

The Body Keeps The Score:

Memory & the Evolving Psychobiology of Post Traumatic Stress

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Background

For more than a century, ever since people's responses to overwhelming experiences were first systematically explored, it has been noted that the psychological effects of trauma are 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 as 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 that had no bearing on current experience. He noted that victims had trouble learning from experience: unable to put the trauma behind them, their energies were absorbed by keeping their emotions under control at the expense of paying attention to current exigencies. They became fixated upon the past, in some cases by being obsessed with the trauma, but more often by behaving and feeling like they were traumatized over and over again without being able to locate the origins of these feelings (2,3).

Freud also considered the tendency to stay 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"(4). Pavlov's investigations continued the tradition of explaining the effects of trauma as the result of lasting physiological alterations. He, and others employing his paradigm, coined the term "defensive reaction" for a cluster of innate reflexive responses to environmental threat (5). Many studies have shown how

the response to potent environmental stimuli (unconditional stimuli-US) becomes a conditioned reaction. After repeated aversive stimulation, intrinsically non-threatening cues associated with the trauma (conditional stimuli-CS) become capable of eliciting the defensive reaction by themselves (conditional response-CR). A rape victim may respond to conditioned stimuli, such as the approach by 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 from "traumatic neuroses" develop an enduring vigilance for and sensitivity to environmental threat, and stated that "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) catalogue the physical symptoms of soldiers in acute posttraumatic states: flexor changes in posture, hyperkinesia, "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 can understand them as the result of stimulation of biological systems, particularly of ascending amine projections. Contemporary research on the biology of PTSD, generally uninformed by this earlier research, confirms that there are persistent and profound alterations in stress hormones secretion and memory processing in people with PTSD.

The Symptomatology of PTSD

Starting with Kardiner(6), and closely followed by Lindemann (8), a vast literature on combat trauma, crimes, rape, kidnapping, natural disasters, accidents and imprisonment have shown that the trauma response is bimodal: hypermnesia, hyper-reactivity to stimuli and traumatic reexperiencing coexist with psychic numbing, avoidance, amnesia and anhedonia (9,10,11,12). These responses to extreme experiences are so consistent across traumatic stimuli that this biphasic reaction appears to be the normative response to any overwhelming and uncontrollable experience. In many people who have undergone severe stress, the post-traumatic response fades over time, while it persists in others. Much work remains to be done to spell out issues of resilience and vulnerability, but magnitude of exposure,

prior trauma, and social support appear to be the three most significant predictors for developing 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; on a psychobiological level, by emotional numbing, which extends to both trauma-related, and everyday experience (15). Thus, people with chronic PTSD tend to suffer from numbing of responsiveness to the environment, punctuated by intermittent hyperarousal in response to conditional traumatic stimuli. However, as Pitman has pointed out (16), 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. Thus, people 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 explain the observation that traumatized people lose the capacity to utilize affect states as signals (18). Instead of using feelings as cues to attend to incoming information, in people with PTSD arousal is likely to precipitate flight or fight reactions (19). Thus, they are prone to go immediately from stimulus to response without making the necessary psychological assessment of the meaning of what is going on. 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 demonstrated on two different levels: 1) in response to specific reminders of the trauma and 2) in response to intense, but neutral stimuli, such as acoustic startle. The first paradigm implies heightened physiological arousal to sounds, images, and thoughts related to specific traumatic incidents. A large number of studies have confirmed that traumatized individuals respond to such stimuli with significant conditioned autonomic reactions, such as heart rate, skin conductance and blood pressure (20,21,22,23, 24,25). The highly elevated physiological responses that accompany 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 generally been understood in the light of Peter 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 that make up these

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 et al (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 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.

Despite the fact that an abnormal acoustic startle response (ASR) has been seen as a cardinal feature of the trauma response for over half a century, systematic explorations of the ASR in PTSD have just begun. The ASR consists of 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 supraspinal level (32). Habituation of the ASR in normals occurs after 3 to 5 presentations (30).

Several studies have demonstrated abnormalities in habituation to the ASR in PTSD (33,34,35,36). Shalev et al (33) found a failure to habituate both to CNS and ANS-mediated responses to ASR in 93% of the PTSD group, compared with 22% of the control subjects.

