a persistent activation of the biological stress response after exposure to stimuli reminiscent of the trauma (Table 1).

Catecholamines

Neuroendocrine studies of Vietnam veterans with PTSD have found good evidence for chronically increased sympathetic nervous system activity in PTSD. One investigation[48] discovered elevated 24-hour urinary excretion of norepinephrine and epinephrine in PTSD combat veterans compared with patients who had other psychiatric diagnoses. Although Pitman and Orr[49] did not replicate these findings in 20 veterans and 15 combat control subjects, the mean urinary excretion of norepinephrine in their combat control subjects (58.0 μg/day) was substantially higher than values previously reported in normal populations. The expected compensatory down-regulation of adrenergic receptors in response to increased levels of norepinephrine was confirmed by a study[50] that found decreased platelet α_2-adrenergic receptors in combat veterans with PTSD compared with normal control subjects. Another study[51] also found an abnormally low α_2-adrenergic receptor–mediated adenylate cyclase signal transduction. Recently Southwick and colleagues[52] used yohimbine injections (0.4 mg/kg), which activate noradrenergic neurons by blocking the α_2-autoreceptor, to study noradrenergic neuronal dysregulation in Vietnam veterans with PTSD. Yohimbine precipitated panic attacks in 70% of subjects and flashbacks in 40%. Subjects responded with larger increases in plasma 3-methoxy-4-hydroxyphenylglycol (MHPG) than control subjects. Yohimbine precipitated significant increases in all PTSD symptoms.

Corticosteroids

Two studies[42,53] have shown that veterans with PTSD have low urinary excretion of cortisol, even when they have comorbid major depressive disorder. Other research[49] failed to replicate this finding. In a series of studies, Yehuda and coworkers[42,54] found increased numbers of lymphocyte glucocorticoid receptors in Vietnam veterans with PTSD. Interestingly, the number of glucocorticoid receptors was proportional to the severity of PTSD symptoms. Yehuda and coworkers[54] also reported the findings of an unpublished study by Heidi Resnick, in which acute cortisol response to trauma was studied in blood samples from 20 rape victims in the emergency room. Three months later, trauma histories were taken and the subjects were evaluated for the presence of PTSD. Development of PTSD after the rape was significantly more likely in victims with histories of sexual abuse than in victims with no such histories. Cortisol levels

shortly after the rape were correlated with histories of previous assaults: the mean initial cortisol levels of individuals with assault histories were 15 µg/dl, compared with 30 µg/dl in the control subjects. These findings can be interpreted to mean that previous exposure to traumatic events results either in a blunted cortisol response to subsequent trauma or in a quicker return of cortisol to baseline after stress. That Yehuda and colleagues[45] also found subjects with PTSD to be hyperresponsive to low doses of dexamethasone argues for an enhanced sensitivity of the HPA feedback in traumatized patients.

Serotonin

Although the role of serotonin in PTSD has not been systematically investigated, the facts that decreased CNS serotonin levels develop in inescapably shocked animals[55] and that serotonin reuptake blockers are effective pharmacological agents in the treatment of PTSD justify a brief consideration of the potential role of this neurotransmitter in PTSD. Decreased serotonin in humans has been correlated repeatedly with impulsivity and aggression.[56-58] The authors of these investigations tend to assume that these relationships are based on genetic traits. However, studies of impulsive, aggressive, and suicidal patients (e.g., Green,[59] van der Kolk et al.,[60] and Lewis[61]) seem to find at least as robust an association between those behaviors and histories of childhood trauma. Probably both temperament and experience affect relative serotonin levels in the CNS.[12]

Low serotonin levels in animals are also related to an inability to modulate arousal, as exemplified by an exaggerated startle response[62,63] and by increased arousal in reaction to novel stimuli, handling, or pain.[63] The behavioral effects of serotonin depletion in animals include hyperirritability, hyperexcitability, hypersensitivity, and an "exaggerated emotional arousal and/or aggressive display to relatively mild stimuli."[63] These behaviors bear a striking resemblance to the phenomenology of PTSD in humans. Furthermore, serotonin reuptake inhibitors have been found to be the most effective pharmacological treatment for obsessive thinking in subjects with obsessive-compulsive disorder[64] and for involuntary preoccupation with traumatic memories in subjects with PTSD.[65,66] Serotonin probably plays a role in the capacity to monitor the environment flexibly and to respond with behaviors that are situation-appropriate, rather than reacting to internal stimuli that are irrelevant to current demands.

Endogenous opioids

Stress-induced analgesia has been described in experimental animals after a variety of inescapable stressors such as electric shock, fighting, starvation, and cold water swim.[67] In severely stressed animals opiate withdrawal symptoms can be produced either by termination of the stress or by naloxone injections. Motivated by the findings that fear activates the secretion of endogenous opioid peptides and that stress-induced analgesia can become conditioned to subsequent stressors and to previously neutral events associated with the noxious stimulus, we tested the hypothesis that in subjects with PTSD, reexposure to a stimulus resembling the original trauma will cause an endogenous opioid response that can be indirectly measured as naloxone-reversible analgesia.[68,69] We found that 2 decades after the original trauma, opioid-mediated analgesia developed in subjects with PTSD in response to a stimulus resembling the traumatic stressor, which we correlated with a secretion of endogenous opioids equivalent to 8 mg of morphine. Self-reports of emotional responses suggested that endogenous opioids were responsible for a relative blunting of emotional response to the traumatic stimulus.

