Neural Mechanisms in Dissociative Amnesia for Childhood Abuse: Relevance to the Current Controversy Surrounding the "False Memory Syndrome"

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Objective: There is considerable controversy about delayed recall of childhood abuse. Some authors have claimed that there is a "false memory syndrome," in which therapists suggest to patients events that never actually occurred. These authors point to findings that suggest that memory traces are susceptible to modification. The purpose of this paper is to review the literature on the potential vulnerability of memory traces to modification and on the effects of stress on the neurobiology of memory. Method: The authors review findings on mechanisms involved in normal memory function, effects of stress on memory in normal persons, children's memory of stressful events, and alterations of memory function in psychiatric disorders. The effects of stress on specific brain regions and brain chemistry are also examined. Results: Neuropeptides and neurotransmitters released during stress can modulate memory function, acting at the level of the hippocampus, amygdala, and other brain regions involved in memory. Such release may interfere with the laying down of memory traces for incidents of childhood abuse. Also, childhood abuse may result in long-term alterations in the function of these neuromodulators. Conclusions: John Nemiah pointed out several years ago that alterations in memory in the form of dissociative amnesia are an important part of exposure to traumatic stressors, such as childhood abuse. The studies reviewed here show that extreme stress has long-term effects on memory. These findings may provide a model for understanding the mechanisms involved in dissociative amnesia, as well as a rationale for phenomena such as delayed recall of childhood abuse.

Recently there has been considerable controversy about the validity of memories of childhood abuse (1–5). Some individuals have reported delayed recall of forgotten abuse that occurred during childhood, many years earlier. These reports of delayed recall of abuse have been challenged on a number of fronts, and in some cases individuals have retracted their allegations. Some authors claim that psychotherapists practicing "recovered memory therapy" created false memories of abuse through leading questions or excessive insisting (2, 4). These therapists reportedly believe that psychopathology is related to childhood trauma and that the goal of therapy is to help patients remember incidents of previously forgotten abuse from childhood.

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The fact that many individuals forget episodes of childhood abuse is well established. As many as 38% of trauma victims who experienced abuse severe enough to result in a visit to a hospital emergency room had no memory of the event 20 or more years later (1, 2). At issue is the meaning of these findings. Some investigators have explained the loss of memory of abuse as secondary to "repression" or dissociative amnesia. They maintain that memories of abuse may not be available to consciousness for many years, or perhaps even for the individual's lifetime, although they are present in the mind (3). The opposite viewpoint holds that the loss of memories of abuse is a process of "normal forgetting" (4). These authors argue that there is a popular misconception that forgotten memories exist somewhere in the brain and are only awaiting the proper stimulus or means to bring them to consciousness (5). Whether there are special mechanisms involved in the loss of memory of episodes of extreme childhood abuse in traumatized patients that are not operative in the normal population is currently not known (6, 7).

Understanding the nature of dissociative amnesia is important in answering this question. In dissociative

amnesia, which can be associated with exposure to psychological trauma, information is not available to conscious awareness for an extended period of time, although it may have an influence on behavior. John Nemiah has long been interested in dissociative amnesia and the role that other cognitive factors, not available to conscious awareness, play in behavior. The delineation of these factors has recently become an important area for research in cognitive psychology, after a long period of neglect following Freud's early impact on the field of psychiatry (8, 9). In 1989 John Nemiah (10) and others (11, 12) drew attention to the important contribution that Janet made to psychiatry at the turn of the century in describing the splitting of consciousness that occurs in response to traumatic stress. Janet described a constellation of symptoms that we now categorize as being a part of posttraumatic stress disorder (PTSD) and the dissociative disorders. Empirical studies have since demonstrated that an increase in the dissociative symptom of amnesia, defined as gaps in memory not explained by ordinary forgetfulness, is associated with PTSD (13).

Findings from neurobiological studies of memory may provide insight into the nature of dissociative amnesia and delayed recall of childhood abuse in PTSD. What is known about the neurobiology of memory supports the idea that special mechanisms may be operative in recall of traumatic events, such as childhood abuse. In animal studies, traumatic stress has been shown to cause long-term changes in brain regions involved in memory. Neuromodulators released during stress have both strengthening and diminishing effects on memory traces, depending on the dose and the particular type of neuromodulator. Changes in brain regions involved in memory may underlie many of the symptoms of stress-related psychiatric disorders, including symptoms of amnesia (13, 14). In summary, there are a variety of reasons to believe that memories of abuse in traumatized patients might be different from normal memories. This paper will review the controversy surrounding the validity of childhood memories of abuse, asking whether special memory mechanisms, such as dissociative amnesia, may be operative in patients with stress-related disorders secondary to childhood abuse and whether these mechanisms can be explained from the standpoint of the neurobiology of memory. This approach may shed some light on the controversy surrounding the so-called "false memory syndrome."