Interestingly, people who previously met criteria for PTSD, but no longer do so now, continue to show failure of habituation of the ASR (van der Kolk et al, unpublished data; Pitman et al, unpublished data), which raises the question whether abnormal habituation to acoustic startle is a marker of, or a vulnerability factor for developing 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 to properly integrate memories of the trauma and, instead, to get mired in a continuous reliving of the past, is mirrored physiologically in the misinterpretation of innocuous stimuli, such as the ASR, as potential threats.

The Hormonal Stress Response & the Psychobiology of PTSD

Post Traumatic Stress Disorder develops following exposure to events that are intensely distressing. Intense stress is accompanied by the release of endogenous, stress-responsive neurohormones, such as cortisol, epinephrine and norepinephrine (NE), vasopressin, oxytocin and endogenous opioids. These stress hormones help the organism mobilize the required energy to deal with the stress, 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. NE is secreted by the Locus Coeruleus(LC) and distributed through much of the CNS, particularly the neocortex and the limbic system, where it plays a role in memory consolidation and helps initiate fight/ flight behaviors.

Adrenocorticotropin (ACTH) is released from the anterior pituitary, and activates a cascade of reactions, eventuating in release of glucocorticoids from the adrenals. 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 NE neurons also increase CRF concentrations in the LC (38), while intracerebral ventricular infusion of CRF increases NE in the forebrain (39). Glucocorticoids and catecholamines may modulate each other's effects: in acute stress, cortisol helps regulate stress hormone release 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, while increased arousal in the presence of low glucocorticoid levels may promote undifferentiated fight or flight reactions (42).

While acute stress activates 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 in chronically stressed organisms, (43), 2) decreased glucocorticoid secretion in response to subsequent stress (42), and 3) increased concentration of glucocorticoid receptors in the hippocampus (44). Yehuda has suggested that increased concentration of glucocorticoid receptors could facilitate a stronger glucocorticoid negative feedback, resulting in a more sensitive HPA axis and a faster recovery from acute stress (45).

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 it interferes with how it copes with subsequent acute stress (45).

Neuroendocrine Abnormalities in PTSD

Since there is an extensive animal literature on the effects of inescapable stress on the biological stress response of other species, such as monkeys and rats, much of the biological research on people with PTSD has focussed on testing the applicability of those research findings to people with PTSD (46,47). People with PTSD, like chronically and inescapably shocked animals, seem to suffer from a persistent activation of the biological stress response upon exposure to stimuli reminiscent of the trauma.

1) Catecholamines. Neuroendocrine studies of Vietnam veterans with PTSD have found good evidence for chronically increased sympathetic nervous system activity in PTSD. One study (48) found elevated 24h excretions of urinary NE and epinephrine in PTSD combat veterans compared with patients with other psychiatric diagnoses. While Pitman & Orr (49) did not replicate these findings in 20 veterans and 15 combat controls, the mean urinary NE excretion values in their combat controls (58.0 ug/day) were substantially higher than those previously reported in normal populations. The expected compensatory downregulation of adrenergic receptors in response to increased levels of norepinephrine was confirmed by a study that found decreased platelet alpha-2 adrenergic receptors in combat veterans with PTSD, compared with normal controls (50). Another study also found an abnormally low alpha-2 adrenergic receptor-mediated adenylate cyclase signal transduction (51). In a recent study Southwick et al (52) used yohimbine injections (0.4 mg/kg), which activate noradrenergic neurons by blocking the alpha-2 auto-receptor, 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 MHPG than controls. Yohimbine precipitated significant increases in all PTSD symptoms.

2) Corticosteroids. Two studies have shown that veterans with PTSD have low urinary cortisol excretion, even when they have comorbid major depressive disorder (42,53). One study failed to replicate this finding (49). In a series of studies, Yehuda et al (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 (54) also has reported the results of an unpublished study by Heidi Resnick, in which acute cortisol response to trauma was studied from blood samples from 20 acute rape victims. Three months later, a prior trauma history was taken, and the subjects were evaluated for the

presence of PTSD. Victims with a prior history of sexual abuse were significantly more likely to have developed PTSD three months following the rape than rape victims who did not develop PTSD. Cortisol levels shortly after the rape were correlated with histories of prior assaults: the mean initial cortisol level of individuals with a prior assault history was 15 ug/dl compared to 30 ug/dl in individuals without. These findings can be interpreted to mean either that prior exposure to traumatic events result in a blunted cortisol response to subsequent trauma, or in a quicker return of cortisol to baseline following stress. The fact that Yehuda et al (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.