Endogenous opioids and stress-induced analgesia: implications for affective function

When young animals are isolated or older ones are attacked, they respond initially with aggression (hyperarousal-fight-protest) and then, if that does not produce the required results, with withdrawal (numbing-flight-despair). Fear-induced attack or protest patterns serve in the young to attract protection and in mature animals to prevent or counteract the predator's activity. During external attacks, pain inhibition is a useful defensive capacity because attention to pain would interfere with effective defense: grooming or licking wounds may attract opponents and stimulate further attack.[70] Thus defensive and pain-motivated behaviors are mutually inhibitory. Stress-induced analgesia protects organisms against feeling pain while engaged in defensive activities. As early as 1946, Beecher,[71] after observing that 75% of severely wounded soldiers on the Italian front did not request morphine, speculated that "strong emotions can block pain." Today, we can reasonably assume that this is caused by the release of endogenous opioids.[68,69]

Endogenous opioids, which inhibit pain and reduce panic, are secreted after prolonged exposure to severe stress. Siegfried and colleagues[70] have observed that memory is impaired in animals when they can no longer actively influence the outcome of a threatening situation. They showed that both the freeze response and panic interfere with effective memory processing: excessive endogenous opioids and norepinephrine both interfere with the storage of experience in explicit memory. Freeze-numbing responses may serve the function of allowing organisms to not "consciously experience" or to not remember situations of overwhelming stress (thus also preventing their learning from experience). We have proposed that the dissociative reactions of subjects in response to trauma may be analogous to this complex of
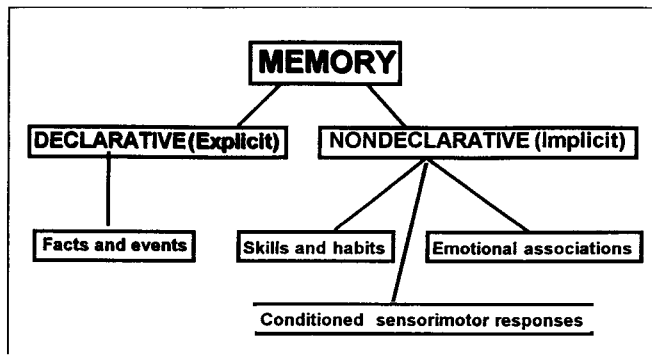
FIGURE 1.
Schematic representation of different forms of memory.

behaviors that occurs in animals after prolonged exposure to severe uncontrollable stress.[68]

DEVELOPMENTAL LEVEL AND THE PSYCHOBIOLOGICAL EFFECTS OF TRAUMA

Although most studies on PTSD have been done on adults, particularly war veterans, in recent years a few prospective investigations have documented the differential effects of trauma at various age levels. Anxiety disorders, chronic hyperarousal, and behavioral disturbances have been regularly described in traumatized children (e.g., Bowlby,[72] Cicchetti,[73] and Terr[74]). In addition to the reactions to discrete, one-time, traumatic incidents documented in these studies, intrafamilial abuse is increasingly recognized to produce complex posttraumatic syndromes[75] that involve chronic affect dysregulation, destructive behavior against self and others, learning disabilities, dissociative problems, somatization, and distortions in concepts about self and others.[76,77] The Field Trials for DSM-IV showed that this conglomeration of symptoms tended to occur together and that the severity of the syndrome was proportional to the duration of the trauma and the age of the child when it began.[78]

Although current research on traumatized children is outside the scope of this review, it is important to recognize that a range of neurobiological abnormalities are beginning to be identified in this population. Frank Putnam's as-yet-unpublished prospective studies (personal communications, 1991, 1992, and 1993) are showing major neuroendocrine disturbances in sexually abused girls compared with non-abused girls. Research on the psychobiology of childhood trauma can be profitably informed by the vast literature on the psychobiological effects of trauma and deprivation in nonhuman primates.[12,79]

TRAUMA AND MEMORY

The flexibility of memory and the engraving of trauma

A century ago, Janet[1] suggested that the most fundamental of mental activities are the storage and categorization of incoming sensations into memory and the retrieval of those memories under appropriate circumstances. He, like contemporary memory researchers, understood that what is now called semantic, or declarative, memory is an active and constructive process and that remembering depends on existing mental schemata:[3,80] once an event or a particular bit of information is integrated into existing mental schemes, it will no longer be accessible as a separate, immutable entity but will be distorted both by previous experience and by the emotional state at the time of recall.[3] PTSD, by definition, is accompanied by memory disturbances that consist of both hypermnesias and amnesias.[9,10] Research into the nature of traumatic memories[3] indicates that trauma interferes with declarative memory (i.e., conscious recall of experience) but does not inhibit implicit, or nondeclarative, memory, the memory system that controls conditioned emotional responses, skills and habits, and sensorimotor sensations related to experience (Figure 1). There is now enough information available about the biology of memory storage and retrieval to start building coherent hypotheses regarding the underlying psychobiological processes involved in these memory disturbances.[3,16,17,25]

Early in this century Janet[81] noted that "certain happenings . . . leave indelible and distressing memories—memories to which the sufferer continually returns, and by which he is tormented by day and by night." Clinicians and researchers dealing with traumatized patients have repeatedly observed that the sensory experiences and visual images related to the trauma seem not to fade over time and appear to be less subject to distortion than ordinary experiences.[1,49,82] When people are traumatized, they are said to experience "speechless terror": the emotional impact of the event may interfere with the capacity to capture the experience in words or symbols. Piaget[83] thought that under such circumstances, failure of semantic memory leads to the organization of memory on a somatosensory or iconic level (such as somatic sensations, behavioral enactments, nightmares, and flashbacks). He pointed out:

> It is precisely because there is no immediate accommodation that there is complete dissociation of the inner activity from the external world. As the external world is solely represented by images, it is assimilated without resistance [i.e., unattached to other memories] to the unconscious ego.

The state dependency of traumatic memories

Research has shown that under ordinary conditions many

traumatized people, including rape victims,[84] battered women,[85] and abused children,[86] have a fairly good psychosocial adjustment. However, they do not respond to stress in the way that other people do. Under pressure they may feel or act as if they were being traumatized all over again. Thus high states of arousal seem selectively to promote retrieval of traumatic memories, sensory information, or behaviors associated with previous traumatic experiences.[9,10] The tendency of traumatized organisms to revert to irrelevant emergency behaviors in response to minor stress has been well documented in animals, as well. Studies at the Wisconsin Primate Laboratory have shown that rhesus monkeys with histories of severe early maternal deprivation display marked withdrawal or aggression in response to emotional or physical stimuli (such as exposure to loud noises or the administration of amphetamines), even after a long period of good social adjustment.[87] In experiments with mice, Mitchell and coworkers[88] found that the relative degree of arousal interacts with previous exposure to high stress to determine how an animal will react to novel stimuli. In a state of low arousal, animals tend to be curious and seek novelty. During high arousal, they are frightened, avoid novelty, and perseverate in familiar behavior, regardless of the outcome. Under ordinary circumstances, an animal will choose the more pleasant of two alternatives. When hyperaroused, it will seek whatever is familiar, regardless of the intrinsic rewards. Thus animals that have been locked in a box in which they were exposed to electric shocks and then released return to those boxes when they are subsequently stressed. Mitchell and colleagues[88] concluded that this perseveration is nonassociative (i.e., uncoupled from the usual reward systems).