MECHANISMS OF NORMAL MEMORY FUNCTION

In order to appreciate the issues involved in this controversy, it is important to review mechanisms in normal memory function. Memory formation involves encoding, consolidation, storage, and retrieval. Encoding is the initial laying down of the memory trace. Consolidation 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 susceptible to modification (15, 16). Storage involves the keeping of the memory trace over time. Retrieval is the process of bringing out a memory from storage into consciousness. The memorability of an event increases when that event is related to preexisting knowledge, is relevant to existing beliefs or expectations, and/or is related to other events at the time of encoding. Memory retrieval is enhanced by cues that are similar to the information supplied at the time of encoding. In addition, the memorability of an event increases when the event is relevant to expectations and beliefs about the event (17). In addition, stressful events are often more memorable than ordinary daily life events.

Memory traces that are available for immediate and conscious recall are known as "explicit" or "declarative" (18). Explicit memory includes free recall of facts and lists, as well as working memory, which is the ability to store information in a visual or verbal buffer while performing a particular operation utilizing that information. Types of memories not available for conscious recall are known as "implicit" memories (8, 9). Implicit memory can be demonstrated through a particular task or skill in which the knowledge is embedded. Memories of the emotions associated with an event are another type of implicit memory, which may not be available for conscious recall in the same way as explicit memories. These types of emotional memories can be studied in the laboratory by using the paradigm of conditioned fear. The conditioned fear paradigm 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, that were previously elicited only by the unconditioned stimulus. This model measures a type of emotional memory that is embedded in the conditioned response and is not available for conscious recall. Explicit memory is not fully developed in very young children, which suggests that memories from early in development are exclusively of the implicit type. Memories of extreme trauma may be stored in an implicit framework, as is suggested by the animal model of conditioned fear. These types of emotional memories may be available for conscious recall only during the experiencing of particular affective states. For these reasons, the mechanisms involved in these types of emotional memory may be of particular relevance to the recall of childhood abuse.

STOP SIGNS AND YIELD SIGNS: HOW MUCH INTEGRITY DO OUR MEMORIES HAVE?

Recently there has been considerable interest in the potential vulnerability of memory traces to modification after the original laying down of the memory trace. A number of studies have investigated the effects of misleading information on recall. For instance, using the verb "smashed" as opposed to the verb "hit" results in

higher estimates of speed of automobiles by subjects who have viewed a film of an automobile accident, as well as an increase in the number of subjects who incorrectly endorse the statement that broken glass was associated with the accident (19). In a well-known study (20) subjects were shown a series of slides that told a story involving a stop sign. These slides were followed by the reading of a similar verbal narrative in which the reference to the stop sign was replaced by a reference to a yield sign. When subjects were tested on recall of material related to the slides they were more likely to (incorrectly) report having seen a yield sign than subjects who did not receive the misleading information. Administration of a memory task in which phrases associated with a word such as "bed" were read off ("sleep," "rest," "awake") resulted in the false recall of the word "bed," even though the word was never administered (21). Memory can also involve a shift in recall toward facts that fit one's expectations. For example, after hearing a story in which the Six Million Dollar Man was said to be too weak to carry a can of paint, children tested 3 weeks later had a shift in their memory toward recall that was more congruous with their pretesting knowledge (22). In summary, several studies have shown that events after the laying down of the memory trace, such as provision of misleading information, are associated with alterations in recall. This has led to the conclusion by some authors that misleading information "overwrites," or replaces, the original memory trace (23).

Other authors have argued against the overwriting hypothesis. They point out that if subjects do not remember the original information, they may make a guess based on their recall of the misleading information. This would mean that their likelihood of getting the correct answer is less than that due to chance alone. In one study (24) subjects viewed slides that included a hammer, were then given misleading verbal information involving a screwdriver, and afterward were given a forced-choice test to identify what they had seen in the slides by choosing between a hammer and an item to which they had previously not been exposed (a wrench). The authors argued that if there is a true overwriting phenomenon related to misleading verbal material, then subjects exposed to misleading information should have poorer recall than subjects who have not been previously exposed to such information. In fact, there was no decrement in recall in the subjects for whom the misleading item was not one of the possible choices in the forced-choice test of recall. These findings argue against the overwriting hypothesis and in favor of other explanations for the effects of misleading information on recall, such as "source amnesia," or the forgetting of the location where the original memory was encoded. This possibility was examined in another study (25) by testing subjects for the source of their memories, as well as for the recalled item. There was no difference in recall between the subjects who had been exposed to misleading information and the control subjects (although see reference 26). On the basis of these studies, there is not sufficient evidence to conclude that suggestive information can result in the rewriting of memory (27, 28). There is not clear evidence in support of or against the idea that misleading information affects memory recall, and one author has concluded that the issue "may never be settled" (26).

