Functional Neuroanatomical Correlates of the Effects of Stress on Memory

J. Douglas Bremner,[1-3] John H. Krystal,[1-3] Steven M. Southwick,[1-3] and Dennis S. Charney[1-3]

Recently there has been an increase in interest in the relationship between stress and memory. Brain regions which are involved in memory function also effect the stress response. Traumatic stress results in changes in these brain regions; alterations in these brain regions in turn may mediate symptoms of posttraumatic stress disorder (PTSD). Neural mechanisms which are relevant to the effects of stress on memory, such as fear conditioning, stress sensitization, and extinction, are reviewed in relation to their implications for PTSD. Special topics including neural mechanisms in dissociation, neurobiological approaches to the validity of childhood memories as they apply to controversies over the "False Memory Syndrome," and implications of the effects of stress on memory for psychotherapy, are also reviewed. The findings discussed in this paper are consistent with the formulation that stress-induced alterations in brain regions and systems involved in memory may underlie many of the symptoms of PTSD, as well as dissociative amnesia, seen in survivors of traumatic stress.

KEY WORDS: PTSD; dissociation; memory; amygdala; hippocampus; amnesia; trauma; stress; neurobiology.

[1]Department of Psychiatry, Yale University School of Medicine, New Haven, Connecticut 06520.
[2]National Center for Posttraumatic Stress Disorder, Division of Clinical Neurosciences, West Haven, Connecticut 06516.
[3]West Haven Veterans Affairs Medical Center, West Haven, Connecticut 06516.

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Stress and Memory: Formulating the Questions

Recently there has been increased attention to the relationship between stress and memory. This is due to several factors. First, there has been an enhanced awareness of the role that dissociation plays in the acute response to trauma, and the importance of dissociative symptoms in the clinical presentation of patients with stress-related psychopathology. These patients dissociate at the time of combat-related trauma (Bremner et al., 1992; Marmar et al., 1994), and recall of traumatic events often occurs in a dissociated form. The "playback" quality of dissociative memories which originally were experienced in a dissociative state suggests that a unique type of encoding and retrieval occurs with trauma-related dissociative memories. Other aspects of dissociation, including the gaps in memory which occur with amnesia, and the forgetting of aspects of identity which are a part of the dissociative splintering of identity, also suggest that dissociation is related to abnormal memory. We speculate in this paper that dissociation may be related to an abnormality of functioning of brain regions and systems involved in memory.

The controversy surrounding recall of childhood abuse experiences has also created an increased interest in the relationship between stress and memory. A substantially larger number of individuals are coming forward with accusations of childhood abuse in comparison to 20 years ago. Some authors feel that many of these reports are not related to historical fact (Loftus, Garry, & Feldman, 1994). They maintain that many psychotherapists are practicing a form of psychotherapy known as "recovered memory therapy", which operates on the principle that a large proportion of psychopathology is related to childhood abuse which is not available for ready recall, and that the goal of therapy is to "dig out" memories of childhood abuse. These authors feel that psychotherapists practicing therapies such as recovered memory therapy may be suggesting events of childhood abuse which never occurred, leading to what has been termed the "false memory syndrome." However, studies have shown that as many as 38% of abuse survivors will not remember significant episodes of abuse many years after the event (Williams, 1994a). An important question related to these findings is whether the forgetting of abuse which has been documented in these studies is due to "normal forgetting", as some authors have claimed (Loftus, Garry, et al., 1994), or whether there are special mechanisms in abuse survivors, which have been termed "amnesia" or "repression," which may result in a special type of forgetting which is followed by recall of actual traumatic events many years after the event first occurred (Williams, 1994b). Some answers to these questions could

possibly be obtained through an understanding of the effects of stress on memory.

Stress also has effects on memory which are clinically relevant to memory functioning in patients with psychopathology related to traumatic stress. Patients with stress-related psychopathology have a variety of memory disturbances, including deficits in new learning, gaps in recall, and overrepresentations of specific trauma-related memories (Pitman, 1989). Memory is in fact a survival mechanism which comes into play during exposure to a traumatic stressor. Efficient recall of memories associated with previous stressors is crucial for survival. If one encounters a dangerous situation, the rapid recall of the memory of a previous encounter with a similar situation could be life-saving. In this paper we review the effects of stress on memory, charting a wide course from the descriptions of symptoms provided by trauma patients to what is known about neurobiological correlates of the effects of stress on memory. We also review several concepts which are important in the understanding of the effects of stress on memory, and how these findings are applicable to clinical practice, including stress sensitization, fear conditioning, and extinction (Bremner, Davis, Southwick, Krystal, & Charney, 1993; Charney, Deutch, Krystal, Southwick, & Davis, 1993). We also review topics relevant to the relationship between stress and memory, such as mechanisms in dissociation, validity of memories of childhood abuse, and principles of psychotherapy for trauma survivors.

Mechanisms of Normal Memory Functioning

Memory formation involves encoding, storage (or consolidation), and retrieval. Encoding is the initial laying down of the memory trace. Storage involves the keeping of the memory trace over time. A related concept is consolidation, which refers to the process, which can occur over several weeks or more, of establishing the permanence of a memory trace, during which time the memory trace is theoretically susceptible to modification. Retrieval is the process of bringing out a memory from storage into consciousness.

Memory can also be categorized according to memory type. Squire & Zola-Morgan (1991) have divided the different types of memory function into declarative ("explicit") and nondeclarative ("implicit" or "procedural") memory (Figure 1). Explicit memory includes free recall of facts and lists, and working memory, which is the ability to store information in a visual or verbal buffer while performing a particular operation utilizing that information. In contrast, implicit memory is demonstrated only through tasks

or skills in which the knowledge is embedded. Forms of implicit memory include priming, conditioning, and tasks or skills. Priming involves providing the first few letters of a word and asking the subject to say the first word that comes to mind. An amnestic patient with deficits in free recall may demonstrate normal recall with the assistance of priming. Conditioning refers to the development of consistent physiological and emotional responses to a previously neutral stimulus. The most common animal model of conditioning (reviewed below) involves pairing a tone or a light (the conditioned stimulus) with an electric shock (the unconditioned stimulus). With repeated trials, the conditioned stimulus alone will be able to evoke responses such as an increase in startle amplitude which were previously only elicited by the unconditioned stimulus. This paradigm implies that a form of learning has occurred which is embedded in the conditioned response, and is not available for conscious recall.

Another way to think about memory is in terms of cognitive and emotional forms of memory. The conditioned response following the pairing of footshock and a tone suggests that there is memory for emotions which can be evoked by stimuli in the environment which trigger recall for the original emotional state. This type of memory is to be distinguished from cognitive recall, which involves the recall of verbal or visual material (i.e., the "facts" as opposed to the "feelings"). Alterations in memory function in PTSD involve both cognitive and emotional memory.

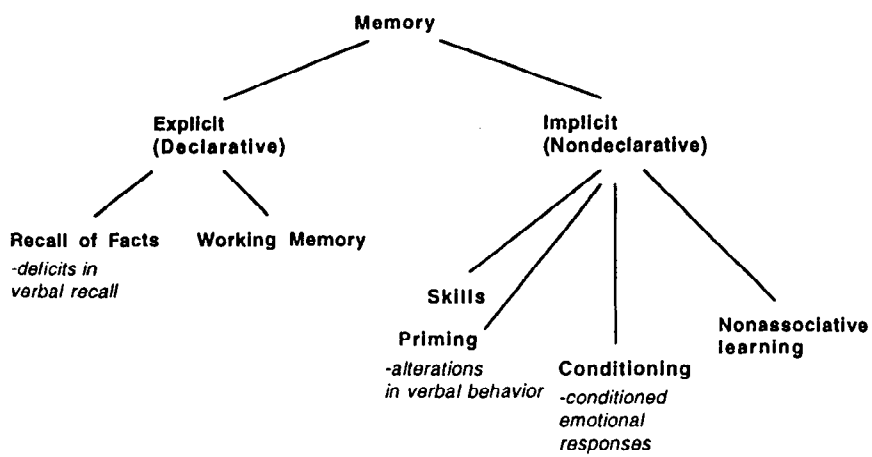

Figure 1. Schematic diagram of the functional organization of memory based on the formulation of Squire & Zola-Morgan (1991). Memory-related abnormalities which have been demonstrated in PTSD patients are indicated in italics.