3) Serotonin. While the role of serotonin in PTSD has not been systematically investigated, both the fact that inescapably shocked animals develop decreased CNS serotonin levels (55), and that serotonin re-uptake 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 repeatedly been correlated with impulsivity and aggression (56,57,58). The literature tends to readily assume that these relationships are based on genetic traits. However, studies of impulsive, aggressive and suicidal patients seem to find at least as robust an association between those behaviors and histories of childhood trauma (e.g. 59,60,61). It is likely that both temperament and experience affect relative CNS serotonin levels (12). Low serotonin in animals is also related to an inability to modulate arousal, as exemplified by an exaggerated startle (62,63), and increased arousal in response to novel stimuli, handling, or pain (63). The behavioral effects of serotonin depletion on animals is characterized by hyperirritability, hyperexcitability, and 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 re-uptake inhibitors have been found to be the most effective pharmacological treatment of both obsessive thinking in people with OCD (64), and of involuntary preoccupation with traumatic memories in people with PTSD (65,66). It is likely that serotonin 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.

4). Endogenous opioids. Stress induced analgesia (SIA) has been described in experimental animals following 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 both by termination of the stressful stimulus or by naloxone injections. Stimulated by the findings that fear activates the secretion of endogenous opioid peptides, and that SIA can become conditioned to subsequent stressors and to previously neutral events associated with the noxious stimulus, we tested the hypothesis that in people with PTSD, re-exposure 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 two decades after the original trauma, people with PTSD developed opioid-mediated analgesia 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 the emotional response to the traumatic stimulus.

Endogenous Opiates & Stress Induced Analgesia: Possible Implications for Affective Function

When young animals are isolated, and older ones attacked, they respond initially with aggression (hyperarousal- fight- protest), and, if that does not produce the required results, with withdrawal (numbing-flight-despair). Fear-induced attack or protest patterns in the young serve 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 due to the release of endogenous opioids(68,69).

Endogenous opioids, which inhibit pain and reduce panic, are secreted after prolonged exposure to severe stress. Siegfried et al (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 NE 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 not to remember situations of overwhelming stress (and which thus will also keep them

from learning from experience). We have proposed that the dissociative reactions in people in response to trauma may be analogous to this complex of behaviors that occur in animals after prolonged exposure to severe uncontrollable stress (68).

Developmental Level Affects the Psychobiological Effects of Trauma

While most studies on PTSD have been done on adults, particularly on war veterans, in recent years a small prospective literature is emerging that documents 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.72,73,74). In addition to the reactions to discrete, one time, traumatic incidents documented in these studies, intrafamilial abuse is increasingly recognized to produce complex post-traumatic syndromes (75), which 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 these this conglomeration of symptoms tended to occur together and that the severity of this syndrome was proportional to the age of onset of the trauma and its duration (78).

While 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 prospective, but as yet unpublished, studies (personal communications, 1991,1992,1993) are showing major neuroendocrine disturbances in sexually abused girls compared with normals. Research on the psychobiology of childhood trauma can be profitably informed by the vast literature on the psychobiological effects of trauma and deprivation in non-human primates (12,79).

Trauma & Memory: The Flexibility of Memory & the Engraving of Trauma

One hundred years ago, Pierre Janet (1) suggested that the most fundamental of mental activities is 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 be distorted both by prior experience, and by the emotional state at the time of recall(3). PTSD, by definition, is accompanied by memory disturbances, consisting 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 non-declarative memory, the memory system that controls conditioned emotional responses, skills and habits, and sensorimotor sensations related to experience. There now is 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).

In the beginning of this century Janet already 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" (81). Clinicians and researchers dealing with traumatized patients have repeatedly made the observation 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".

Traumatic memories are state dependent.

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 the way other people do. Under pressure, they may feel, or act as if they were traumatized all over again. Thus, high states of arousal seem to selectively promote retrieval of traumatic memories, sensory information, or behaviors associated with prior 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 his colleagues (88) found that the relative degree of arousal interacts with prior 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 persevere in familiar behavior, regardless of the outcome. Under ordinary circumstances, an animal will choose the most pleasant of two alternatives. When hyperaroused, it will seek whatever is familiar, regardless of the intrinsic rewards. Thus, animals who 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 concluded that this perseveration is nonassociative, i.e. uncoupled from the usual reward systems.

In people, analogous phenomena have been documented: 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 people 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 amnesic 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 prior traumatic experiences in people with PTSD, but not in controls. 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.

Trauma, neurohormones and memory consolidation.