Analogous phenomena have been documented in humans: memories (somatic or symbolic) related to the trauma are elicited by heightened arousal.[89] Information acquired in an aroused or otherwise altered state of mind is retrieved more readily when subjects are brought back to that particular state of mind.[90,91] State-dependent memory retrieval may also be involved in dissociative phenomena in which traumatized persons may be wholly or partially amnestic for memories or behaviors enacted while in altered states of mind.[2,3,92]

Contemporary biological researchers have shown that medications that stimulate autonomic arousal may precipitate visual images and affect states associated with previous traumatic experiences in people with PTSD but not in control subjects. In patients with PTSD, the injection of drugs such as lactate[93] and yohimbine[52] tends to precipitate panic attacks, flashbacks (exact reliving experiences) of earlier trauma, or both. In our own laboratory approximately 20% of PTSD subjects responded with a flashback of a traumatic experience when they were presented with acoustic startle stimuli.
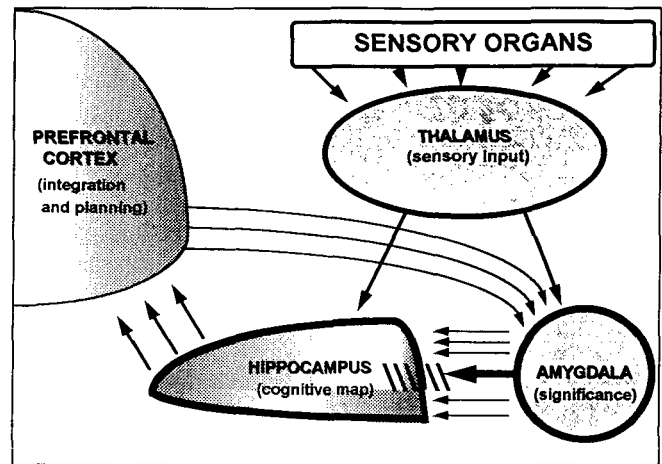

FIGURE 2.
Schematic representation of the effects of emotional arousal on declarative memory. The thalamus, amygdala, and hippocampus are all involved in the integration and interpretation of incoming sensory information. Moderate to high activation of the amygdala enhances the long-term potentiation of declarative memory that is mediated by the hippocampus, accounting for hypermnesias for stressful experiences. Excessive stimulation of the amygdala interferes with hippocampal functioning, inhibiting cognitive evaluation of experience and semantic representation. Memories are then stored in sensorimotor modalities: somatic sensations and visual images. These emotional memories are thought to be relatively indelible, but their expression can be modified by feedback from the prefrontal cortex.[3,16,95,98,118]

Trauma, neurohormones, and memory consolidation

When humans are under severe stress, they secrete endogenous stress hormones that affect the strength of memory consolidation. Based on animal models, researchers have widely assumed that massive secretion of neurohormones at the time of the trauma plays a role in the long-term potentiation (and thus, the overconsolidation) of traumatic memories.[3,46,94] Mammals seem to be equipped with memory-storage mechanisms that ordinarily modulate the strength of memory consolidation according to the strength of the accompanying hormonal stimulation.[95,96] This capacity helps the organism to evaluate the importance of subsequent sensory input according to the relative strength of associated memory traces. The phenomenon appears to be largely mediated by input of norepinephrine to the amygdala[97,98] (Figure 2). In traumatized organisms the capacity to access relevant memories appears to have gone awry: they become overconditioned to access memory traces of the trauma and to "remember" the trauma whenever aroused. Although norepinephrine seems to be the principal hormone involved in producing long-term potentiation, other neurohormones secreted under particular stressful circumstances

TABLE 2. Functions of Limbic Structures and Effects of Lesions

Hippocampus	Amygdala
Functions of limbic structures	
Categorization of experience	Conditioning of fear responses
Creation of a spatial map	Attachment of affect to neutral stimuli
Storage of simple memory	Establishment of associations between sensory modalities
Creation of summary sketch/index	
Effects of lesions	
Declarative memory lost	Loss of fear responses
Skill-based memory spared	Meaningful social interaction lost
Immediate memory spared	Declarative memory intact

(endorphins and oxytocin, for example) actually inhibit memory consolidation.[99]

The role of norepinephrine in consolidating memory has been shown to have an inverted U-shaped function:[95,96] both very low and very high levels of norepinephrine activity in the CNS interfere with memory storage. The release of excessive norepinephrine, as well as of other neurohormones such as endogenous opioids, oxytocin, and vasopressin, at the time of the trauma probably plays a role in creating the hypermnesias and amnesias that are a quintessential part of PTSD.[9,10] Interestingly, childbirth, which can be extraordinarily stressful, almost never seems to result in posttraumatic problems.[100] Oxytocin may protect against the overconsolidation of memories surrounding childbirth.

Physiological arousal in general can trigger trauma-related memories; conversely, trauma-related memories precipitate generalized physiological arousal. The frequent reliving of a traumatic event in flashbacks or nightmares probably causes a rerelease of stress hormones that further kindles the strength of the memory trace.[46] Such a positive feedback loop could cause subclinical PTSD to escalate into clinical PTSD,[16] in which the strength of the memories appears to be so deeply engraved that Pitman and Orr[17] have called it "the black hole" in the mental life of the PTSD patient: it attracts all associations to it and saps current life of its significance.