Traumatic Memories, Lost and Found: The Role of Dissociative Amnesia in Stress-Induced Psychiatric Disorders

Memory function is altered in patients with stress-related psychiatric disorders, and traumatic memories are stored and retrieved in a different way than the types of stressful memories outlined above. Traumatic stress can lead to both a strengthening of particular memory traces related to traumatic events, as well as gaps in memory, which are known as amnestic episodes. For instance, in one study of World War II (WWII) combatants it was found that immediately after a major campaign, about 5% of the soldiers who had been combatants had no memory for the events which had just occurred (Torrie, 1944). Amnesia can be defined as gaps in memory which are not due to ordinary forgetting. Some authors use the term "repression" in a way which is essentially synonymous with amnesia. Understanding the mechanisms involved in amnesia may provide important insights into the effects of stress on memory. Amnesia has been found to be the dissociative symptom area which is most elevated in Vietnam combat veterans with posttraumatic stress disorder (PTSD) in comparison to Vietnam combat veterans without PTSD as measured with the Structured Clinical Interview for DSM for Dissociative Disorders (SCID-D) (Bremner, Steinberg, Southwick, Johnson, & Charney, 1993). Amnestic symptoms in these patients ranged from gaps of memory which lasted from minutes to hours to days. Some patients reported driving down the highway from Boston to New Haven, and suddenly realizing that they had covered 2 hr of the trip and had no recall of what had happened during that time. One patient said that he was walking down a street in Boston, and the next thing he knew he was in a motel room in Texas. Another patient disappeared from an inpatient psychiatric unit, and found himself in the woods somewhere in Illinois, in the middle of the night, wearing combat fatigues. A patient of one of the authors with a history of childhood sexual abuse reported that she was on the telephone at her day hospital program, and the next thing she knew she was at home in bed. One patient had symptoms of PTSD and had been in combat in Vietnam, although he had no recall of anything related to the 12 months he was there. These clinical case examples provide a feeling for the wide range of phenomena which characterize dissociative amnesia in patients with a history of exposure to extreme psychological trauma.

It is unclear why amnestic memories emerge at certain times and not at others. One possibility is that state-dependency determines recall of amnestic material. According to this model, specific memories may only be available for retrieval when certain mood states are present, such as

anger or depression. Studies in fact show that retrieval is facilitated when the mood state at the time of retrieval is the same as the mood state which was present at the time of encoding (Bower, 1981). Consistent with this, PTSD patients often report that when they are in a particular physiological or emotional state they will have the recall of a trauma-related event for which they previously were amnestic. One of the authors of the current review first became interested in PTSD when, as a psychiatry resident, he was called in the middle of the night by a Vietnam combat veteran with PTSD who had just been in a house fire. He had to go back into the burning house in order to rescue other people who were trapped inside. He had had previous experiences pulling comrades from a burning helicopter while in Vietnam, an event for which he was previously amnestic. After the house fire incident he had a sustained flashback to the original event in Vietnam, and when he called the psychiatrist on duty he could not be communicated with, and all he could say was "Got to get them out, got to get them out!". Traumatic recall often occurs in dissociated states which are reminiscent of the state in which the event originally was experienced. It may be that during states of arousal, release of neuromodulators such as norepinephrine (as reviewed below) leads to pathological recall of traumatic memories for which the patient may have been previously amnestic.

Dissociative identity disturbances are also relevant to understanding the effects of stress on memory. One way to view identity is as a series of memories related to one's life story which have been collected over the course of a lifetime. Traumatic stress can interrupt the thread of that series of memories, or result in special memories which do not fit in with the others in a continuous way, leading to a splintering of identity. An example of this is survivors of childhood abuse who will ascribe abuse experiences to a shameful or wicked persona (which is related to the phenomenon of childhood abuse victims blaming themselves for what others inflict upon them), leaving pleasant memories for other aspects of the self which are ascribed with more positive qualities. Aspects of the self which are associated with the abuse can then be forgotten, only to reemerge at a later date. Combat veterans will frequently describe a "warrior," often with their radio name attached to it (the special nickname they used on the radio while in Vietnam), which they describe as having developed while in Vietnam, and to which they attribute special capacities, such as exceptional strength when challenged and the ability to fight others without fear. This is in contrast with other "peacetime" personalities which interact with their families and other people in civilian life. Often the "warrior" personality will come out during times of stress, for example, when the person is challenged to a fight. In summary, dissociative symptoms of amnesia and identity disturbance may be related to alterations in memory function in trauma survivors.

Neuropsychological Studies Show Deficits in Memory Function in Trauma Survivors with Psychiatric Disorders

Evidence from a variety of studies from throughout the greater part of this century have provided evidence for deficits in explicit memory function with traumatic stress. Concentration camp survivors from the second World War were found to have high rates of impairment in explicit memory function (Helweg-Larsen et al., 1952). In one group of 321 Danish survivors of WWII concentration camps with high levels of psychiatric symptomatology who were seeking compensation for disability, there were complaints of memory impairment suggestive of deficits in explicit recall 10 or more years after release from internment in 87% of individuals. Severe intellectual impairment was also found on testing in 61% of cases (Thygesen, Hermann, & Willanger, 1970). Prisoners of the Korean War have been found to have an impairment on explicit memory tasks of free verbal recall, measured with the Logical Memory component of the Wechsler Memory Scale, in comparison to Korean veterans without a history of containment (Sutker, Winstead, Galina, & Allain, 1991), although these findings may be due to a decrease in body mass due to starvation (Sutker, Galina, West, & Allain, 1990). We have measured explicit memory function with the Wechsler Memory Scale (WMS)-Logical (verbal memory) and Figural (visual memory) components in Vietnam combat veterans with PTSD (n = 26) and controls matched for factors which could affect memory function (n = 15). PTSD patients had significantly lower free verbal recall (explicit memory) as measured by the WMS-Logical component, without deficits in IQ as measured by the Wechsler Adult Intelligence Scale-Revised (WAIS-R; Bremner et al., 1993). PTSD patients also had deficits in explicit recall as measured with the Selective Reminding Test (SRT), for both verbal and visual components. We have subsequently found deficits in explicit memory tasks of free verbal recall measured by the WMS-Logical component in adult survivors of childhood abuse seeking treatment for psychiatric disorders (Bremner et al., unpublished data). Studies have found deficits in explicit short-term memory as assessed with the Auditory Verbal Learning Test (AVLT) in Vietnam combat veterans with PTSD in comparison to National Guard veterans without PTSD (Uddo, Vasterling, Brailey, & Sutker, 1993) and using other measures of new learning and memory in Vietnam combat veterans with PTSD in comparison to controls (Yehuda et al., 1995). Studies are currently in progress in female Vietnam combat nurses

with PTSD (J. Wolfe, personal communication, 10/94). Deficits in academic performance have also been shown in Beirut adolescents with PTSD in comparison to Beirut adolescents without PTSD (P. Saigh, personal communication, 8/94). These studies suggest deficits in encoding on explicit memory tasks. Other studies in patients with PTSD have shown enhanced recall on explicit memory tasks for trauma-related words relative to neutral words in comparison to controls (Zeitlin & McNally, 1991). In summary, the findings are consistent with both deficits in encoding on explicit memory tasks, deficits in retrieval, as well as enhanced encoding or retrieval for specific trauma-related material.

Another area which will probably receive increased attention in coming years is the role of alterations in implicit memory function in patients with PTSD [for a review of implicit memory, see Schacter (1995)]. A relatively understudied phenomenon is the effect that cognitive processes which are not available to active consciousness have on mental life (Kihlstrom, 1987). Studies are needed to examine the effect of unconscious trauma-related material on cognition. An initial approach to this area has been a study which showed that patients with PTSD had an enhancement of implicit recall (i.e., recall following priming) for trauma-related words relative to neutral words in comparison to controls (Zeitlin & McNally, 1991). These findings may have implications for the intrusiveness of trauma-related memories relative to normal memories in patients with PTSD.

Abnormalities in the Stroop test, which are associated with activation of the cingulate cortex, have been associated with PTSD. Delays in color-naming with trauma-related words such as "body-bag" are involuntary, and provide quantitative measures of the intrusive cognition which is an important part of PTSD. Vietnam combat veterans with PTSD have been found to take longer to color-name "PTSD" words than obsessive words, positive words, and neutral words, and this delay was correlated with severity of PTSD symptomatology as measured by the Mississippi Scale (McNally, English, & Lipke, 1993; McNally, Kaspi, Riemann, & Zeitlin, 1990). Stroop interference has also been shown in patients with PTSD related to the trauma of rape (Cassiday, McNally, & Zeitlin, 1992; Foa, Feske, Murdock, Kozak, & McCarthy, 1991). These studies therefore make Stroop interference a highly-replicated finding in PTSD.