When people are under severe stress, they secrete endogenous stress hormones that affect the strength of memory consolidation. Based on animal models it has been widely assumed (3,46,94) that massive secretion of neurohormones at the time of the trauma plays a role in the long term potentiation (LTP) (and thus, the over- consolidation) of traumatic memories. Mammals seem 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 evaluate the importance of subsequent sensory input according to the relative strength of associated memory traces. This phenomenon appears to be largely mediated by NE input 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. While norepinephrine (NE) seems to be the principal hormone involved in producing LTP, other neurohormones secreted under particular stressful circumstances, such as endorphins and oxytocin, actually inhibit memory consolidation (99). The role of NE in memory consolidation has been shown to have an inverted U-shaped function (95,96): both very low and very high levels of CNS NE activity interfere with memory storage. Excessive NE release at the time of the trauma, as well as the release of other neurohormones, such as endogenous opioids, oxytocin and vasopressin, are likely to play a role in creating the hypermnesias and the amnesias that are a quintessential part of PTSD (9,10). It is of interest that childbirth, which can be extraordinarily stressful, almost never seems to result in post traumatic problems (100). Oxytocin may play a protective role that prevents the overconsolidation of memories surrounding childbirth.

Physiological arousal in general can trigger trauma-related memories, while, conversely, trauma-related memories precipitate generalized physiological arousal. It is likely that the frequent re-living of a traumatic event in flashbacks or nightmares cause a re-release of stress hormones which further kindle 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 appear so deeply engraved that Pitman and Orr (17) have called it "the Black Hole" in the mental life of the PTSD patient, that attracts all associations to it, and saps current life of its significance.

Memory, Trauma & 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 survival of the species (101), and that 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 whence they are distributed to the cortex (setting up a "stream of thought"), to the basal ganglia (setting up a "stream of movement") and to the limbic system where they set up a "stream of emotions"(102), that determine the emotional significance of the sensory input. It appears that most processing of sensory input occurs outside of conscious awareness, and only novel, significant or threatening information is selectively passed on to the neocortex for further attention. Since people with PTSD appear to over-interpret sensory input as a recurrence of past trauma and since 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 (also see 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 (101,106,107,108). 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 septo-hippocampal system, which anatomically 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 necessary for explicit or declarative memory (109). The hippocampus is thought 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, with reward, punishment, novelty or non-reward (107,110). The hippocampus is also implicated in playing a role in the inhibition of exploratory behavior and in obsessional thinking, while hippocampal damage is associated with hyper-responsiveness to environmental stimuli (111,112).

The slow maturation of the hippocampus, which is not fully myelinated till after the third or fourth year of life, is seen as the cause of infantile amnesia (113,114). In contrast, it is thought that the memory system that subserves 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 modes of 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). A variety of external and internal stimuli, such as stress induced corticosterone production (117), decreases

hippocampal activity. However, even when stress interferes with hippocampally mediated memory storage and categorization, it is likely that some mental representation of the experience is laid down by means of a system that records affective experience, but that has no capacity for symbolic processing and placement in space and time (figure 2).

Decreased hippocampal functioning causes behavioral disinhibition, possibly by stimulating incoming stimuli to be interpreted in the direction of "emergency" (fight/flight) responses. The neurotransmitter serotonin plays a crucial role in the capacity of the septo-hippocampal 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. In mature animals one-time intense stimulation of the amygdala 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 et al (119) have shown that, following growth in amplitude of amygdala and hippocampal seizure activity, permanent changes in limbic physiology cause a lasting changes in defensiveness and in predatory aggression. Pre-existing "personality" played a significant role in the behavioral effects of amygdala stimulation in cats: animals that are temperamentally insensitive to threat and prone to attack tend become more aggressive, while in highly defensive animals different pathways were activated, increasing behavioral inhibition (119).

In a series of experiments, LeDoux has utilized repeated electrical stimulation of the amygdala to produce conditioned fear responses. He found that cortical lesions prevent their extinction. This led him to conclude that, once formed, the subcortical traces of the conditioned fear response are indelible, and that "emotional memory may be forever" (118). In 1987, Lawrence Kolb (29) postulated that patients with PTSD suffer from impaired cortical control over 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 septo-hippocampal 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 nightmares), with aging, and after exposure to strong reminders of the traumatic past. It is conceivable that traumatic memories then could emerge, not in the distorted fashion of ordinary recall, but as affect states, somatic sensations or as visual images (nightmares [81] or flashbacks [52]) that are timeless and unmodified by further experience.