These studies, however, may not be relevant to the current controversy surrounding delayed recall of incidents of childhood abuse. They involve assessments of nonstressful memories in normal individuals. Several lines of evidence suggest that stressful memories are stored in a manner that is different from storage of normal memories. Memories of stressful events are more likely to be stored as implicit memories and therefore to be less available for conscious recall. These types of memories may also be more resistant to permanent forgetting. Amnesia for episodes of childhood abuse may actually represent implicit memories of this type that are resistant to permanent forgetting but that are not available for conscious recall under normal circumstances.

EFFECTS OF STRESS ON MEMORY IN NORMAL PERSONS

Some investigators have started to look at recall of highly stressful (upsetting) events. After President Kennedy's assassination it was observed that most people had an enhanced awareness of where they were and what they were doing at the time they received news of his death. This led to a hypothesis formulated by Brown and Kulik (29) that certain events that are surprising and consequential (emotionally charged), which they described as "flashbulb memories," lead to an enhancement of memory of personal circumstances surrounding the event. These include such facts as what the person was wearing and doing at the time he or she received the news. In a study of memories of the attempt to assassinate President Reagan, stronger emotional reactions to hearing the news were associated with a greater consistency from 1 to 7 months after the event in memory of the details of personal circumstances at the time the news was received (30). Some studies of the explosion on Jan. 28, 1986, of the *Challenger* space shuttle (31, 32) but not others (33) showed a relationship between emotional upset at the time the news was received and ability to recall personal circumstances several months after the explosion. A relationship of high emotionality and surprise to vividness of memories has been found in memories of significant events that are of personal importance (as opposed to being of national importance) (34). Differences among study findings in the "flashbulb memory" literature may be related to differences in study design, for instance in the timing of the assessments.

Experimental paradigms have also been used to examine differences in memory of details regarding stressful and nonstressful situations. Subjects exposed to a mentally shocking film, in which a young boy is shot in the face, had impaired recall of details in the film that

preceded the outbreak of violence (35) and of words associated with the face (36), relative to subjects asked to recall details from a neutral film. Compared to subjects asked to recall details of neutral slides, subjects who viewed traumatic slides (in which someone has been injured) had better recall of central details of the slides and worse recall of peripheral details (37, 38). Subjects shown pictures depicting a crime scene focused on such objects as a knife or a gun to the exclusion of peripheral details (23). Recall of central details in stress-related slides is better than recall of peripheral content, even after the greater eye fixation on the central details of a stressful slide is controlled for (39). In summary, memory associated with stressful events, especially central and critical details but not peripheral details, appears to be greater than memory of nonstressful events. Studies showing impaired recall of traumatic slides have involved memory tests that assessed recall of peripheral material (40).

EFFECTS OF STRESS ON MEMORY IN CHILDREN: RELEVANCE FOR VALIDITY OF RECALL OF CHILDHOOD ABUSE

Studies have begun to examine memory in children for events that are similar to those of childhood abuse. Much of this research has been stimulated by a quest to determine the reliability of small children as eyewitnesses in court. Visits to the doctor have been utilized, since they involve touching of private areas or procedures such as blood drawing and injections, which bear some similarity to events that occur in childhood abuse. These studies have shown that small children are remarkably reliable and resistant to suggestion (40–42), although as the age of the children decreases there is an increase in suggestibility and a decrease in reliability (43, 44). Four-year-olds are better able to resist suggestion if they were participants in the event, rather than bystanders. In addition, children are very resistant to suggestions regarding abuse; studies show that it is very rare for children to make errors of commission, even with suggestive questions such as "He took your clothes off, didn't he?" (45, 46). Greater suggestibility is seen in very young children who are questioned by an adult (as opposed to another child), indicating that an eagerness to please authority figures plays a role in suggestibility for young children (43). Children undergoing physical examinations have been shown to be very reliable in the reporting of genital contact, in both open-ended and direct questioning, and reliability for questions about the genital examination is actually better than for questions about the nongenital physical examination (45, 46). Most of the children have not reported genital contact unless directly asked (43). These studies have implications for clinical treatment of childhood abuse. A lack of direct questioning about abuse experiences in history taking will probably result in many unreported cases of abuse.