Neuroanatomical Correlates of Explicit Memory Function: Free Recall and Working Memory

Neuroanatomical studies support a role for the hippocampus in explicit memory. In the famous case of H.M., bilateral resection of the medial temporal lobes (i.e., hippocampus and adjacent structures) was associated with severe deficits in explicit memory measured with free verbal recall (Scolville & Milner, 1984). Lesions studies in monkeys have shown that the hippocampal formation (dentate gyrus, hippocampus proper, subicular complex, and entorhinal cortex), and surrounding perirhinal and parahippocampal cortices (but not the amygdala) (Zola-Morgan, Squire, & Amaral, 1989), play an important role in explicit recall as measured with delayed matching to sample memory tasks (a test of the working memory type of explicit memory function) (Mishkin, 1978; Murray & Mishkin, 1986; Zola-Morgan, Squire, Amaral, & Suzuki, 1989). The medial nucleus of the thalamus is also involved with the hippocampus in short-term recall.

The prefrontal cortex has been described as being an interface between interoceptive and exteroceptive, or internal and external, experience (Goldman-Rakic, 1988). This makes it well suited for the integration of sensory phenomena during states of stress. One area in the prefrontal cortex is involved in explicit recall as measured by working memory tasks and has been termed the dorsolateral prefrontal cortex, principal sulcus, or middle frontal gyrus (Goldman, 1971). Positron emission tomography (PET) oxygen-15 water studies of cerebral blood flow in normal human subjects have shown activation of left dorsolateral prefrontal cortex during explicit memory encoding (reviewed in Tulving, Kapur, Craik, Moscovitch, & Houle, 1994), and visual and verbal association (Petersen, Fox, Posner, Mintun, & Raichle, 1988), and activation of right dorsolateral prefrontal cortex during explicit memory retrieval (reviewed in Tulving et al., 1994) and with sustained attentional tasks (Pardo, Fox, & Raichle, 1991). These findings together provide strong evidence for the role of prefrontal cortex in explicit recall, as well as the sustained attention required for memory formation.

Parietal cortex has been demonstrated to play an important role in spatial memory and attention. Lesions of the posterior parietal lobe in rats result in deficits in spatial memory processing, as measured by the capacity to explore displaced objects (Save, Poucet, Foreman, & Buhot, 1992). Single-cell recordings from alert monkeys have shown an activation of the parietal cortex when monkeys are required to attend to a visual location (Posner, Petersen, Fox, & Raichle, 1988). PET oxygen-15 water studies of sustained vigilance and attention in healthy volunteers have shown increases in blood flow in the right prefrontal and superior parietal cortex during sustained attention (Pardo et al., 1991). Tasks of working memory have also shown activation of right parietal cortex (Jonides et al., 1993).

Explicit memory formation is not instantaneous. After the laying down of the original memory trace there is a process which can take from weeks to months, called consolidation, during which the stored memory is subject to modification or deletion. Electroconvulsive treatments (ECT) af-

ter training sessions in rats impair memory for the training experience. As the interval between the ECT and the training session increases, the severity of memory impairment decreases (McGaugh & Herz, 1972). Studies of humans who have received ECT suggest that the process of memory consolidation has a much longer time course. ECT results in an impairment for recall of television programs for 1 to 2 years before administration of ECT, while memory for older programs is normal (Squire, Slater, & Chace, 1975). These findings suggest that modification of the original memory traces can occur for a considerable period of time after the original event.

Although the hippocampus and adjacent structures are important in encoding and retrieval, they do not play a major role in the long-term storage of explicit memory. Monkeys with lesions of the hippocampus are impaired in the recall of recently learned objects, although their recall of objects learned in the distant past is normal, suggesting that memories are stored initially in the hippocampus, and after several weeks are reorganized, with storage in other brain areas such as the neocortex (Zola-Morgan & Squire, 1990). The evidence is more consistent with the fact that memories are stored in the primary neocortical sensory and motor areas and later evoked in those same cortical areas (Damasio, 1990; Squire, 1986). Visual information is stored in the occipital cortex, tactile information in the sensory cortex, auditory information in the middle temporal gyrus, and olfactory information in the orbitofrontal cortex. It has been hypothesized (Zola-Morgan & Squire, 1990) that the role of the hippocampus is to bring together memory elements from diverse neocortical areas at the time of retrieval of explicit memory.

Neuroanatomical Correlates of Implicit Memory Function: Conditioned Fear, Priming, and Cued Recall

The amygdala is an important mediator of emotional memory (Sarter & Markowitsch, 1977). The paradigm of conditioned fear has been utilized as an animal model for stress-induced abnormalities of emotional memory (reviewed in Davis, 1992; LeDoux, 1993). Conditioned fear responses mediated by the amygdala are measured with the acoustic startle response. The acoustic startle response is a primitive reflex which is part of the animal's response to threat. The startle response can be potentiated by the addition of something aversive, such as electric shock. The neuroanatomy and neurophysiology of emotional memory (measured by the conditioned fear response in animals) have been well characterized (Davis, 1992; LeDoux, 1993). Lesions of the central nucleus of the amygdala have been shown to completely block fear-potentiated startle (Hitchcock & Davis, 1986), while electrical stimulation of the central nucleus increases acoustic startle (Rosen & Davis, 1988). The amygdala integrates information which is necessary for the proper execution of the stress response, including (internal) emotion and information from the external environment (Turner & Herkenham, 1991). The central nucleus of the amygdala projects to a variety of brain structures which are involved in effecting the stress response (Hitchcock & Davis, 1991; Rosen, Hitchcock, Sananes, Miserendino, & Davis, 1991). The hippocampus also plays a role in fear responses to the context in which the electric shock took place (Kim & Fanselow, 1992; Phillips & LeDoux, 1992).

The neocortex plays a role in some types of implicit memory function. Procedural (or "implicit") memory is accessible only through performance by engaging skills or operations in which the knowledge is embedded, as demonstrated by priming. An example of priming is providing the first few letters of the forgotten word and asking the subject to say the first word that comes to mind. Priming can improve memory performance in patients with anterograde amnesia (i.e., deficits in explicit memory, or the recall of things such as names and facts) (Moscovitch, 1985). Priming effects require only the intactness of the cortical sensory area in which the memory was originally stored (Squire, 1986).

Effects of Stress on Brain Regions Involved in Memory

Brain regions involved in memory are also involved in effecting the stress response. Removal of the cerebral cortex results in extreme fear responses and aggressive behavior (reviewed in LeDoux, 1977), which is due to a loss of cortical inhibition of subcortical (limbic) brain regions, including the hypothalamus, thalamus, hippocampus, amygdala, orbitofrontal cortex, and cingulate (Figure 2). Limbic brain regions mediate memory function, fear-related behaviors, and the stress response, and in turn are affected by exposure to traumatic stress. The effects of stress on these brain regions are reviewed individually below.

Stress has effects on the hippocampus which lead to both changes in its cytoarchitecture as well as deficits in explicit recall. Studies of monkeys who died spontaneously following exposure to severe stress due to improper caging and overcrowding were found on autopsy to have damage to the CA2 and CA3 subfields of the hippocampus (Uno, Tarara, Else, Suleman, & Sapolsky, 1989). High levels of glucocorticoids which are released during stress have been found to be associated with hippocampal damage (Sapolsky, Uno, Rebert, & Finch, 1990), including a loss of pyramidal neurons (Uno et al., 1989) and decreased dendritic branching (McEwen, Gould, &

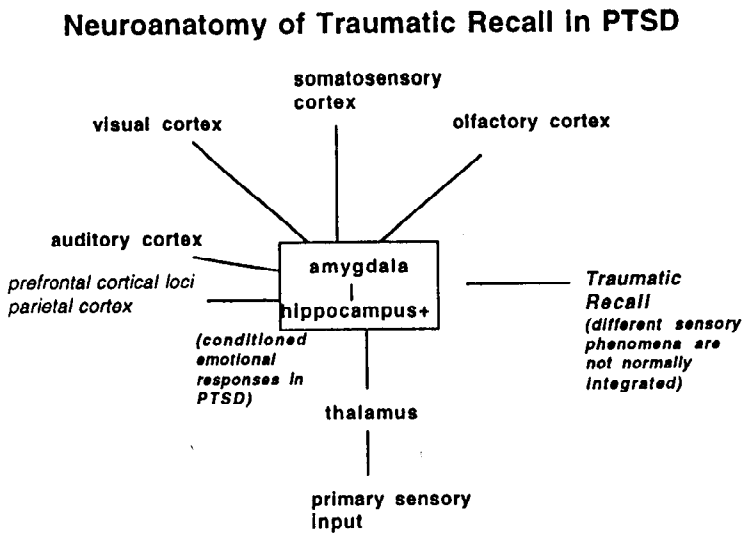

Figure 2. Diagram of brain structures involved in memory. As described in the text, sensory information is gated through the thalamus to hippocampus, amygdala, neocortex, and other areas. Explicit memory encoding and consolidation takes place in hippocampus and adjacent cortical areas (hippocampus+), thalamus, and prefrontal cortical loci, while long-term storage occurs in primary sensory cortical areas. Implicit memory functions are also mediated by neocortical areas, while emotional memory is mediated by amygdala and prefrontal cortical loci.