Psychopharmacological Treatment

The goal of treatment of 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 distinguished 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. While 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, up until recently, only medications which seem to be of limited therapeutic usefulness have been the subject of adequate scientific scrutiny. While the only published double blind studies of medications in the treatment of PTSD have been tricyclic antidepressants and MAO Inhibitors (122,123,124), it is sometimes assumed that they therefore also are the most effective. Three double-blind trials of tricyclic antidepressants have been published (122,124,125), two of which demonstrated modest improvement in PTSD symptoms. While 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), monoamine oxidase inhibitors (122,129) lithium carbonate (127), beta adrenergic blockers and clonidine (130), carbamazepine (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 inhibition of locus coeruleus noradrenergic activity with clonidine and the beta adrenergic blockers (130,132), or by increasing the inhibitory effect of the gaba-ergic system with gaba-ergic agonists

(the benzodiazepines). During the past two years a number of case reports and open clinical trials of fluoxetine were followed by our double blind study of 64 PTSD subjects 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 whole spectrum of PTSD symptoms. It also acted more rapidly than the tricyclics. The fact that fluoxetine has proven to be such an effective treatment for PTSD supports a larger role of the serotonergic system in PTSD (66). Rorschach tests administered by blind scorers revealed that subjects on fluoxetine became able to take distance from the emotional impact of incoming stimuli and to become able to utilize cognition to harness the emotional responses to unstructured visual stimuli (van der Kolk et al, unpublished).

While the subjects improved clinically, their startle habituation got worse (van der Kolk et al, unpublished). 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 (NMDA) receptor and of glutamate in PTSD (134), opening up potential new avenues for the psychopharmacological treatment of PTSD.

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 Psychiat* 1989;146:1530-1540.
- 3** van der Kolk BA & van der Hart O. The intrusive past: The flexibility of memory and the engraving of trauma. *American Imago*, 1991;48:425-454.
- 4** Freud S. *Introduction to Psychoanalysis and the War Neuroses*. Standard Edition 17: 207-210. Translated and edited by Strachey. London, Hogarth Press, 1919/1954.
- 5** Pavlov IP. Edited and translated by GV Anrep *Conditioned reflexes: An Investigation of the Physiological Activity of the Cerebral Cortex* 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; 101:141-148.

- 9** American Psychiatric Association. Diagnostic and statistical manual of mental disorders (3rd edition, revised). Washington, D.C.: American Psychiatric Association, 1987.
- 10** American Psychiatric Association. Diagnostic and statistical manual of mental disorders (4th edition). Washington, DC: American Psychiatric Association, 1993 (in press).
- 11** Horowitz M. Stress Response Syndromes, second edition. 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; 176:30-39.
- 15** Litz BT, Keane TM. Information processing in anxiety disorders: Application to the understanding of post-traumatic stress disorder. Clin Psychol Rev 1989; 9:243-257.
- 16** Pitman R, Orr S, Shalev A. Once bitten twice shy: beyond the conditioning model of PTSD. Biol Psychiat 1993,33:145-146.
- 17** Pitman R & Orr S: The Black Hole of Trauma. Biol Psychiat 1990; 26: 221-223.
- 18** Krystal, H. Trauma & Affects. Psychoanalytic Study of the Child, 1978; 33: 81-116.
- 19** Strian F, Klicpera C. Die Bedeutung psychoautonomische Reaktionen im Entstehung und Persistenz von Angstzustanden. Nervenarzt 1978;49:576-583.
- 20** van der Kolk BA, Ducey CP. The psychological processing of traumatic experience: Rorschach patterns in PTSD. J Traum Stress 1989; 2:259-274.
- 21** Dobbs D, Wilson WP. Observations on the persistence of traumatic war neurosis. J Ment Nerv Dis 1960;21:40-46.
- 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. Psychiatric Annals 1982; 12:979-987.
- 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. Behavior Therapy 1986; 17:592- 606.