Studies have also examined the relationship between stress and memory in children. In one experiment (47) children underwent either blood drawing or an interaction with a friendly stranger. There was no difference in memory between the stressful and nonstressful events as measured by identification of the blood-drawing technician or the friendly stranger. Other studies have also not shown an effect of the stress of blood drawing on memory in children. However, events deemed more stressful by doctors and nurses (and corroborated by children's self-reports), such as inoculation, have been associated with an enhancement of memory and a resistance to misleading suggestions. The stress of inoculation was also associated with a relative enhancement of memory for central details related to the procedure (41). These findings are convergent with those already cited, in that memory for central and emotionally relevant information is enhanced, while peripheral and unimportant information is not.

TRAUMATIC MEMORIES, LOST AND FOUND: THE ROLE OF DISSOCIATIVE AMNESIA IN STRESS-INDUCED PSYCHIATRIC DISORDERS

There is evidence that patients with stress-related psychiatric disorders, such as PTSD, manifest differences in memory function relative to normal persons. For instance, immediately after a major campaign in north Africa during World War II, about 5% of the soldiers who had been combatants had no memory of the events that had just occurred (48). Follow-up studies of World War II combat veterans have shown that many veterans continue to suffer from "blackouts," or loss of memory, many years after their periods of service. This phenomenon would be described today as the dissociative symptom of amnesia. Dissociative amnesia is not typically a normal phenomenon of memory, and Vietnam combat veterans with PTSD have higher levels than do Vietnam combat veterans without PTSD (13). Amnestic symptoms in these patients include gaps of memory that last from minutes to days. Some patients have reported driving down the highway from Boston to New Haven, Conn., and suddenly realizing that they had covered 2 hours 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 with a history of childhood sexual abuse reported to one of us that she had been talking on the telephone at her day hospital program and the next thing she knew she was at home in bed. These clinical case examples provide a feeling for the wide range of phenomena that characterize dissociative amnesia in patients with a history of exposure to extreme psychological trauma. A number of other studies have documented the existence of dissociative amnesia in patients with PTSD (49–55).

OTHER ALTERATIONS IN MEMORY FUNCTION IN PSYCHIATRIC DISORDERS RELATED TO TRAUMATIC STRESS

There are other types of alterations in memory, besides dissociative amnesia, that are associated with stress-related psychiatric disorders. A variety of studies have shown a relationship between exposure to traumatic stress and deficits in explicit memory function (free recall of facts or lists). Concentration camp survivors from World War II were found to have high rates of impairment in explicit memory function (56, 57). Veterans who were prisoners of war during the Korean conflict have worse performance on explicit memory tasks of free verbal recall, measured with the logical memory component of the Wechsler Memory Scale, than Korean conflict veterans without a history of containment (58, 59). Using the Wechsler Memory Scale logical (verbal memory) and figural (visual memory) components, we measured explicit memory function in Vietnam combat veterans with PTSD (N=26) and comparison subjects matched for factors that could affect memory function (N=15) (60). The PTSD patients had significantly poorer free verbal recall (explicit memory), without deficits in IQ as measured by the WAIS-R. We subsequently found deficits in explicit memory tasks of free verbal recall, measured by the Wechsler Memory Scale logical component, in adult survivors of childhood abuse seeking treatment for psychiatric disorders (our unpublished data). Deficits in explicit short-term memory among Vietnam combat veterans with PTSD have been shown by comparing those veterans with National Guard veterans without PTSD (on the Auditory Verbal Learning Test) (61) and with normal comparison subjects (on the California Verbal New Learning Test) (62). Lower IQ in combat veterans with PTSD than in comparison subjects may be due to a greater risk for the development of PTSD with lower IQ or a secondary effect of exposure to trauma (63). Studies of female Vietnam combat nurses with PTSD are currently in progress (J. Wolfe, personal communication, October 1994). Beirut adolescents with PTSD have also been shown to have worse academic performance than Beirut adolescents without PTSD (P. Saigh, personal communication, August 1994). These studies suggest deficits in explicit memory. Other studies of patients with PTSD involving explicit memory tasks have shown that these patients have greater enhancement of recall of trauma-related words, relative to recall of neutral words, than do comparison subjects (64). In summary, the findings are consistent with deficits in encoding on explicit memory tasks, deficits in retrieval, and enhanced encoding or retrieval of specific trauma-related material.

EFFECTS OF STRESS ON BRAIN REGIONS INVOLVED IN MEMORY FUNCTION

Different brain regions are involved in the mediation of individual aspects of memory function. The hippocampus and adjacent cortex, as well as dorsal medial nucleus of the thalamus, play important roles in explicit recall (65–67). The dorsolateral prefrontal cortex (also known as principal sulcus or middle frontal gyrus) is involved in explicit recall, as shown by working memory tasks (68). Parietal cortex has been demonstrated to be important in spatial memory and attention (69, 70). Memories are stored initially in the hippocampus and after several weeks are reorganized and stored in other brain areas, such as the neocortex (71). 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. Zola-Morgan and Squire (71) hypothesized that the role of the hippocampus is to bring together memory elements from diverse neocortical areas at the time of retrieval of explicit memory.