Sakai, 1992; Watanabe, Gould, & McEwen, 1992; Wooley, Gould, & McEwen, 1990) which are associated with deficits in memory (Luine, Villages, Martinex, & McEwen, 1994). Glucocorticoids appear to exert their effect by increasing the vulnerability of hippocampal neurons to endogenously released excitatory amino acids (Armanini, Hutchins, Stein, & Sapolsky, 1990).

Studies utilizing neuroimaging techniques have found that stress in humans may be associated with changes in brain structure, including the morphology of the hippocampus. Studies in concentration camp survivors from World War II were assessed with pneumoencephalography and found to have "[cerebral] atrophy of varying degrees . . . . In the majority" (Thygesen et al., 1970). Other authors utilizing pneumoencephalography in concentration camp survivors reported "diffuse encephalopathy" in 81% of cases (reviewed in Thygesen et al., 1970). We compared hippocampal volume measured with MRI in Vietnam combat veterans with PTSD (n = 26) and healthy subjects (n = 22) matched for factors which could affect hippocampal volume, including age, sex, race, years of education, height, weight, handedness, and years of alcohol abuse. Patients with combat-related PTSD had an 8% decrease in right hippocampal volume in comparison to controls ($p < .05$), but no significant decrease in volume of comparison structures including temporal lobe and caudate. Deficits in free verbal recall (explicit memory) as measured by the Wechsler Memory Scale-Logical Component, percent retention, were associated with lower right hippocampal volume in the PTSD patients ($r = .64$; $p < .05$) but not in the controls. There was not a significant difference between PTSD patients and controls in left hippocampal volume, or in volume of the comparison regions measured in this study, left or right caudate and temporal lobe volume (minus hippocampus) (Bremner et al., 1994). Recently we have found a statistically significant 12% reduction in left hippocampal volume in 17 adult survivors of childhood physical and sexual abuse in comparison to 17 controls who were matched on a case-by-case basis for age, sex, race, handedness, years of education, and years of alcohol abuse. We have also used PET and [^{18}F]2-fluoro-2-deoxyglucose (FDG) in the measurement of cerebral glucose metabolic rate following administration of yohimbine and placebo in Vietnam combat veterans with PTSD (n = 10) and healthy controls (n = 10). We have previously found evidence for alterations in noradrenergic function as demonstrated with increased PTSD symptoms, intrusive memories, flashbacks, and anxiety, following administration of the alpha-2 antagonist, yohimbine, which stimulates brain norepinephrine release, in PTSD patients in comparison to controls (Southwick et al., 1993). Animal studies have shown a decrease in metabolism in several neocortical brain regions with electrical stimulation or yohimbine-induced release of norepinephrine in the brain. Administration of yohimbine resulted in a differential effect on brain metabolism in PTSD patients in comparison to controls in orbitofrontal, temporal, parietal, and prefrontal cortex, with PTSD patients showing a tendency to decrease brain metabolism while controls showed a tendency to increase brain metabolism with yohimbine in comparison to placebo. PTSD patients also had a decrease in hippocampal metabolism in the hippocampus in PTSD patients which was not seen in the controls (Bremner et al., 1992). These findings are consistent with an increased release of norepinephrine in the brain following yohimbine in PTSD. Considering the role of norepinephrine in the hippocampus as a neuromodulator which has effects on memory encoding and retrieval, this suggests the possibility that enhanced norepinephrine release in the hippocampus with stressors may be associated with the pathological recall which is typical of traumatic memories in patients with PTSD.

Modulation of Memory by Neurotransmitters and Neuropeptides Released During Stress

Brain chemicals released during stress, which are highly concentrated in brain regions involved in memory such as hippocampus, amygdala and prefrontal cortex, modulate memory function (reviewed in De Wied & Croiset, 1991; McGaugh, 1989; McGaugh, 1990). For instance, removal of the adrenal medulla, site of most of the body's epinephrine, results in an impairment in new learning, which is restored by administration of adequate amounts of epinephrine (Borrell, De Kloet, Versteeg, & Bohus, 1983). Posttraining administration of epinephrine after a learning task influences retention with an inverted U-shaped curve: retention is enhanced at moderate doses and impaired at high doses (Gold & van Buskirk, 1975; Liang, Juler, & McGaugh, 1986; McGaugh, 1990). These effects appear to be mediated by increasing levels of glucose in the brain, which facilitates memory function (Gold, 1992). Low-dose (0.2 μg) injections of norepinephrine into the amygdala facilitate memory function in an inhibitory avoidance task, while higher doses (0.5 microgram) impair memory function (Liang et al., 1986).

There are a variety of other neurotransmitters and neuropeptides which are released during stress and which modulate memory function. These include ACTH, glucocorticoids, dopamine, acetylcholine, endogenous opiates, vasopressin, oxytocin, and gamma-aminobutyric acid. It is beyond the scope of this paper to review all of these neuromodulators and their effects on memory (for reviews see De Wied & Croiset, 1991; McGaugh, 1990).

Recent studies have begun to address the question of neuromodulation of memory function with stress in human subjects. In one recent study, the alpha-adrenergic antagonist, propranolol, or placebo, was administered one hour before a neutral or an emotionally arousing (stress-related) story in healthy human subjects. Propranolol, but not placebo, interfered with recall of the emotionally arousing story, but not the neutral story. This study suggests that activation of alpha-adrenergic receptors in the brain enhances the encoding of emotionally arousing memories (Cahill, Prins, Weber, & McGaugh, 1994).

Findings related to neuromodulation of memory function are of importance for understanding the symptomatology of PTSD. Increased release of neurotransmitters and neuropeptides with modulatory actions on memory function during stress probably plays a role in deficits in encoding and retrieval, as well as the enhancement of specific traumatic memories, which is part of the clinical presentation of PTSD (Pitman, 1989). Chronic abnormalities in the function of these neurotransmitter and neuropeptide systems in PTSD may contribute to the abnormalities in memory seen in these patients. For instance, vasopressin has been shown to facilitate traumatic recall in patients with PTSD (Pitman, Orr, & Lasko, 1993). Hopefully, an extension of preclinical findings on the effects of stress-related neuromodulators on memory function to clinical populations will enhance our understanding of memory alterations in PTSD.

Neural Mechanisms Mediating the Effects of Stress on Memory

The mechanism of *stress sensitization* has implications for understanding the symptomatology of patients with PTSD. Stress sensitization refers to the phenomenon where repeated exposure to a stressor results in an amplification of responsiveness to subsequent stressors. For example, acute stress results in an increased release of norepinephrine in the hippocampus as well as other brain regions. Animals with a history of exposure to prior stressors become sensitized to exposure to subsequent stressors, so that there is an accentuation of norepinephrine release in the hippocampus with a subsequent stressor (reviewed in Bremner et al., 1993; Charney et al., 1993). As reviewed elsewhere in this paper, norepinephrine (in addition to other neurotransmitters and neuropeptides) modulates memory formation and retrieval. This raises the possibility that stress sensitization, acting through neuromodulators such as norepinephrine, may be associated with alterations in memory encoding and retrieval, which may have implications for understanding the mechanisms of traumatic recall in PTSD.

Stress sensitization is clinically applicable to PTSD. Patients with PTSD have a very difficult time with ordinary stressful events which normal persons can tolerate without too much trouble. For instance, the stress of getting in a fender-bender, or having an argument with one's spouse, can lead to a total decompensation in these patients. We have found that exposure to the stressor of childhood physical abuse increases the risk for the development of combat-related PTSD. This study suggests that sensitization resulting from early childhood stress may increase the vulnerability for the development of psychopathology in response to a subsequent stressor (combat stress in Vietnam) (Bremner, Southwick, Johnson, Yehuda, & Charney, 1993). There are other examples of how a history of exposure to prior stress increases the risk for stress-related symptomatology upon reexposure to stressors (reviewed in Bremner, Southwick, & Charney, 1994).