MEMORY, TRAUMA, AND THE LIMBIC SYSTEM

The limbic system is thought to be the part of the CNS that maintains and guides the emotions and behavior necessary for self-preservation and for survival of the species[101] and is critically involved in the storage and retrieval of memory. During both waking and sleeping states, signals from the sensory organs continuously travel to the thalamus, from which they are distributed to the cortex (setting up a "stream of thought"), the basal ganglia (setting

up a "stream of movement"), and the limbic system (setting up a "stream of emotions"[102] that determines the emotional significance of the sensory input). Most processing of sensory input occurs outside of conscious awareness, with only novel, significant, or threatening information being selectively passed on to the neocortex for further attention. Because subjects with PTSD appear to overinterpret sensory input as a recurrence of past trauma and because recent studies have suggested limbic-system abnormalities in brain-imaging studies of traumatized patients,[103,104] a review of the psychobiology of trauma would be incomplete without considering the role of the limbic system in PTSD (see also Teicher et al.[105]). Two particular areas of the limbic system have been implicated in the processing of emotionally charged memories: the amygdala and the hippocampus (Table 2).

The amygdala

Of all areas in the CNS, the amygdala is most clearly implicated in the evaluation of the emotional meaning of incoming stimuli.[106] Several investigators have proposed that the amygdala assigns free-floating feelings of significance to sensory input, which the neocortex then further elaborates and imbues with personal meaning.[101,106-108] Moreover, it is thought to integrate internal representations of the external world in the form of memory images with emotional experiences associated with those memories.[80] After assigning meaning to sensory information, the amygdala guides emotional behavior by projections to the hypothalamus, hippocampus, and basal forebrain.[106,107,109]

The septohippocampal system

The septohippocampal system, which is adjacent to the amygdala, is thought to record in memory the spatial and temporal dimensions of experience and to play an important role in the categorization and storage of incoming stimuli in memory. Proper functioning of the hippocampus is neces-

sary for explicit or declarative memory.[109] The hippocampus is believed to be involved in the evaluation of spatially and temporally unrelated events, comparing them with previously stored information and determining whether and how they are associated with each other and with reward, punishment, novelty, or nonreward.[107,110] The hippocampus also plays a role in the inhibition of exploratory behavior and in obsessional thinking. Damage to the hippocampus is associated with hyperresponsiveness to environmental stimuli.[111,112]

The slow maturation of the hippocampus, which is not fully myelinated until after the third or fourth year of life, is believed to be the cause of infantile amnesia.[113,114] In contrast, the memory system that encodes the affective quality of experience (roughly speaking, procedural, or "taxon," memory) matures earlier and is less subject to disruption by stress.[112] As the CNS matures, memory storage shifts from primarily sensorimotor (motoric action) and perceptual representations (iconic) to symbolic and linguistic organization of mental experience.[83] With maturation, there is an increasing ability to categorize experience and link it with existing mental schemes. However, even as the organism matures, this capacity, and with it the hippocampal localization system, remains vulnerable to disruption.[45,107,110,115,116] Various external and internal stimuli, including stress-induced corticosterone production,[117] decrease hippocampal activity. However, even when stress interferes with hippocampally mediated memory storage and categorization, some mental representation of the experience is probably laid down by means of a system that records affective experience but has no capacity for symbolic processing or placement in space and time (Figure 2).

Decreased hippocampal functioning causes behavioral disinhibition, possibly by causing incoming stimuli to be interpreted in the direction of "emergency" (fight-or-flight) responses. The neurotransmitter serotonin plays a crucial role in the capacity of the septohippocampal system to activate inhibitory pathways that prevent the initiation of emergency responses until it is clear that they will be of use.[110] This observation made us very interested in a possible role for serotonergic agents in the treatment of PTSD.

"Emotional memories are forever"

In animals high-level stimulation of the amygdala interferes with hippocampal functioning.[107,109] This implies that intense affect may inhibit proper evaluation and categorization of experience. One-time intense stimulation of the amygdala in mature animals will produce lasting changes in neuronal excitability and enduring behavioral changes in the direction of either fight or flight.[118] In kindling experiments with animals, Adamec and colleagues[119] showed that, after growth in amplitude of amygdaloid and hippocampal seizure activity, permanent alterations in limbic physiology

cause lasting changes in defensiveness and predatory aggression. Preexisting "personality" played a significant role in the behavioral effects of stimulation of the amygdala in cats: animals that are temperamentally insensitive to threat and prone to attack tend to become more aggressive, whereas defensive animals show increased behavioral inhibition.[119]

In a series of experiments, LeDoux and coworkers[118] used repeated electrical stimulation of the amygdala to produce conditioned fear responses. They found that cortical lesions prevent their extinction. This led them to conclude that, once formed, the subcortical traces of the conditioned fear response are indelible, and that "emotional memory may be forever." In 1987 Kolb[29] postulated that patients with PTSD suffer from impaired cortical control over the subcortical areas responsible for learning, habituation, and stimulus discrimination. The concept of indelible subcortical emotional responses, held in check to varying degrees by cortical and septohippocampal activity, has led to the speculation that delayed-onset PTSD may be the expression of subcortically mediated emotional responses that escape cortical, and possibly hippocampal, inhibitory control.[3,16,94,120,121]

Decreased inhibitory control may occur under a variety of circumstances: under the influence of drugs and alcohol, during sleep (as in nightmares), with aging, and after exposure to strong reminders of the traumatic past. Conceivably, traumatic memories then could emerge, not in the distorted fashion of ordinary recall but as affect states, somatic sensations, or visual images (for example, nightmares[81] or flashbacks[52]) that are timeless and unmodified by further experience.

PSYCHOPHARMACOLOGICAL TREATMENT

The goal of treating PTSD is to help people live in the present, without feeling or behaving according to irrelevant demands belonging to the past. Psychologically, this means that traumatic experiences need to be located in time and place and differentiated from current reality. However, hyperarousal, intrusive reliving, numbing, and dissociation get in the way of separating current reality from past trauma. Hence, medications that affect these PTSD symptoms are often essential for patients to begin to achieve a sense of safety and perspective from which to approach their tasks.