The amygdala is an important mediator of emotional memory (72). Conditioned fear is measured with the acoustic startle response, a primitive reflex that is part of the animal's response to threat. Lesions of the central nucleus of the amygdala have been shown to completely block fear-potentiated startle (73, 74), while electrical stimulation of the central nucleus increases acoustic startle (75). The amygdala integrates information that is necessary for the proper execution of the stress response, including (internal) emotion and information from the external environment (76).

Traumatic stress can result in long-term changes in brain regions involved in memory (7). Monkeys and other animal species exposed to extreme stress have been found to have damage to the CA2 and CA3 subfields of the hippocampus (77). It has been suggested that such damage is due to a relationship between high levels of glucocorticoids and stress (77–82). These structural changes are associated with deficits in memory (83).

The hippocampus also plays an important role in emotional memory for the context of a fear-inducing situation. In experiments involving conditioned fear responses, when a tone (conditioned stimulus) is paired with electric foot shock (unconditioned stimulus), reexposure of the animal to the tone results in conditioned fear responses (an increase in "freezing" responses, which are characteristic of fear), even in the absence of the shock. In addition, reintroduction to the context of the shock or to the environment where the shock took place (i.e., the testing box), even in the absence of the shock or the tone, results in conditioned fear responses. Lesions of the amygdala before fear conditioning block fear responses to both the simple stimulus (tone) and to the context of the foot shock. Lesions of the hippocampus, on the other hand, do not interfere with acquisition of conditioned emotional responses to the tone in the absence of the shock, although they do interfere with acquisition of conditioned emotional responses to the context (84). Lesions of the hippocampus 1 day after fear conditioning (but not as much as 28 days afterward) also abolish context-related fear responses, but not fear related to the cue (tone), while lesions of the amygdala block fear responses to both the cue and the context (85). These studies suggest that the hippocam-

pus has a time-limited role in fear responses to complex phenomena with stimuli from multiple senses, but not to stimuli from simple sensory stimuli.

It is unclear how information from the hippocampus reaches hypothalamic and brainstem targets that are involved in the expression of conditioned fear responses. The hippocampus may project to the bed nucleus of the stria terminalis, which has hypothalamic and brainstem projections similar to the projections of the central nucleus of the amygdala (86). The bed nucleus of the stria terminalis has been shown to be important in conditioned fear responses to contextual stimuli (87).

We compared hippocampal volume measured with magnetic resonance imaging in Vietnam combat veterans with PTSD (N=26) and healthy subjects (N=22) matched for factors that could affect hippocampal volume, including age, sex, race, years of education, height, weight, handedness, and years of alcohol abuse (88). The right hippocampal volume of the patients with combat-related PTSD was 8% smaller than that of the comparison subjects ($p<0.05$), but there was no significant difference in the volumes of comparison structures, including temporal lobe and caudate. Deficits in free verbal recall (explicit memory), as measured by percent retention on the Wechsler Memory Scale logical component, were associated with smaller right hippocampal volume in the PTSD patients ($r=0.64$, $p<0.05$) but not in the comparison subjects. Pitman et al. recently found lower left and right hippocampal volumes in patients with PTSD than in comparison subjects (R.K. Pitman, personal communication, May 19, 1995), while Stein et al. found smaller left hippocampal volumes in survivors of childhood abuse than in comparison subjects (M. Stein, personal communication, May 19, 1995). We also found a statistically significant 12% lower left hippocampal volume in 17 adult survivors of childhood physical and sexual abuse than in 17 comparison subjects who were matched on a case-by-case basis for age, sex, race, handedness, years of education, and years of alcohol abuse (our unpublished findings). We have also used positron emission tomography (PET) and [^{18}F]fluorodeoxyglucose to measure cerebral glucose metabolism following administration of yohimbine, which stimulates brain norepinephrine release and increases PTSD symptoms in patients with PTSD (89), and placebo to Vietnam combat veterans with PTSD (N=10) and healthy comparison subjects (N=10) (90). 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. In our PET study, the PTSD patients and comparison subjects differed in the effects of yohimbine administration on brain metabolism in orbitofrontal, temporal, parietal, and prefrontal cortex; the PTSD patients showed a tendency toward slower brain metabolism and the comparison subjects showed a tendency toward greater brain metabolism with yohimbine than with placebo. These findings are consistent with an increased release of norepinephrine in the brain following yohimbine administration to patients with PTSD. Since in the hippocampus norepinephrine acts as a neuromodulator that has effects on memory encoding and retrieval, this suggests that enhanced norepinephrine release in the hippocampus with stressors may be associated with the pathological recall that is typical of traumatic memories in patients with PTSD.