Fear conditioning is another neural mechanism which can be modelled in the laboratory and is highly relevant to PTSD. In fear conditioning, a normally neutral stimulus (or something which typically has no effect on the animal, such as a bright light), is paired with an aversive stimulus such as electric shock. With repetitive pairing of the light and the shock, a learning process occurs (conditioning) in which the light alone eventually causes a fear response (Davis, 1992). The role of conditioned emotional responses in PTSD is illustrated by the case of a Vietnam veteran with PTSD who got onto the elevator with a woman who had ash on her forehead for Ash Wednesday. This was a visual cue related to a traumatic event where he had seen his friend dead with a single bullet hole in his forehead. The patient immediately felt very upset, agitated, anxious, and had an increase in heart rate and blood pressure. There is evidence that the amygdala mediates alterations in emotional memory as manifested by conditioned responses and other phenomena in humans (in addition to animals). For example, electrical stimulation of the amygdala in healthy human subjects has been shown to elicit feelings of anxiety (Chapman et al., 1954) and activation of the stress response system, as manifested by increases in peripheral catecholamines (Gunne & Reis, 1963). Exaggerated startle response (which is mediated by the amygdala in animals) has been associated with PTSD (Butler et al., 1990). We have not found a difference in amygdala volume measured with MRI between patients with combat-related PTSD and healthy controls (Bremner et al., in press).

The psychophysiology paradigm is an excellent method for studying conditioned emotional responses in patients with PTSD. Patients with PTSD have a heightened physiological responsiveness (increased heart rate and blood pressure) to reminders of the original trauma (combat films and sounds, scripts of traumatic events) which resemble conditioned responses. These conditioned responses to cues related to the original trauma are parallel to those seen with the conditioned fear paradigm in animals (reviewed in Prins & Kaloupek, 1995).

A *failure of extinction to fear-inducing stimuli* is also characteristic of PTSD. Extinction refers to an inhibition of conditioned responding to cues associated with a fearful stimulus which takes place gradually over time following the removal of the original fearful stimulus. As an example of a failure of extinction, childhood abuse survivors who were subjected to being locked in a dark closet as children may continue to have anxiety responses every time they are in a dark and enclosed place, even though these cues are no longer representative of a real threat to their person. On a neuroanatomical level, extinction involves neocortical (Jarrell, Gentile, Romanski, McCabe, & Sneidermann, 1987; LeDoux, 1993) and orbitofrontal (Morgan & LeDoux, 1994) inhibition of amygdala function. We have found a decrease in glucose metabolism at baseline in the temporal cortex in patients with PTSD in comparison to controls as measured with PET (Bremner et al., 1992). One might speculate that a decrease in temporal neocortex function (which includes auditory neocortex) is involved in the failure of extinction seen in patients with PTSD.

Could Alterations in Brain Regions Involved in Memory Mediate Symptoms of Dissociation?

There has recently been an increased interest in the link between symptoms of dissociation and trauma (Nemiah, 1989; Putnam, Guroff, Silberman, Barban, & Post, 1986; Spiegel & Cardena, 1991; van der Kolk & van der Hart, 1989). Dissociation has been shown to be only modestly correlated with other constructs which are seen in the general population and are not related to psychopathology, such as hypnotizability, openness to experience, fantasy proneness and the capacity for absorption (Kihlstrom, Glisky, & Angiulo, 1994). On the other hand, our group (Bremner et al., 1992; Bremner et al., 1993) as well as others (Carlson & Rosser-Hogan, 1991; Koopman, Classen, & Spiegel, 1994; Loewenstein & Putnam, 1988; Marmar et al., 1994) have found higher dissociative symptomatology in patients with PTSD in comparison to controls, and an increase in dissociative states at the time of trauma in patients who later develop PTSD (Bremner et al., 1992; Marmar et al., 1994). Recall of the traumatic event appears to occur in a dissociated fashion similar to the way the event was originally experienced.

Little is known about the etiology of dissociative states. The automatic, almost seizure-like quality of dissociative states, and the fact that they often involve a replay of traumatic memories, suggests that abnormalities of brain regions involved in memory, such as the hippocampus, are involved in their etiology. Consistent with this, electrical stimulation of the hippocampus, amygdala, and adjacent cortex in human subjects has been shown to result in symptoms which are similar to those seen in dissociation in many cases, including the subjective sensation of fear, complex visual hallucinations (i.e., dissociative states), memory recall, deja vu, and emotional distress (Andermann & Horowitz, 1982; Gloor, Olivier, Quesney, Andermann, & Horowitz, 1982; Halgren, Walter, Cherlow, & Crandall, 1978). We have found an increase in dissociative symptomatology as measured with the Clinician Administered Dissociative States Scale (CADSS) and disruption of delayed word recall in normal subjects following intravenous administration of ketamine hydrochloride, a noncom-

petitive antagonist of the N-methyl-D-aspartate (NMDA) receptor. The NMDA receptor, which is highly concentrated in the hippocampus, is involved in memory function at the molecular level, through long-term potentiation (LTP). Subjects in this study had a wide range of dissociative symptoms with ketamine, including out of body experiences, feeling like their arms were like toothpicks, having gaps in time, feeling that time stood still, disturbances in the sense of self identity, and derealization (Krystal et al., 1994). Abnormalities of hippocampal function in PTSD may result in the altered memory recall typical of dissociation. Other possible mechanisms in dissociative states include dysfunction of thalamic gating of sensory information, resulting in a blocking of transmission of sensory information from the outside, combined with the generation of internal images derived from recalled memories which have the unreal quality typical of dream or dissociative states (Krystal et al., 1994).

Relevance of Stress-Induced Changes in Brain Regions Involved in Memory for the Current Controversy Surrounding the Validity of Childhood Memories of Abuse

Recently there has been considerable controversy concerning the validity of recall many years after the fact of events of childhood abuse. Some authors have claimed that some therapists, practicing specific types of therapy such as "recovered memory therapy," are suggesting to their patients abuse incidents which never occurred (Loftus, Garry, et al., 1994).

A number of experiments have suggested that insertions, deletions, and distortions occur which alter the nature of memory traces. Some authors have proposed that misleading questions result in enduring distortions of recall. In one study, subjects were asked to view a series of slides depicting stages in an auto-pedestrian accident. Over 80% of the subjects who had received misleading information after viewing the slides incorrectly identified the slides at the recall stage, whereas 90% of subjects who received correct information correctly identified the slides at the recall stage (Loftus & Loftus, 1980). These types of studies have been quoted as evidence that recalled memories of childhood abuse are subject to distortion and insertion of events which do not have a basis in historical fact. Other recent studies have shown that many individuals later forgot episodes of abuse (Loftus et al., 1994; Williams, 1994a). In one study, 38% of individuals forgot episodes of abuse 20 years after the fact which were serious enough to merit an emergency room visit at the time when they occurred (Williams, 1994a). The author of this study suggested that this is due to amnesia (repression) (Williams, 1994b), although other investigators claim that this could be due to "normal forgetting" (Loftus et al., 1994). An important issue here is whether patients with stress-related psychopathology have normal recall and whether traumatic events are stored in memory following the same rules as normal or mildly stressful memories (as in "flashbulb" memories).

The evidence suggests that memories for the types of events that resemble those experienced by childhood abuse victims are recalled in a similar fashion to normal memories or memories of "normal stressors" (reviewed in Ceci & Bruck, 1993). One study looked at 5- and 7-year-old children's recall of the details of a doctor's exam which involved either a genital exam or a routine checkup. There were no cases of free recall of genital touching in cases where children received the nongenital exam; with direct questioning, only one child incorrectly reported being genitally touched. Direct questioning revealed that a substantial number of children who had had a genital exam reported being touched in genital areas, who had not reported this event on the free recall condition. Accuracy of recall was better for the genital exam than for the nongenital exam. Children were highly resistant to misleading questions regarding details of the exam (Saywitz, Goodman, Nicholas, & Moan, 1991). This study suggests that the types of events which form the basis of childhood abuse may not be as subject to distortions, insertions and deletions as more "mundane" memories.

Based on what is known about the effects of stress on brain systems involved in memory, mechanisms other than "normal forgetting" are probably involved in the inability to remember events of childhood abuse. The hippocampus and adjacent perirhinal and parahippocampal cortices through the reciprocal connections with multiple neocortical areas have been hypothesized to bind together information from multiple sensory cortices into a single memory at the time of retrieval (Squire & Zola-Morgan, 1991). Abnormalities of hippocampal function in PTSD may affect this normal function of the hippocampus in bringing together memory elements from diverse neocortical sensory areas. This may account for the abnormal intrusion of some traumatic memories into consciousness, disintegration of dissociated traumatic memories, and the total lack of recall (amnesia) for other events. As reviewed above, neuromodulators released during stress acting on the hippocampus and other brain regions involved in memory can modulate memory function, suggesting that they could cause changes in memory formation and retrieval in survivors of childhood abuse. These are some neural mechanisms which might explain amnesia and delayed recall of childhood abuse experiences in abuse victims with stress-related psychopathology.