Although numerous articles have been written about the drug treatment of PTSD, to date only 134 people with PTSD have been enrolled in published double-blind studies. Most of these have been Vietnam combat veterans. Unfortunately, until recently only medications that seem to be of limited therapeutic usefulness have been subjected to adequate scientific scrutiny. Because the only published double-blind studies of medications for treating PTSD have in-

volved tricyclic antidepressants and monoamine oxidase (MAO) inhibitors,[122–124] it is sometimes assumed that these agents are the most effective. Three double-blind trials of tricyclic antidepressants have been published;[122,124–126] two showed modest improvement in PTSD symptoms. Although positive results have been claimed for numerous other medications in case reports and open studies, at the present time there are no data about which patient and which PTSD symptom will predictably respond to any of them. Success has been claimed for just about every class of psychoactive medication, including benzodiazepines,[127] tricyclic antidepressants,[122,125,128] MAO inhibitors,[122,129] lithium carbonate,[127] β-adrenergic blockers,[130] clonidine,[130] carbamazapine,[131] and antipsychotic agents. The accumulated clinical experience seems to indicate that understanding the basic neurobiology of arousal and appraisal is the most useful guide in selecting medications for people with PTSD.[124,125] Autonomic arousal can be reduced at different levels in the CNS: through inhibiting noradrenergic activity in the locus ceruleus with clonidine and the β-adrenergic blockers,[130,132] or by increasing the inhibitory effect of the γ-aminobutyric acid (GABA)-ergic system with GABA-ergic agonists (the benzodiazepines). During the past 2 years several case reports and open clinical trials of fluoxetine have been published, followed by our double-blind study of 64 PTSD subjects treated with fluoxetine.[65] Unlike the tricyclic antidepressants, which were effective on either the intrusive (imipramine) or numbing (amitriptyline) symptoms of PTSD, fluoxetine proved to be effective for the entire spectrum of PTSD symptoms. It also acted more rapidly than the tricyclics. The fact that fluoxetine has proved to be such an effective treatment for PTSD supports a larger role for the serotonergic system in PTSD.[66] Rorschach tests administered by "blinded" scorers revealed that subjects taking fluoxetine became able to achieve distance from the emotional impact of incoming stimuli and to use cognition in harnessing emotional responses to unstructured visual stimuli (van der Kolk et al., unpublished data, 1991–1992).

Although the subjects improved clinically, their startle habituation worsened (van der Kolk et al., unpublished data, 1991–1992). The 5-HT$_{1A}$ agonist buspirone shows some promise in facilitating habituation[133] and thus may play a useful adjunctive role in the pharmacotherapy of PTSD. Even newer research has suggested abnormalities of the N-methyl-D-aspartate receptor and of glutamate in PTSD,[134] opening up potential new avenues for the psychopharmacological treatment of this disorder.

REFERENCES

1. Janet P. L'automatisme psychologique. Paris: Alcan, 1889.

2. van der Kolk BA, van der Hart O. Pierre Janet and the breakdown of adaptation in psychological trauma. Am J Psychiatry 1989;146:1530–40.

3. van der Kolk BA, van der Hart O. The intrusive past: the flexibility of memory and the engraving of trauma. Am Imago 1991;48:425–54.

4. Freud S. Introduction to psychoanalysis and the war neuroses. Standard ed 17:207–10. Strachey J, trans/ed. London: Hogarth Press, 1919/1954.

5. Pavlov IP. Conditioned reflexes: an investigation of the physiological activity of the cerebral cortex. Anrep GV, trans/ed. New York: Dover Publications, 1926.

6. Kardiner A. The traumatic neuroses of war. New York: Hoeber, 1941.

7. Grinker RR, Spiegel JJ. Men under stress. New York: McGraw-Hill, 1945.

8. Lindemann E. Symptomatology and management of acute grief. Am J Psychiatry 1944;101:141–8.

9. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 3rd ed, revised. Washington, DC: American Psychiatric Association, 1987.

10. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed. Washington, DC: American Psychiatric Association, 1994.

11. Horowitz M. Stress response syndromes. 2nd ed. New York: Jason Aronson, 1978.

12. van der Kolk BA. Psychological trauma. Washington, DC: American Psychiatric Press, 1987.

13. Kulka RA, Schlenger WE, Fairbank JA, Hough RL, Jordan BK, Marmar CR. Trauma and the Vietnam War generation: report of findings from the National Vietnam Veterans' Readjustment Study. New York: Brunner Mazel, 1990.

14. McFarlane AC. The longitudinal course of posttraumatic morbidity: the range of outcomes and their predictors. J Nerv Ment Dis 1988;176:30–9.

15. Litz BT, Keane TM. Information processing in anxiety disorders: application to the understanding of post-traumatic stress disorder. Clin Psychol Rev 1989;9:243–57.

16. Pitman R, Orr S, Shalev A. Once bitten twice shy: beyond the conditioning model of PTSD. Biol Psychiatry 1993;33:145–6.

17. Pitman R, Orr S. The black hole of trauma. Biol Psychiatry 1990;26:221–3.

18. Krystal H. Trauma and affects. Psychoanal Study Child 1978;33:81–116.

19. Strian F, Klicpera C. Die Bedeutung psychoautonomische Reaktionen im Entstehung und Persistenz von Angstzustanden. Nervenarzt 1978;49:576–83.

20. van der Kolk BA, Ducey CP. The psychological processing of traumatic experience: Rorschach patterns in PTSD. J Traum Stress 1989;2:259–74.

21. Dobbs D, Wilson WP. Observations on the persistence of traumatic war neurosis. J Ment Nerv Dis 1960;21:40–6.

22. Malloy PF, Fairbank JA, Keane TM. Validation of a multimethod assessment of post traumatic stress disorders in Vietnam veterans. J Consult Clin Psychol 1983;51:4–21.

23. Kolb LC, Multipassi LR. The conditioned emotional response: a subclass of chronic and delayed post traumatic stress disorder. Psychiatr Ann 1982;12:979–87.

24. Blanchard EB, Kolb LC, Gerardi RJ. Cardiac response to relevant stimuli as an adjunctive tool for diagnosing post traumatic stress disorder in Vietnam veterans. Behav Ther 1986;17:592–606.

25. Pitman RK, Orr SP, Forgue DF, de Jong J, Claiborn JM. Psychophysiologic assessment of posttraumatic stress disorder imagery in Vietnam combat veterans. Arch Gen Psychiatry 1987;44:970–5.

26. Lang PJ. A bio-informational theory of emotional imagery. Psychophysiology 1979;16:495–512.

27. Keane TM, Kaloupek DG. Imaginal flooding in the treatment of post-traumatic stress disorder. J Consult Clin Psychol 1982;50:138–40.