STRESS-INDUCED NEUROMODULATION OF MEMORY TRACES

Neuropeptides and neurotransmitters released during stress can modulate memory function. Neurotransmitters and neuropeptides released during stress that affect learning and memory include norepinephrine, epinephrine, ACTH, glucocorticoids, corticotropin-releasing factor (CRF), opioid peptides, endogenous benzodiazepines, dopamine, vasopressin, and oxytocin (91). Brain regions involved in memory, including the hippocampus and adjacent cortex, amygdala, and prefrontal cortex, are richly innervated by these neurotransmitters and neuropeptides.

Epinephrine has a modulatory effect on memory function. Studies of the effects of epinephrine (and other neuromodulators) have used the one-trial passive (inhibitory) avoidance test of memory. In this paradigm, the animal is placed in the starting chamber of an alley with two compartments and punished with foot shock as it enters the second compartment. The amount of time that passes (or the latency) before the animal enters the second chamber when it is placed there on the second day is used as an index of retention of the training experience. Removal of the adrenal medulla, site of most of the body's epinephrine, results in a blocking of passive avoidance behavior, which is restored by administration of adequate amounts of epinephrine (92). 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 (93, 94). Low-dose injections (0.2 μg) of norepinephrine into the amygdala facilitate memory function in an inhibitory avoidance task, while higher doses (0.5 μg) impair memory function (95). In summary, epinephrine and norepinephrine released during stress enhance the formation of memory traces.

ACTH and glucocorticoids also affect learning and memory. Low doses of ACTH given immediately after a new learning task enhance retention, while a 10-fold higher dose has the opposite effect (96, 97). ACTH also delays extinction of the avoidance response (97). The effects of ACTH on learning and memory are mediated through the hippocampus (98) and amygdala (99). Glucocorticoids, in contrast, enhance extinction in the conditioned fear paradigm (97). The neuropeptide CRF, which stimulates release of ACTH from the pituitary and hence glucocorticoids from the adrenal gland, has anxiogenic effects when administered into the cerebral ventricles. In low doses by this route of administration CRF also facilitates passive avoidance behavior (100).

Other neurotransmitters and neuropeptides released during stress have effects on learning and memory. Both the dopamine and acetylcholine brain systems play roles in enhancing memory formation (101). Opiate receptor agonists, when administered after training in a learning task, impair retention, while opiate receptor antagonists, such as naloxone, enhance retention (102). Opiate antagonists (naloxone) enhance retention of recently acquired information when injected into the amygdala (103). Vasopressin injected 3 hours before or after a task involving new learning increases resistance to extinction. The time course of vasopressin's effects suggests that it affects the consolidation phase of new learning. Vasopressin also facilitates passive avoidance behavior (104), while oxytocin has the opposite effect (91). γ-Aminobutyric acid (GABA) is the main inhibitory neurotransmitter in the brain and has receptor sites for benzodiazepines, which play a role in the stress response. GABA antagonists, such as bicuculline, which block the action of GABA, impair memory retention following administration into the amygdala, as measured by the inhibitory avoidance task, while GABA agonists have the opposite effect (105). The GABA antagonist picrotoxicin enhances the extinction of conditioned fear (97).

Recent studies have begun to address the question of neuromodulation of memory function with stress in human subjects. In one study (106), the β-adrenergic antagonist propranolol or placebo was administered to healthy human subjects 1 hour before a neutral or an emotionally arousing (stress-related) story. Propranolol, but not placebo, interfered with recall of the emotionally arousing story but not the neutral story. One interpretation of this study is that activation of β-adrenergic receptors in the brain enhances the encoding of emotionally arousing memories.

Findings related to neuromodulation of memory function are of importance for understanding delayed recall of childhood abuse. Increased release of neurotransmitters and neuropeptides during episodes of childhood abuse, with modulatory actions on memory function, may result in alterations in the laying down of memory traces for incidents of childhood abuse. These neurotransmitters and neuropeptides may also result in the enhancement of specific abuse-related traumatic memories (6). Long-term alterations in stress-related peptides and neurotransmitters in abused patients may affect recall of traumatic memories. For instance, Pitman et al. (107) showed that vasopressin enhances recall of trauma-related memories, while oxytocin diminishes recall, in patients with PTSD. These differences may be considered as due to the fact that abuse-related memories are of the implicit type while normal memories are of the explicit type. These classifications, however, may be an oversimplification of the variety of ways in which traumatic stress can result in a modulation of memory function. There are other mechanisms of memory function, which may represent subtypes of implicit memory, that can be modeled in the laboratory and are related to the pathophysiology of traumatic stress; these include stress sensitization, failure of extinction, and conditioned fear. These mechanisms, which are of relevance to understanding delayed recall of childhood abuse, are reviewed in the following section.