Implications of the Effects of Stress on Memory for Treatment

Alterations in memory are an important component of the clinical presentation of patients with stress-related disorders such as PTSD. Psychotherapy can involve integrating dissociated fragments of memories into a single unified whole with the associated affect. In order for this to take place, there must be discussion at some point of the traumatic events. Many therapists are concerned, however, about how to proceed with psychotherapy in light of the recent controversy concerning the engendering of false memories of abuse. They feel that if they ask directly about abuse, they may be accused of suggesting abuse events to their patients which did not in fact take place. It is accepted practice in psychotherapy to not lead the patient along by putting words into their mouths, or providing premature formulations. Patients should be allowed to tell their own story, not the story of their therapists. In addition, there is ample evidence that normal persons are susceptible to misleading questions, and victims of trauma may be even more susceptible to these effects than normal persons. In light of these facts, a neutral stance to taking a history about a range of events seems most appropriate, with positive responses being followed up. In patients who fail to report abuse, it probably is not good practice to pursue or "dig" based on hunches or suspicions.

The development of chronic PTSD symptomatology appears to be associated with an increased resistance to treatment (van der Kolk et al., 1994). If explicit memory traces are transferred from the hippocampus to neocortical areas in PTSD patients, as is suggested by the animal studies, one might speculate that this leads to an indelibility of the memory trace, and may be a marker of the change from acute to chronic PTSD. This in turn would lead to chronic flashbacks and intrusive memories which are resistant to subsequent modification through psychotherapy, unless an intervention can be made in the acute phase of PTSD.

Concluding Remarks

Stress exerts a wide range of effects on memory function and on brain regions involved in memory. Brain regions involved in memory function, such as the hippocampus and adjacent cortical regions, thalamus, prefrontal cortical loci (anteromedial prefrontal cortex, dorsolateral prefrontal cortex, and anterior cingulate), amygdala, parietal cortex, and sensory neocortical regions are affected by exposure to stress. These brain regions in turn mediate the stress response.

The effects of stress on memory has implications for understanding the symptomatology of patients with PTSD, the etiology of dissociative states, and the validity of childhood memories of abuse. Brain regions involved in memory probably mediate many of the symptoms of PTSD, such as intrusive memories and flashbacks. The gaps of memory, or amnestic episodes, seen in patients with PTSD may relate to deficient hippocampal function. Processes in which the hippocampus normally pulls together memory elements from diverse primary sensory cortical areas and recreate a unified multi-sensory memory may not occur normally, leading to the subjective experience of amnestic episodes. Deficits in function of the hippocampus and possibly adjacent cortical areas could lead to deficits in explicit memory encoding as well. Alterations in neuromodulators which have effects on memory formation could be responsible for the abnormal strengthening of some traumatic memories and amnesia for others.

The neural mechanisms of sensitization, fear conditioning and failure of extinction are relevant to understanding the effects of stress on memory. Stress sensitization occurs when there is an enhanced responsiveness to stressors following exposure to chronic stress. The amygdala is responsible for conditioned fear responses which are seen clinically in patients with PTSD. In conditioned fear, the pairing of a stimulus with a threat (such as electric shock) leads to an increase in fear responsiveness to the stimulus when it is presented alone. Sensitization refers to the increase in physiological responsiveness which occurs with repeated stimulation. Sensitization to stress may result in increased release of neuromodulators such as norepinephrine in the hippocampus, amygdala and other areas, leading to pathological retrieval of traumatic memories. Extinction is the decrease in responding to a stimulus which was previously paired with a threat, after the threat has been removed. Extinction to conditioned stimuli is mediated by neocortical and orbitofrontal inhibition of amygdala function. A failure of neocortical areas to inhibit the amygdala may explain a failure of extinction in PTSD. This results in the phenomenon commonly seen in traumatized patients in which reminders of the trauma continue to evoke marked anxiety and fear responses many years after exposure to the original trauma.

Understanding alterations in brain systems which play a role in memory has relevance to the treatment of PTSD. Psychotherapy can have the goal of integration of fragments of dissociated memories into a single unified whole with the appropriate affect and cognitions. Addressing abnormalities of emotional memory manifested by conditioned emotional responses with techniques such as implosion therapy may be of benefit (Keane, Fairbank, Caddell, & Zimering, 1989). Finally, understanding the brain mechanisms involved in alterations in memory in patients with PTSD

may lead to the development of new pharmacological treatments for PTSD which target these brain regions.

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References

Armanini, M. P., Hutchins, C., Stein, B. A., & Sapolsky, R. M. (1990). Glucocorticoid endangerment of hippocampal neurons is NMDA-receptor dependent. *Brain Research, 532,* 7-1.

Borrell, J., De Kloet, E. R., Versteeg, D. H. G., & Bohus, B. (1983). Inhibitory avoidance deficit following short-term adrenalectomy in the rat: The role of adrenal catecholamines. *Behavioral Neurology and Biology, 39,* 241.

Bower, G. H. (1981). Mood and memory. *American Psychologist, 36,* 129-148.

Bremner, J. D., Davis, M., Southwick, S. M., Krystal, J. H., & Charney, D. S. (1993). The neurobiology of posttraumatic stress disorder. In J. M. Oldham, M. G. Riba, & A. Tasman (Eds.), *Review of Psychiatry, Vol. 12* (pp. 182-204). Washington, DC: American Psychiatric Press.

Bremner, J. D., Ng, C. K., Staib, L., Markey, J., Duncan, J., Zubal, G., Krystal, J. H., Mazza, S., Rich, D., Southwick, S. M., Capelli, S., Seibyl, J. P., Dey, H., Soufer, R., Charney, D. S., & Innis, R. B. (1992). PET measurement of cerebral metabolism following a noradrenergic challenge in patients with posttraumatic stress disorder and in healthy subjects (abst.). *Journal of Nuclear Medicine, 34,* 205P-206P.

Bremner, J. D., Randall, P., Scott, T. M., Bronen, R. A., Seibyl, J. P., Southwick, S. M., Delaney, R. C., McCarthy, G., Charney, D. S., & Innis, R. B. (1995). MRI-based measurement of hippocampal volume in combat-related posttraumatic stress disorder. *American Journal of Psychiatry, 152,* 973-981.

Bremner, J. D., Scott, T. M., Delaney, R. C., Southwick, S. M., Mason, J. W., Johnson, D. R., Innis, R. B., McCarthy, G., & Charney, D. S. (1993). Deficits in short-term memory in post-traumatic stress disorder. *American Journal of Psychiatry, 150,* 1015-1019.

Bremner, J. D., Southwick, S. M., Brett, E., Fontana, A., Rosenheck, R., & Charney, D. S. (1992). Dissociation and posttraumatic stress disorder in Vietnam combat veterans. *American Journal of Psychiatry, 149,* 328-332.

Bremner, J. D., Southwick, S. M., & Charney, D. S. (1994). Etiologic factors in the development of posttraumatic stress disorder. In C. M. Mazure (Ed.), *Stress and psychiatric disorders* (pp. 149-186). Washington, DC: American Psychiatric Press.

Bremner, J. D., Southwick, S. M., Johnson, D. R., Yehuda, R., & Charney, D. S. (1993). Childhood physical abuse in combat-related posttraumatic stress disorder. *American Journal of Psychiatry, 150,* 235-239.

Bremner, J. D., Steinberg, M., Southwick, S. M., Johnson, D. R., & Charney, D. S. (1993). Use of the Structured Clinical Interview for DSMIV-Dissociative Disorders for systematic assessment of dissociative symptoms in posttraumatic stress disorder. *American Journal of Psychiatry, 150,* 1011-1014.

Butler, R. W., Braff, D. L., Rausch, J. L., Jenkins, M. A., Sprock, J., & Geyer, M. A. (1990). Physiological evidence of exaggerated startle response in a subgroup of Vietnam veterans with combat-related PTSD. *American Journal of Psychiatry, 147,* 1308-1312.

Cahill, L., Prins, B., Weber, M., & McGaugh, J. L. (1994). Alpha-adrenergic activation and memory for emotional events. *Nature, 371,* 702-703.

Carlson, E. B., & Rosser-Hogan, R. (1991). Trauma experiences, posttraumatic stress, dissociation, and depression in Cambodian refugees. *American Journal of Psychiatry, 148,* 1548-1552.

Cassiday, K. L., McNally, R. J., & Zeitlin, S. B. (1992). Cognitive processing of trauma cues in rape victims with posttraumatic stress disorder. *Cognitive Therapy Research, 16,* 283-295.

Ceci, S. J., & Bruck, M. (1993). Suggestibility of the child witness: A historical review and synthesis. *Psychological Bulletin, 113,* 403-439.

Chapman, W. P., Schroeder, H. R., Guyer, G., Brazier, M. A. B., Fager, C., Poppen, J. L., Solomon, H. C., & Yakolev, P. I. (1954). Physiological evidence concerning the importance of the amygdaloid nuclear region in the integration of circulating functions and emotion in man. *Science, 129,* 949-950.