28. Shalev AY, Orr SP, Peri T, Schreiber S, Pitman RK. Physiologic responses to loud tones in Israeli patients with post-traumatic stress disorder. Arch Gen Psychiatry 1992;49:870–5.

29. Kolb LC. Neurophysiological hypothesis explaining posttraumatic stress disorder. Am J Psychiatry 1987;144:989–95.

30. Shalev AY, Rogel-Fuchs Y. Psychophysiology of PTSD: from sulfur fumes to behavioral genetics. J Ment Nerv Dis [In press].

31. Davis M. The mammalian startle response. In: Eaton RC, ed. Neural mechanisms of startle behavior. New York: Plenum Press, 1984.

32. Davis M. Pharmacological and anatomical analysis of fear conditioning using the fear-potentiated startle paradigm. Behav Neurosci 1986;100:814–24.

33. Shalev AY, Orr SP, Peri T, Schreiber S, Pitman RK. Physiologic responses to loud tones in Israeli patients with post traumatic stress disorder. Arch Gen Psychiatry 1993;49:870–5.

34. Ornitz EM, Pynoos RS. Startle modulation in children with post traumatic stress disorder. Am J Psychiatry 1989;146:866–70.

35. Butler RW, Braff DL, Rausch JL, Jenkins MA, Sprock J, Geyer MA. Physiological evidence of exaggerated startle response in a subgroup of Vietnam veterans with combat-related PTSD. Am J Psychiatry 1990;147:1308–12.

36. Ross RJ, Ball WA, Cohen ME. Habituation of the startle response in post traumatic stress disorder. J Neuropsychiatry 1989;1:305–7.

37. Axelrod J, Reisine TD. Stress hormones, their interaction and regulation. Science 1984;224:452–9.

38. Dunn AJ, Berridge CW. Corticoptropin-releasing factor administration elicits stresslike activation of cerebral catecholamine systems. Pharmacol Biochem Behav 1987;27:685–91.

39. Valentino RJ, Foote SL. Corticotropin releasing hormone increases tonic, but not sensory-evoked activity of noradrenergic locus coeruleus in unanesthetized rats. J Neurosci 1988;8:1016–25.

40. Munck A, Guyre PM, Holbrook NJ. Physiological functions of glucocorticoids in stress and their relation to pharmacological actions. Endocr Rev 1984;93:9779–83.

41. Bohus B, DeWied D. Pituitary-adrenal system hormones and adaptive behavior. In: Chester-Jones I, Henderson IW, eds. General, comparative, and clinical endocrinology of the adrenal cortex, vol 3. New York: Academic Press, 1978.

42. Yehuda R, Southwick SM, Mason JW, Giller EL. Interactions of the hypothalamic-pituitary adrenal axis and the catecholaminergic system in posttraumatic stress disorder. In: Giller EL, ed. Biological assessment and treatment of PTSD. Washington, DC: American Psychiatric Press, 1990.

43. Meaney MJ, Aitken DH, Viau V, Sharma S, Sarieau A. Neonatal handling alters adrenocortical negative feedback sensitivity and hippocampal type II glucocorticoid binding in the rat. Neuroendocrinology 1989;50:597–604.

44. Sapolsky R, Krey L, McEwen BS. Stress down-regulates corticosterone receptors in a site specific manner in the brain. Endocrinology 1984;114:287–92.

45. Yehuda R, Giller EL, Southwick SM, Lowy MT, Mason JW. Hypothalmic-pituitary-adrenal dysfunction in posttraumatic stress disorder. Biol Psychiatry 1991;30:1031–48.

46. van der Kolk BA, Greenberg MS, Boyd H, Krystal JH. Inescapable shock, neurotransmitters and addiction to trauma: towards a psychobiology of post traumatic stress. Biol Psychiatry 1985;20:314–25.

47. Krystal JH, Kosten TR, Southwick S, Mason JW, Perry BD, Giller EL. Neurobiological aspects of PTSD: review of clinical and preclinical studies. Behav Ther 1989;20:177–98.

48. Kosten TR, Mason JW, Giller EL, Ostroff RB, Harkness L. Sustained urinary norepinephrine and epinephrine elevation in PTSD. Psychoneuroendocrinology 1987;12:13–20.

49. Pitman RK, Orr SP. Twenty-four hour urinary cortisol and cathecholamine excretion in combat-related post-traumatic stress disorder. Biol Psychiatry 1990;27:245–7.

50. Perry BD, Giller EL, Southwick SM. Altered plasma alpha-2 adrenergic receptor affinity states in PTSD. Am J Psychiatry 1987;144:1511–2.

51. Lerer B, Bleich A, Kotler M. Post traumatic stress disorder in Israeli combat veterans: effect of phenylzine treatment. Arch Gen Psychiatry 1987;44:976–81.

52. Southwick SM, Krystal JH, Morgan A, Johnson D, Nagy L, Nicolaou A, et al. Abnormal noradrenergic function in post traumatic stress disorder. Arch Gen Psychiatry 1993;50:266–74.

53. Mason J, Giller EL, Kosten TR. Elevated norepinephrine/cortisol ratio in PTSD. J Ment Nerv Dis 1988;176:498–502.

54. Yehuda R, Lowy MT, Southwick SM. Lymphocyte glucortoid receptor number in posttraumatic stress disorder. Am J Psychiatry 1991;148:499–504.

55. Valzelli L. Serotonergic inhibitory control of experimental aggression. Psychopharmacol Res Commun 1982;12:1–13.

56. Brown GL, Ballenger JC, Minichiello MD, Goodwin FK. Human aggression and its relationship to cerebrospinal fluid 5-hydroxy-indolacetic acid, 3-methoxy-4-hydroxy-phenyl-glycol, and homovannilic acid. In: Sandler M, ed. Psychopharmacology of aggression. New York: Raven Press, 1979.

57. Mann JD. Psychobiologic predictors of suicide. J Clin Psychiatry 1987;48:39–43.

58. Coccaro EF, Siever LJ, Klar HM, Maurer G. Serotonergic studies in patients with affective and personality disorders. Arch Gen Psychiatry 1989;46:587–98.