NEURAL MECHANISMS MEDIATING EFFECTS OF STRESS ON MEMORY

Stress Sensitization

Stress sensitization refers to the phenomenon by which 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 and 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 subsequent stressors (108). The clinical correlate of stress sensitization is the greater likelihood of PTSD in individuals who are repeatedly abused over a period of time than in individuals exposed to a single episode of abuse. 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, is associated with alterations in memory encoding and retrieval, which may have implications for understanding the mechanisms of delayed recall of childhood abuse.

Adult survivors of childhood abuse have a very difficult time with ordinary stressful events that normal persons can tolerate without much trouble. For instance, the stress of experiencing a minor automobile accident or having an argument with one's spouse can lead to a total decompensation in these patients. We found that a history of childhood physical abuse increases the risk for the development of combat-related PTSD (109). That study suggested 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). Israeli veterans with previous combat-related acute stress reactions have been found to be at greater risk for combat-related stress reactions than are combat veterans without a history of stress reaction in response to combat (110). There are other examples of how a history of exposure to prior stress increases the risk for stress-related symptoms upon reexposure to stressors (111).

Fear Conditioning

Fear conditioning is another neural mechanism that can be modeled in the laboratory and is highly relevant to victims of childhood abuse. In fear conditioning, a normally neutral stimulus (something that 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, learning

(conditioning) occurs so that the light alone eventually causes a fear response (72). Cues related to the original abuse can be very upsetting to victims of childhood abuse. For instance, being around a very dominating man can be very upsetting to a woman who was sexually abused by a dominating older male figure. There is evidence, as manifested by conditioned responses and other phenomena, that the amygdala mediates alterations in emotional memory 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 (112) and activation of the stress response system, as manifested by increases in levels of peripheral catecholamines (113). Exaggerated startle response (which is mediated by the amygdala in animals) has been associated with PTSD (114, 115).

Failure of Extinction

A failure of extinction of responses to fear-inducing stimuli is characteristic of individuals exposed to extreme stressors. Extinction refers to an inhibition of conditioned responding to cues associated with a fear-inducing stimulus that takes place gradually over time following the removal of the original fear-inducing stimulus. For instance, a survivor of childhood abuse who was locked in a dark closet during childhood may continue to have anxiety responses every time he or she is in a dark and enclosed place, even though such a cue no longer represents a real threat. On a neuroanatomical level, extinction involves neocortical (116, 117) and orbitofrontal (118) inhibition of amygdala function. Using PET, we found lower glucose metabolism at baseline in the temporal cortex of patients with PTSD than in comparison subjects (90). 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.

WORKING MODEL FOR NEUROBIOLOGY OF MEMORY ALTERATIONS IN SURVIVORS OF CHILDHOOD ABUSE

From what is known about the effects of stress on brain systems involved in memory, there is evidence that mechanisms other than "normal forgetting" are probably operative in the delayed recall of childhood abuse. As noted earlier, the hippocampus and adjacent cortices have been hypothesized to bind together information from multiple sensory cortices into a single memory at the time of retrieval. For instance, during an episode of sexual abuse there is the smell of the perpetrator, the sounds involved in the abuse, the visual appearance of the perpetrator, the scene where the abuse takes place, and the tactile sensations. All of these individual elements are stored in the primary sensory cortical areas to which they correspond. For instance, smell is stored in the olfactory cortex, vision in visual cortex, and sound in auditory cortex. When a similar situation recurs, the hippocampus and adjacent cortex activates cortical areas and brings together the diverse sensory elements in the recreation of the memory. 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 fragmentation of traumatic memories that is often seen in these patients and the clinical phenomenon of dissociative amnesia.

The amygdala is involved in several types of emotional memory (implicit memory), including conditioned fear and failure of extinction. The symptoms of patients with a history of childhood abuse are similar to the conditioned fear responses and failure of extinction that can be modeled in the laboratory. This similarity and the fact that alterations in amygdala function are seen with extreme stress in the laboratory suggest that altered amygdala function plays a prominent role in the symptoms of patients with a history of childhood abuse. The orbitofrontal cortex is also involved in extinction, so it is reasonable to assume that altered orbitofrontal cortical function plays a role in the failure of extinction seen clinically in victims of childhood abuse. Brain regions besides the amygdala and orbitofrontal cortex are involved in implicit memory function, which we have postulated is an important component in delayed recall of childhood abuse.