Charney, D. S., Deutch, A. Y., Krystal, J. H., Southwick, S. M., & Davis, M. (1993). Psychobiologic mechanisms of posttraumatic stress disorder. *Archives of General Psychiatry, 50,* 294-299.

Damasio, A. R. (1990). Category-related recognition defects as a clue to the neural substrates of knowledge. *Trends in Neurosciences, 13,* 95-98.

Davis, M. (1992). The role of the amygdala in fear and anxiety. *Annual Reviews of Neuroscience, 15,* 353-375.

De Wied, D., & Croiset, G. (1991). Stress modulation of learning and memory processes. *Methods and Achievements in Experimental Pathology, 15,* 167-199.

Foa, E. B., Feske, U., Murdock, T. B., Kozak, M. J., & McCarthy, P. R. (1991). Processing of threat-related information in rape victims. *Journal of Abnormal Psychology, 100,* 156-162.

Gloor, P., Olivier, A., Quesney, L. F., Andermann, R., & Horowitz, S. (1982). The role of the limbic system in experiential phenomena of temporal lobe epilepsy. *Annals of Neurology, 12,* 129-144.

Goldman, P. S. (1971). Functional development of the prefrontal cortex in early life and the problem of neuronal plasticity. *Experimental Neurology, 32,* 366-387.

Goldman-Rakic, P. S. (1988). Topography of cognition: Parallel distributed networks in primate association cortex. *Annual Reviews of Neuroscience, 11,* 137-156.

Gold, P. E., & van Buskirk, R. (1975). Facilitation of time-dependent memory processes with posttrial epinephrine injections. *Behavioral Biology, 13,* 145-153.

Gold, P. E. (1992). A proposed neurobiological basis for regulating memory storage for significant events. In E. Winograd & U. Neisser (Eds.), *Affect and accuracy in recall: Studies in "flashbulb memories"* (pp. 141-161). London: Cambridge Press.

Gunne, L. M., & Reis, D. J. (1963). Changes in brain catecholamines associated with electrical stimulation of amygdaloid nucleus. *Life Science, 11,* 804-809.

Halgren, E., Walter, R. D., Cherlow, D. G., & Crandall, P. H. (1978). Mental phenomena evoked by electrical stimulation of the human hippocampal formation and amygdala. *Brain, 101,* 83-117.

Helweg-Larsen, P., Hoffmeyer, H., Kieler, J., Thaysen, E. H., Thaysen, J. H., Thygesen, P., & Wulff, M. H. (1952). Famine disease in German concentration camps: Complications and sequels. *Acta Medica Scandinavica, 274,* 235-460.

Hitchcock, J. M., & Davis, M. (1986). Lesions of the amygdala, but not of the cerebellum or red nucleus, block conditioned fear as measured with the potentiated startle paradigm. *Behavioral Neuroscience, 100,* 11-22.

Hitchcock, J. M., & Davis, M. (1991). Efferent pathway of the amygdala involved in conditioned fear as measured with the fear-potentiated startle paradigm. *Behavioral Neuroscience, 105,* 826-842.

Jarrell, T. W., Gentile, C. G., Romanski, L. M., McCabe, P. M., & Schneiderman, N. (1987). Involvement of cortical and thalamic auditory regions in retention of differential

bradycardiac conditioning to acoustic conditioned stimuli in rabbits. *Brain Research, 412,* 285-294.

Jonides, J., Smith, E. E., Koeppe, R. A., Awh, E., Minoshima, S., & Mintun, M. A. (1993). Spatial working memory in humans as revealed by PET. *Nature, 363,* 623-625.

Keane, T. M., Fairbank, J. A., Caddell, J. M., & Zimering, R. T. (1989). Implosive (flooding) therapy reduces symptoms of PTSD in Vietnam combat veterans. *Behavior Therapist, 20,* 245-260.

Kihlstrom, J. F. (1987). The cognitive unconscious. *Science, 237,* 1445-1452.

Kihlstrom, J. F., Glisky, M. L., & Angiulo, M. J. (1994). Dissociative tendencies and dissociative disorders. *Journal of Abnormal Psychology, 103,* 117-124.

Kim, J. J., & Fanselow, M. S. (1992). Modality-specific retrograde amnesia of fear. *Science, 256,* 675-677.

Koopman, C., Classen, C., & Spiegel, D. (1994). Predictors of posttraumatic stress symptoms among survivors of the Oakland/Berkeley, Calif., firestorm. *American Journal of Psychiatry, 151,* 888-894.

Krystal, J. H., Karper, L. P., Seibyl, J. P., Freeman, G. K., Delaney, R., Bremner, J. D., Heninger, G. R., Bowers, M. B., Jr., & Charney, D. S. (1994). Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans. *Archives of General Psychiatry, 51,* 199-214.

Krystal, J. H., Bennnett, A., Bremner, J. D., Southwick, S. M., & Charney, D. S. (in press). Toward a cognitive neuroscience of dissociation and altered memory functions in posttraumatic stress disorder. In M. J. Friedman, D. S. Charney, & A. Y. Deutch (Eds.), *Neurobiological and clinical consequences of stress: From normal adaptation to PTSD,* Washington DC: American Psychiatric Press.

LeDoux, J. E. (1977). Emotion. In *Handbook of physiology-The nervous system V* (pp. 419-459).

LeDoux, J. L (1993). Emotional memory: In search of systems and synapses. *Annals of the New York Academy of Sciences,* 149-157.

Liang, K. C., Juler, R. G., & McGaugh, J. L. (1986). Modulating effects of posttraining epinephrine on memory: involvement of the amygdala noradrenergic system. *Brain Research, 368,* 125-133.

Loftus, E. F., & Loftus, G. R. (1980). On the permanence of stored information in the human brain. *American Psychologist, 35,* 409-420.

Loftus, E. F., Garry, M., & Feldman, J. (1994). Forgetting sexual trauma: What does it mean when 38% forget? *Journal of Consulting and Clinical Psychology, 62,* 1177-1181.

Loftus, E. F., Polonsky, S., & Fullilove, M. T. (1994). Memories of childhood sexual abuse: Remembering and repressing. *Psychology of Women Quarterly, 18,* 67-84.

Loewenstein, R. J., & Putnam, F. (1988). A comparison study of dissociative symptoms in patients with partial-complex seizures, MPD, and PTSD. *Dissociation, 1,* 17-23.

Luine, V., Villages, M., Martinex, C., & McEwen, B. S. (1994). Repeated stress causes reversible impairments of spatial memory performance. *Brain Research, 639,* 167-170.

Marmar, C. R., Weiss, D. S., Schlenger, W. E., Fairbank, J. A., Jordan, B. K., Kulka, R. A., & Hough, R. L. (1994). Peritraumatic dissociation and posttraumatic stress in male Vietnam theater veterans. *American Journal of Psychiatry, 151,* 902-908.

McEwen B. S., Gould, E. A., & Sakai, R. R. (1992). The vulnerability of the hippocampus to protective and destructive effects of glucocorticoids in relation to stress. *British Journal of Psychiatry, 160,* 18-24.

McGaugh, J. L. (1989). Involvement of hormonal and neuromodulatory systems in the regulation of memory storage: Endogenous modulation of memory storage. *Annual Review of Neurosciences, 12,* 255-287.

McGaugh, J. L. (1990). Significance and remembrance: The role of neuromodulatory systems. *Psychological Sciences, 1,* 15-25.

McNally, R. J., Kaspi, S. P., Riemann, B. C., & Zeitlin, S. B. (1990). Selective processing of threat cues in posttraumatic stress disorder. *Journal of Abnormal Psychology, 99,* 398-402.

McNally, R. J., English, G. E., & Lipke, H. J. (1993). Assessment of intrusive cognition in PTSD: Use of the modified Stroop paradigm. *Journal of Traumatic Stress, 6,* 33-41.

Mishkin, M. (1978). Memory in monkeys severely impaired by combined but not separate removal of amygdala and hippocampus. *Nature, 173,* 297-298.

Morgan, M. A., & LeDoux, J. E. (1994). Medial orbital lesions increase resistance to extinction but do not affect acquisition of fear conditioning. *Proceedings of the Society for Neuroscience, 2,* 1006.

Moscovitch, M. (1985). Memory from infancy to old age: Implications for theories for normal and pathological memory. *Annals of the New York Academy of Sciences, 444,* 78-96.

Murray, E. A., & Mishkin, M. (1986). Visual recognition in monkeys following rhinal cortical ablations combined with either amygdalectomy or hippocampectomy. *Journal of Neurosciences, 6,* 1991-2003.

Nemiah, J. C. (1989). Janet redivivus: The centenary of *l'Automatisme Psychologique. American Journal of Psychiatry, 146,* 1527-1530.