59. Green AH. Self-destructive behavior in battered children. Am J Psychiatry 1978;135:579–82.

60. van der Kolk BA, Perry JC, Herman JL. Childhood origins of self-destructive behavior. Am J Psychiatry 1991;148:1665–71.

61. Lewis DO. From abuse to violence: psychophysiological consequences of maltreatment. J Am Acad Child Adolesc Psychiatry 1992;31:383–91.

62. Gerson SC, Baldessarini RJ. Motor effects of serotonin in the central nervous system. Life Sci 1980;27:1435–51.

63. Dupue RA, Spoont MR. Conceptualizing a serotonin trait: a behavioral model of constraint. Ann NY Acad Sci 1989;12:47–62.

64. Jenike MA, Baer L, Summergrad P, Minichiello WE, Holland A, Seymour K. Sertroline in obsessive-compulsive disorder: a double blind study. Am J Psychiatry 1990;147:923–8.

65. van der Kolk BA, Dreyfuss D, Michaels M, Saxe G, Berkowitz R. Fluoxetine in post traumatic stress disorder. J Clin Psychiatry [In press].

66. van der Kolk BA, Saporta J. The biological response to psychic trauma: mechanisms and treatment of intrusion and numbing. Anxiety Res 1991;4:199–212.

67. Akil H, Watson SJ, Young E. Endogenous opioids: biology and function. Annu Rev Neurosci 1983;7:223–55.

68. van der Kolk BA, Greenberg MS, Orr SP, Pitman RK. Endogenous opioids and stress induced analgesia in post traumatic stress disorder. Psychopharmacol Bull 1989;25:108–12.

69. Pitman RK, van der Kolk BA, Orr SP, Greenberg MS. Naloxone reversible stress induced analgesia in post traumatic stress disorder. Arch Gen Psychiatry 1990;47:541–7.

70. Siegfried B, Frischknecht HR, Nunez de Souza R. An ethological model for the study of activation and interaction of pain, memory, and defensive systems in the attacked mouse: role of endogenous opoids. Neurosci Biobehav Rev 1990;14:481–90.

71. Beecher HK. Pain in men wounded in battle. Ann Surg 1946;123:96–105.

72. Bowlby J. Attachment and loss; vol 1. New York: Basic Books, 1969.

73. Cicchetti D. The emergence of developmental psychopathology. Child Dev 1985;55:1–7.

74. Terr LC. Childhood traumas: an outline and overview. Am J Psychiatry 1991;148:10–20.

75. Cole PM, Putnam FW. Effect of incest on self and social functioning: a developmental psychopathology perspective. J Consult Clin Psychol 1991;60:174–84.

76. van der Kolk BA. The trauma spectrum: the interaction of biological and social events in the genesis of the trauma response. J Traum Stress 1988;1:273–90.

77. Herman JL. Complex PTSD: a syndrome in survivors of prolonged and repeated trauma. J Traum Stress 1992;5:377–91.

78. van der Kolk BA, Roth S, Pelcovitz D. Field trials for DSM IV, post traumatic stress disorder II: disorders of extreme stress. Washington, DC: American Psychiatric Association, 1992.

79. Reite M, Field T, eds. The psychobiology of attachment and separation. Orlando, Florida: Academic Press, 1985.

80. Calvin WH. The cerebral symphony. New York: Bantam Books, 1990.

81. Janet P. Les medications psychologiques. Paris: Felix Alcan, 1919/1925.

82. van der Kolk BA, Blitz R, Burr W, Hartmann E. Nightmares and trauma. Am J Psychiatry 1984;141:187–90.

83. Piaget J. Play, dreams, and imitation in childhood. New York: W W Norton, 1962.

84. Kilpatrick DG, Veronen LJ, Best CL. Factors predicting psychological distress in rape victims. In: Figley C, ed. Trauma and its wake. New York: Brunner/Mazel, 1985.

85. Hilberman E, Munson M. Sixty battered women. Victimology 1978;2:460–1.

86. Green A. Child maltreatment. New York: Aronson, 1980.

87. Kraemer GW. Effects of differences in early social experiences on primate neurobiological-behavioral development. In: Reite M, Field T, eds. The psychobiology of attachment and separation. Orlando, Florida: Academic Press, 1985.

88. Mitchell D, Osborne EW, O'Boyle MW. Habituation under stress: shocked mice show non-associative learning in a T-maze. Behav Neurol Biol 1985;43:212–7.

89. Solomon Z, Garb R, Bleich A, Grupper D. Reactivation of combat-related post-traumatic stress disorder. Am J Psychiatry 1985;144:51–5.

90. Phillips AG, LePiane FG. Disruption of conditioned taste aversion in the rat by stimulation of amygdala: a conditioning effect, not amnesia. J Comp Physiol Psychol 1980;94:664–74.

91. Rawlins JNP. Associative and non-associative mechanisms in the development of tolerance for stress: the problem of state dependent learning. In: Levine S, Ursin H, eds. Coping and health. New York: Plenum Press, 1980.

92. Putnam FW. Diagnosis and treatment of multiple personality disorder. New York: Guilford Press, 1989.

93. Rainey JM, Aleem A, Ortiz A, Yaragani V, Pohl R, Berchow R. Laboratory procedure for the inducement of flashbacks. Am J Psychiatry 1987;144:1317–9.

94. Charney DS, Deutch AY, Krystal JH, Southwick SM, Davis M. Psychobiologic mechanisms of post traumatic stress disorder. Arch Gen Psychiatry 1993;50:294–305.

95. McGaugh JL, Weinberger NM, Lynch G, Granger RH. Neural mechanisms of learning and memory: cells, systems and computations. Naval Res Rev 1985;37:15–29.

96. McGaugh JL. Involvement of hormonal and neuromodulatory systems in the regulation of memory storage. Ann Rev Neurosci 1989;2:255–87.

97. LeDoux JE. Information flow from sensation to emotion: plasticity of the neural computation of stimulus value. In: Gabriel M, Morre J, eds. Learning computational neuroscience: foundations of adaptive networks. Cambridge, Massachusetts: MIT Press, 1990.