- 25** Pitman RK, Orr SP, Forgue DF, de Jong J, Claiborn JM. Psychophysiological assessment of posttraumatic stress disorder imagery in Vietnam combat veterans. *Arch Gen Psychiat* 1987;44:970-975.
- 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: 138-140.
- 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 Psych* 1992;49:870-875.
- 29** Kolb LC. Neurophysiological hypothesis explaining posttraumatic stress disorder. *Am J Psychiatry* 1987;144:989-995.
- 30** Shalev AY, Rogel-Fuchs Y. Psychophysiology of PTSD: from sulfur fumes to behavioral genetics. *J Ment Nerv Dis* 1993; In press.
- 31** Davis M. The mammalian startle response. In Eaton RC (ed): *Neural mechanisms of startle behavior*. Plenum Press New York-London, 1984.
- 32** Davis M. Pharmacological and anatomical analysis of fear conditioning using the fear-potentiated startle paradigm. *Beh Neurosci* 1986;100:814-824.
- 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 Psych* 1993; 49:870-875.
- 34** Ornitz EM, Pynoos RS. Startle modulation in children with post traumatic stress disorder. *Am J Psychiat* 1989;146:866-870.
- 35** Butler RW, Braff DL, Rausch JL. Physiological evidence of exaggerated startle response in a subgroup of Vietnam veterans with combat-related PTSD. *Am J Psychiat* 1990; 1308-1312.
- 36** Ross RJ, Ball WA, Cohen ME. Habituation of the startle response in Post Traumatic Stress Disorder. *J Neuropsychiat* 1989; 1:305-307.
- 37** Axelrod J, Neisline. Stress hormones, their interaction and regulation. *Science* 1984;224:452-459.
- 38** Dunn AJ, Berridge CW. Corticotropin-releasing factor administration elicits stresslike activation of cerebral catecholamine systems. *Pharmacol Biochem Behav* 1987;27:685-691.
- 39** Valentino RJ, Foote SL: Corticotropin releasing hormone increases tonic, but not sensory-evoked activity of noradrenergic locus coeruleus in unanesthetized rats. *J Neuroscience* 1988; 8:1016-1025.
- 40** Munck A, Guyre PM, Holbrook NJ. Physiological functions of glucocorticoids in stress and their relation to pharmacological actions. *Endocr Rev* 1984;93:9779-9783.

- 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;114:287-292.
- 45** Yehuda R, Giller EL, Southwick SM, Lowy MT, Mason JW. Hypothalamic-pituitary-adrenal dysfunction in posttraumatic stress disorder. *Biol Psychiatry* 1991c;30:1031-1048.
- 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; 20:314-325.
- 47** Krystal JH, Kosten TR, Southwick S, Mason JW, Perry BD, Giller EL. Neurobiological aspects of PTSD: review of clinical and preclinical studies. *Behavior Therapy* 1989;20:177-198.
- 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 catecholamine excretion in combat-related post-traumatic stress disorder. *Biol Psychiatry* 1990;27:245-247.
- 50** Perry BD, Giller EL, Southwick SM. Altered plasma alpha-2 adrenergic receptor affinity states in PTSD. *Am J Psychiat* 1987;144: 1511-1512.
- 51** Lerer B, Bleich A, Kotler M. Post traumatic stress disorder in Israeli combat veterans: Effect of phenylzine treatment. *Arch Gen Psychiat* 1987;44:976-981.
- 52** Southwick SM, Krystal JH, Morgan A, Johnson D, Nagy L, Nicolaou A, Henninger GR, Charney DS: Abnormal Noradrenergic function in Post Traumatic Stress Disorder. *Arch Gen Psychiat* 1993: 50: 266-274.
- 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 glucocorticoid receptor number in posttraumatic stress disorder. *Am J Psychiatry* 1991d; 148:499-504.
- 55** Valzelli L. Serotonergic inhibitory control of experimental aggression. *Psychopharmacological Research Communications* 1982; 12:1-13.
- 56** Brown, G.L., Ballenger, J.C., Minichiello, M.D. & Goodwin, F.K. Human aggression and its relationship to cerebrospinal fluid 5-hydroxy-indolacetic acid, 3-methoxy-4-hydroxy-phenyl-glycol, and homovanillic acid. In: *Psychopharmacology of Aggression*, ed. M. Sandler. New York: Raven Press, 1979.
- 57** Mann JD. Psychobiologic predictors of suicide. *J Clin Psychiatry* 1987; 48:39-43.
- 58** Coccaro, E.F., Siever, L.J., Klar, H.M., Maurer, G. Serotonergic studies in patients with affective and personality disorders. *Arch Gen Psychiat* 1989; 46:587-598.
- 59** Green AH. Self-destructive behavior in battered children. *Am J Psychiatry* 1978; 135:579-582.
- 60** van der Kolk BA, Perry JC, Herman JL. Childhood origins of self-destructive behavior. *Am J Psychiatry* 1991;148:1665-1671.
- 61** Lewis DO. From abuse to violence: psychophysiological consequences of maltreatment. *J Am Acad Child Adolesc Psychiat* 1992;31:383-391.
- 62** Gerson SC, Baldessarini RJ. Motor effects of serotonin in the central nervous system. *Life Sciences* 1980; 27:1435-1451.
- 63** Dupue RA, Spont MR. Conceptualizing a serotonin trait: a behavioral model of constraint. *Ann N. Y. Acad Sc* 1989;12:47-62.
- 64** Jenike MA, Baer L, Summergrad P, Minichiello WE, Holland A, Seymour K. Sertraline in Obsessive-Compulsive Disorder: A double blind study. *Am J Psychiatry* 1990; 147:923-928.
- 65** van der Kolk BA, Dreyfuss D, Michaels M, Saxe G, Berkowitz R. Fluoxetine in Post Traumatic Stress Disorder. *J Clin Psychiatry* 1993; (in press).
- 66** van der Kolk BA & Saporta J. The biological response to psychic trauma: mechanisms and treatment of intrusion and numbing. *Anxiety Research* 1991;4:199-212.
- 67** Akil H, Watson SJ, Young E. Endogenous opioids: Biology and function. *Annu Rev Neurosci* 1983; 7:223-255.
- 68** van der Kolk BA, Greenberg MS, Orr SP & Pitman RK. Endogenous opioids and stress induced analgesia in Post Traumatic Stress Disorder. *Psychopharm Bull* 1989;25:108-112.
- 69** Pitman RK, van der Kolk BA, Orr SP, Greenberg MS. Naloxone reversible stress induced analgesia in Post Traumatic Stress Disorder. *Arch Gen Psychiat* 1990;47:541-547.