Pardo, J. V., Fox, P. T., & Raichle, M. E. (1991). Localization of a human system for sustained attention by positron emission tomography. *Nature, 349,* 61-64.

Petersen, S. E., Fox, P. T., Posner, M. I., Mintun, M., & Raichle, M. E. (1988). Positron emission tomographic studies of the cortical anatomy of single-word processing. *Nature, 331,* 585-589.

Phillips, R. G., & LeDoux, J. E. (1992). Differential contribution of amygdala and hippocampus to cued and contextual fear conditioning. *Behavioral Neuroscience, 106,* 274-285.

Pitman, R. K. (1989). Posttraumatic stress disorder, hormones, and memory (editorial). *Biological Psychiatry, 26,* 221-223.

Pitman, R. K., Orr, S. P., & Lasko, N. B. (1993). Effects of intranasal vasopressin and oxytocin on physiologic responding during personal combat imagery in Vietnam veterans with posttraumatic stress disorder. *Psychiatry Research, 48,* 107-117.

Posner, M. I., Petersen, S. E., Fox, P. T., & Raichle, M. E. (1988). Localization of cognitive operations in the human brain. *Science, 240,* 1627-1631.

Prins, A., Kaloupek, D. G., & Keane, T. M. (in press). Psychophysiological evidence for autonomic arousal and startle in traumatized adult populations. In M. J. Friedman, D. S. Charney, & A. Y. Deutch (Eds.), *Neurobiological and clinical consequences of stress: From normal adaptation to PTSD.*

Putnam, F. W., Guroff, J. J., Silberman, E. K., Barban, L., & Post, R. M. (1986). The clinical phenomenology of multiple personality disorder: Review of 100 recent cases. *Journal of Clinical Psychiatry, 47,* 285-293.

Rosen, J. B., & Davis, M. (1988). Enhancement of acoustic startle by electrical stimulation of the amygdala. *Behavioral Neuroscience, 102,* 195-202.

Rosen, J. B., Hitchcock, J. M., Sananes, C. B., Miserendino, M. J., & Davis, M. (1991). A direct projection from the central nucleus of the amygdala to the acoustic startle pathway: Anterograde and retrograde tracing studies. *Behavioral Neuroscience, 105,* 817-825.

Sapolsky, R. M. (1985). A mechanism for glucocorticoid toxicity in the hippocampus: Increased neuronal vulnerability to metabolic insults. *Journal of Neuroscience, 5,* 1228-1232.

Sapolsky, R. M., Uno, H., Rebert, C. S., & Finch, C. E. (1990). Hippocampal damage associated with prolonged glucocorticoid exposure in primates. *Journal of Neuroscience, 10,* 2897-2902.

Sarter, M., & Markowitsch, H. J. (1985). Involvement of the amygdala in learning and memory: A critical review, with emphasis on anatomical relationship. *Behavioral Neuroscience, 99,* 342-380.

Save, E., Poucet, B., Foreman, N., & Buhot, M-C. (1992). Object exploration and reactions to spatial and nonspatial changes in hooded rats following damage to parietal cortex or hippocampal formation. *Behavioral Neuroscience, 106,* 447-456.

Saywitz, K. J., Goodman, G. S., Nicholas, E., & Moan, S. F. (1991). Children's memories of a physical examination involving genital touch: Implications for reports of child sexual abuse. *Journal of Consulting and Clinical Psychology, 59,* 682-691.

Schacter, D. (1995). Implicit memory: A new frontier for cognitive neuroscience. In M. S. Gazzaniga (Ed.), *The cognitive neurosciences* (pp. 815-819). Cambridge, MA: MIT Press.

Scoville, W. B., & Milner, B. (1957). Loss of recent memory after bilateral hippocampal lesions. *Journal of Neurology and Psychiatry, 20,* 11-21.
Southwick, S. M., Krystal, J. H., Morgan, C. A., Johnson, D., Nagy, L. M., Nicolaou, A., Heninger, G. R., & Charney, D. S. (1993). Abnormal noradrenergic function in posttraumatic stress disorder. *Archives of General Psychiatry, 50,* 266-274.
Spiegel, D., & Cardena, E. (1991). Disintegrated experiences: The dissociative disorders revisited. *Journal of Abnormal Psychology, 100,* 366-378.
Squire, L. R., Slater, P. C., & Chace, P. M. (1975). Retrograde amnesia: Temporal gradient in very long term memory following electroconvulsive therapy. *Science, 187,* 77-79.
Squire, L. R., & Zola-Morgan, S. (1991). The medial temporal lobe memory system. *Science, 253,* 1380-1386.
Sutker, P. B., Galina, H., West, J. A., & Allain, A. N. (1990). Trauma-induced weight loss and cognitive deficits among former prisoners of war. *American Journal of Psychiatry, 58,* 323-328.
Sutker, P. B., Winstead, D. K., Galina, Z. H., & Allain, A. N. (1991). Cognitive deficits and psychopathology among former prisoners of war and combat veterans of the Korean conflict. *American Journal of Psychiatry, 148,* 67-72.
Thygesen, P., Hermann, K., & Willanger, R. (1970). Concentration camp survivors in Denmark: Persecution, disease, disability, compensation. *Danish Medical Bulletin, 17,* 65-108.
Torrie, A. (1944). Psychosomatic casualties in the Middle East. *Lancet, 29,* 139-143.
Tulving, E., Kapur, S., Craik, F. I. M., Moscovitch, M., Houle, S. (1994). Hemispheric encoding/retrieval asymmetry in episodic memory: Positron emission tomography findings. *Proceedings of the National Academy of Sciences, USA, 91,* 2016-2020.
Turner, B. H., & Herkenham, M. (1991). Thalamoamygdaloid projections in the rat: A test of the amygdala's role in sensory processing. *Journal of Comparative Neurology, 313,* 295-325.
Uddo, M., Vasterling, J. T., Brailey, K., & Sutker, P. B. (1993). Memory and attention in posttraumatic stress disorder. *Journal of Psychopathology and Behavioral Assessment, 15,* 43-52.
Uno, H., Tarara, R., Else, J. G., Suleman, M. A., & Sapolsky, R. M. (1989). Hippocampal damage associated with prolonged and fatal stress in primates. *Journal of Neurosciences, 9,* 1705-1711.
van der Kolk, B. A., & van der Hart, O. (1989). Pierre Janet and the breakdown of adaptation in psychological trauma. *American Journal of Psychiatry, 146,* 12-17.
van der Kolk, B. A., Dreyfuss, D., Michaels, M., Shera, D., Berkowitz, R., Fisher, R., & Saxe, G. (1994). Fluoxetine in posttraumatic stress disorder. *Journal of Clinical Psychiatry, 55,* 517-522.
Watanabe, Y., Gould, E., & McEwen, B. S. (1992). Stress induces atrophy of apical dendrites of hippocampal CA3 pyramidal neurons. *Brain Research, 588,* 341-345.
Williams, L. M. (1994a). Recall of childhood trauma: A prospective study of women's memories of child sexual abuse. *Journal of Consulting and Clinical Psychology, 62,* 1167-1176.
Williams, L. M. (1994b). What does it mean to forget child sexual abuse? A reply to Loftus, Garry, and Feldman (1994). *Journal of Consulting and Clinical Psychology, 62,* 1182-1186.
Wooley, C. S., Gould, E., & McEwen, B. S. (1990). Exposure to excess glucocorticoids alters dendritic morphology of adult hippocampal pyramidal neurons. *Brain Research, 531,* 225-231.
Yehuda, R., Keefer, R. S. E., Harvey, P. D., Levengood, R. A., Gerber, D. K., Geni, J., & Siever, L. J. (1995). Learning and memory in combat veterans with posttraumatic stress disorder. *American Journal of Psychiatry, 152,* 137-139.
Zeitlin, S. B., & McNally, R. J. (1991). Implicit and explicit memory bias for threat in posttraumatic stress disorder. *Behavioral Research and Therapeutics, 29,* 451-457.
Zola-Morgan, S., Squire, L. R., & Amaral, D. G. (1989): Lesions of the amygdala that spare adjacent cortical regions do not impair memory or exacerbate the impairment following lesions of the hippocampal formation. *Journal of Neuroscience, 9,* 1922-36.

Zola-Morgan, S., Squire, L. R., Amaral, D. G., & Suzuki, W. A. (1989). Lesions of perirhinal and parahippocampal cortex that spare the amygdala and hippocampal formation produce severe memory impairment. *Journal of Neuroscience, 9,* 4355-4370.
Zola-Morgan, S. M., & Squire, L. R. (1990). The primate hippocampal formation: Evidence for a time-limited role in memory storage. *Science, 250,* 288-290.