98. Adamec RE. Normal and abnormal limbic system mechanisms of emotive biasing. In: Livingston KE, Hornykiewicz O, eds. Limbic mechanisms. New York, Plenum Press, 1978.

99. Zager EL, Black PM. Neuropeptides in human memory and learning processes. Neurosurgery 1985;17:355–69.

100. Moleman N, van der Hart O, van der Kolk BA. The partus stress reaction: a neglected etiological factor in post-partum psychiatric disorders. J Nerv Ment Dis 1992;180:271–2.

101. MacLean PD. Brain evolution relating to family, play, and the separation call. Arch Gen Psychiatry 1985;42:405–17.

102. Papez JW. A proposed mechanism of emotion. Arch Neurol Psychiatry 1937;38:725–43.

103. Saxe GN, Vasile RG, Hill TC, Bloomingdale K, van der Kolk BA. SPECT imaging and multiple personality disorder. J Nerv Ment Dis 1992;180:662–3.

104. Bremner JD, Seibyl JP, Scott TM. Depressed hippocampal volume in posttraumatic stress disorder [New Research Abstract 155]. Proceedings of the 145th Annual Meeting of the American Psychiatric Association, Washington, DC, May 1992.

105. Teicher MH, Glod CA, Surrey J, Swett C. Early childhood abuse and limbic system ratings in adult psychiatric outpatients. J Neuropsychiatry Clin Neurosci [In press].

106. LeDoux J. Mind and brain: dialogues in cognitive neuroscience. New York: Cambridge University Press, 1986.

107. Adamec RE. Partial kindling of the ventral hippocampus: identification of changes in limbic physiology which accompany changes in feline aggression and defense. Physiol Behav 1991;49:443–54.

108. O'Keefe J, Bouma H. Complex sensory properties of certain amygdala units in the freely moving cat. Exp Neurol 1969;23: 384–98.

109. Squire LR, Zola-Morgan S. The medial temporal lobe memory system. Science 1991;253:2380–6.

110. Gray J. The neuropsychology of anxiety. An inquiry into the functions of the septo-hippocampal system. London: Oxford University Press, 1982.

111. Altman J, Brunner RL, Bayer SA. The hippocampus and behavioral maturation. Behav Biol 1973;8:557–96.

112. O'Keefe J, Nadel L. The hippocampus as a cognitive map. Oxford: Clarendon Press, 1978.

113. Jacobs WJ, Nadel L. Stress-induced recovery of fears and phobias. Psychol Rev 1985;92:512–31.

114. Schacter DL, Moscovitch M. Infants, amnesics, and dissociable memory systems. In: Moscovitch M, ed. Infant memory. New York: Plenum Press, 1984.

115. Nadel L, Zola-Morgan S. Infantile amnesia: a neurobiological perspective. In: Moscovitch M, ed. Infant memory. New York: Plenum Press, 1984.

116. Sapolsky RM, Hideo U, Rebert CS, Finch CE. Hippocampal damage associated with prolonged glucocorticoid exposure in primates. J Neurosci 1990;10:2897–902.

117. Pfaff DW, Silva MT, Weiss JM. Telemetered recording of hormone effects on hippocampal neurons. Science 1971;172: 394–5.

118. LeDoux JE, Romanski L, Xagoraris A. Indelibility of subcortical emotional memories. J Cogn Neurosci 1991;1:238–43.

119. Adamec RE, Stark-Adamec C, Livingston KE. The development of predatory aggression and defense in the domestic cat. Neural Biol 1980;30:389–447.

120. Nijenhuis F. Multiple personality disorder, hormones, and memory. Paper presented at the International Conference on Multiple Personality Disorder, Chicago, Illinois, November 5, 1991.

121. Shalev A, Rogel-Fuchs Y, Pitman R. Conditioned fear and psychological trauma. Biol Psychiatry 1992;31:863–5.

122. Frank JB, Kosten TR, Giller EL, Dan E. A randomized clinical trial of phenelzine and imipramine in PTSD. Am J Psychiatry 1988;145:1289–91.

123. Bleich A, Siegel B, Garb B, Kottler A, Lerer B. PTSD following combat exposure: clinical features and pharmacological management. Br J Psychiatry 1987;149:365–9.

124. Davidson JRT, Nemeroff CB. Pharmacotherapy in PTSD: historical and clinical considerations and future directions. Psychopharmacol Bull 1989;25:422–5.

125. Reist C, Kauffman CD, Haier RJ. A controlled trial of desipramine in 18 men with post-traumatic stress disorder. Am J Psychiatry 1989;146:513–6.

126. Davidson J, Kudler H, Smith R. Treatment of post-traumatic stress disorder with amitriptyline and placebo. Arch Gen Psychiatry 1990;47:259–66.

127. van der Kolk BA. Drug treatment of post traumatic stress disorder. J Affective Disord 1987;13:203–13.

128. Falcon S, Ryan C, Chamberlain K. Tricyclics: possible treatment for posttraumatic stress disorder. J Clin Psychiatry 1985;46:385–9.

129. Hogben GL, Cornfield RB. Treatment of traumatic war neurosis with phenelzine. Arch Gen Psychiatry 1981;38:440–5.

130. Kolb LC, Burris BC, Griffiths S. Propranolol and clonidine in the treatment of post traumatic stress disorders of war. In: van der Kolk BA, ed. Post traumatic stress disorder: psychological and biological sequelae. Washington, DC: American Psychiatric Press, 1984.

131. Lipper S, Davidson JRT, Grady TA, Edinger JD, Hammett EB, Mahorney SL, et al. Preliminary study of carbamazepine in post-traumatic stress disorder. Psychosomatics 1986;27:849–54.

132. Famularo R, Kinscherff R, Fenton T. Propanolol treatment for childhood posttraumatic stress disorder, acute type: a pilot study. Am J Dis Child 1988;142:1244–7.

133. Giral P, Martin P, Soubrie P. Reversal of helpless behavior in rats by putative 5-HT$_{1A}$ agonists. Biol Psychiatry 1988;23: 237–42.

134. Krystal J. Neurobiological mechanisms of dissociation. Paper presented at the American Psychiatric Association Meeting, San Francisco, California, May 1993.