- 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 opioids. *Neuroscience and Biobehavioral Reviews* 1990; 14:481-490.
- 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 Cons Clin Psychology* 1991; 60:174-184.
- 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; 1:273-290.
- 77** Herman JL. Complex PTSD: A syndrome in survivors of prolonged and repeated trauma. *J Traum Stress* 1992; 5:377-391.
- 78** van der Kolk BA, Roth S, Pelcovitz D. *Field trials for DSM IV, Post Traumatic Stress Disorder II: Disorders of Extreme Stress*. Washington D.C.: American Psychiatric Association, 1992.
- 79** Reite M, & Fields F (eds). *The psychobiology of attachment and separation*. Orlando, FL: Academic Press, Inc., 1985.
- 80** Calvin WH. *The Cerebral Symphony*. New York: Bantam, 1990.
- 81** Janet P. *Les Medications Psychologiques*. Three Volumes. Paris: Felix Alcan, 1919/1925.
- 82** van der Kolk BA, Blitz R, Burr W, Hartmann E. Nightmares and trauma. *Am J Psychiatry* 1984; 141:187-190.
- 83** Piaget J. *Play, Dreams, and Imitation in Childhood*. New York: W.W. Norton and Co, 1962.
- 84** Kilpatrick DG, Veronen LJ, Best CL. Factors predicting psychological distress in rape victims. In: C. Figley: *Trauma and its Wake*. N.Y.: Brunner/Mazel 1985.
- 85** Hilberman E, Munson M. Sixty battered women. *Victimology* 1978; 2:460-461.
- 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 et al, *The Psychobiology of Attachment and Separation*. Orlando, FL: 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 Neuro Biol* 1985; 43:212-217.
- 89** Solomon Z, Garb R, Bleich A, Grupper D. Reactivation of combat-related post-traumatic stress disorder. *Am J Psychiatry* 1985;144:51-55.
- 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 Psychology* 1980; 94:664-674.
- 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; 144:1317-1319.
- 94** Charney DS, Deutch AY, Krystal JH, Southwick SM, Davis M. Psychobiologic Mechanisms of Post Traumatic Stress Disorder. *Arch Gen Psychiat* 1993; 50:294-305.
- 95** McGaugh JL, Weinberger NM, Lynch G, Granger RH. (1985). Neural mechanisms of learning and memory: Cells, systems and computations. *Naval Research Reviews* 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- 287.
- 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, MA, MIT Press, 1990.
- 98** Adamec RE. Normal and abnormal limbic system mechanisms of emotive biasing. In Livingston KE, Hornykiewicz O (eds): *Limbic Mechanisms*. N.Y. Plenum Press 1978.
- 99** Zager EL, Black PM. Neuropeptides in human memory and learning processes. *Neurosurgery* 1985;17:355-369.
- 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; 180:271-272.
- 101** MacLean PD. Brain evolution relating to family, play, and the separation call. *Arch Gen Psychiat* 1985;42:505-417.
- 102** Papez J.W. A proposed mechanism of emotion. *Arch Neurol and Psychiat* 1937;38:725-743.

- 103** Saxe GN, Vasile RG, Hill TC, Bloomingdale K, van der Kolk BA. SPECT imaging and Multiple Personality Disorder. *J Nerv Ment Dis* 1992;180:662-663.
- 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 1992a.
- 105** Teicher MH, Glod CA, Surrey J, Swett C. Early childhood abuse and limbic system ratings in adult psychiatric outpatients. *J Neuropsychiat Clin Neurosci* 1993; (In press).
- 106** LeDoux J. *Mind and Brain: Dialogues in cognitive neuroscience*. N.Y. 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. *Physiology and Behavior* 1991; 49:443-454.
- 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; 253:2380-2386.
- 110** Gray J. *The neuropsychology of anxiety. An inquiry into the functions of the septo-hippocampal system*. Oxford University Press 1982.
- 111** Altman J, Brunner RL, Bayer SA. The hippocampus and behavioral maturation. *Behav Biol* 1973; 8:557-596.
- 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 Review* 1985;92:512-531.
- 114** Schacter DL, Moscovitch M. Infants, amnesics, and dissociable memory systems. In Moscovitch M (ed): *Infant Memory*. New York: Plenum Press, 1982.
- 115** Nadel L, Zola-Morgan S. Infantile amnesia: A neurobiological perspective. In Moscovitch M (ed), *Infant Memory*. New York: Plenum, 1984.
- 116** Sapolsky RM, Uno Hideo, Rebert CS, Finch CE. Hippocampal damage associated with prolonged glucocorticoid exposure in primates. *J Neurosci* 1990;10:2897-2902.
- 117** Pfaff DW, Silva MT, Weiss JM. Telemetered recording of hormone effects on hippocampal neurons. *Science* 1971;172:394-395.
- 118** LeDoux JE, Romanski L, Xagoraris A. Indelibility of subcortical emotional memories. *J Cog Neurosci* 1991; 1:238-243.

- 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, Ill, 1991.
- 121** Shalev A, Rogel-Fuchs Y, Pitman R Conditioned fear and psychological trauma. *Biol Psychiat* 1992;31:863-865.
- 122** Frank JB, Kosten TR, Giller EL, Dan E. A randomized clinical trial of phenelzine and imipramine in PTSD. *Am J Psychiatry* 1988;145: 1289-1291.
- 123** Bleich A, Siegel B, Garb B, Kottler A, Lerer B. PTSD following combat exposure: clinical; features and pharmacological management. *Br J Psychiat* 1987;149: 365-369.
- 124** Davidson JRT, Nemeroff CB. Pharmacotherapy in PTSD: historical and clinical considerations and future directions. *Psychopharm Bull* 1989;25:422-425.
- 125** Reist C, Kauffman CD, Haier RJ. A controlled trial of desipramine in 18 men with post-traumatic stress disorder. *Am J Psychiatry* 1989; 146:513-516.
- 126 Davidson J, Kudler H, Smith R. Treatment of post-traumatic stress disorder with amitriptylene and placebo. *Arch Gen Psychiat* 1990;47:259-266.
- 127** van der Kolk BA. Drug treatment of Post Traumatic Stress Disorder. *J Aff Disorders* 1987; 13:203-213.
- 128** Falcon S, Ryan, C, Chamberlain K. Tricyclics: Possible Treatment for Posttraumatic Stress Disorder. *J Clin Psychiat* 1985;46:385-389.
- 129** Hogben GL, Cornfield RB. Treatment of traumatic war neurosis with phenalzine. *Arch Gen Psychiat* 1981;38:440-445.
- 130** Kolb LC, Burriss BC, Griffiths S. Propranolol and clonidine in the treatment of post traumatic stress disorders of war. In BA van der Kolk (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, Cavenar JO. Preliminary study of Carbamezapine in post-traumatic stress disorder. *Psychosomatics* 1986;27:8479-854.
- 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: 1244-1247.
- 133** Giral P, Martin P, Soubrie P. Reversal of helpless behavior in rats by putative 5-HT1A agonists. *Biol Psychiat* 1988; 23:237- 242.
- 134** Krystal J. Neurobiological mechanisms of dissociation. Paper presented at the American Psychiatric Association Meeting; San Francisco May 1993.

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