Neural mechanisms associated with traumatic stress may play a role in altered recall of childhood abuse. Fear conditioning manifests itself in abuse survivors by an increase in physiological responding with exposure to environmental cues that are reminiscent of the original trauma. For example, many sexual abuse survivors are sexually dysfunctional, because sexual activity reminds them of the original trauma and leads to an increase in physiological responding. In stress sensitization, ordinary stressors may lead to disproportionate responses by persons with prior histories of extreme stress. Failure of extinction results in repeated adverse emotional responses to reminders of the abuse for many years after it has occurred; the responses do not fade over time as they normally should. Neuropeptides and neurotransmitters released during stress can modulate memory function, acting at the level of the hippocampus, amygdala, and other brain regions involved in memory. Childhood abuse may result in long-term alterations in the function of these neuromodulators, which could lead to an overenhancement of memory traces related to abuse. Exposure to subsequent stressors could also be associated with altered release of neuromodulators, resulting in altered memory recall in PTSD patients. It may be that amnesia represents a self-protective mechanism by which abuse survivors avoid the conscious recall of traumatic memories or suppress responsiveness to environmental cues that could trigger responsiveness. This process could be a compensatory response to other neural mechanisms associated with traumatic stress, including fear conditioning, stress sensitization, and failure of extinction, which are associated with an increase in responsiveness to ordinary cues

that trigger recall of abuse-related memories. Consistent with this hypothesis, emerging findings suggest that a worsening of stress-related symptoms occurs upon recall of memories of abuse that had not been available to consciousness for many years because of dissociative amnesia.

Mechanisms involving state-dependent recall may also be applicable to amnesia for abuse (119). State-dependent recall refers to facilitation of memory retrieval by an affective state that is similar to the state at the time of encoding. For instance, memories that were encoded during a state of sadness will have a facilitated retrieval during similar states of sadness. Similar situations can occur for other emotional states. For victims of childhood abuse, emotions such as extreme fear or sadness may have predominated at the time of the original abuse. In a life free of major stressors, extreme fear or sadness rarely occurs and thus would not typically represent a state-dependent cue for recall. However, if these strong emotions were to recur, they could facilitate recall of apparently forgotten childhood abuse. For instance, a woman victimized by rape as an adult experiences extreme fear, which triggers the state-dependent recall of an event of childhood sexual abuse, during which she had experienced similar feelings.

Psychotherapy may be associated with recall of these types of events. Psychotherapy naturally involves the facilitation of recall through encouraging the investigation of feelings related to traumatic events. The psychotherapist may provide a supportive environment that allows the patient to experience strong emotions he or she may be afraid to experience outside of the therapeutic setting. It is therefore not surprising that traumatic events are often fully recalled for the first time during psychotherapy. This has led to a controversy about whether these recalled events are true or false. The fact that traumatic events are recalled during therapy does not necessarily imply, however, that they represent false memories.

IMPLICATIONS FOR TREATMENT

Many therapists are currently concerned 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 to their patients abuse events that did not in fact take place. Patients should be allowed to tell their own stories, not the stories of their therapists (120–123). Because of the ongoing questions regarding the effects of suggestibility on recall of abuse, it is important for the therapist to avoid imposing on the patient the therapist's own ideas regarding a past history of abuse. Patients with PTSD and dissociative disorders may be even more susceptible to suggestion than normal persons. However, it can be seen from studies such as those cited earlier that many patients, because of issues of shame and other reasons, will not report abuse unless asked directly. For instance, a patient treated by one of us reported that he had been in psychotherapy for 20 years without reporting his abuse, which was subsequently revealed through a direct question in an initial evaluation.

CONCLUSIONS

We have examined the question of the validity of memories of childhood abuse as it relates to the current controversy surrounding the so-called "false memory syndrome" from both theoretical and biological perspectives. Studies in cognitive psychology have provided evidence for an enhancement of memory of central details related to stressful events, to the exclusion of peripheral details, in normal human subjects. Much has been made in the popular press about the potential effects of suggestion on memory. A review of this literature raises as many questions as it answers.

Patients with PTSD have been shown to have greater than normal self-reported dissociative amnesia, which is defined as gaps in memory not due to normal forgetting. Other aspects of memory function, including verbal recall, are deficient in patients with chronic PTSD. Both preclinical and clinical studies support the idea that traumatic stress is associated with alterations in brain regions involved in memory, with associated functional memory deficits. Other concepts, such as state-dependent memory, stress sensitization, fear conditioning, failure of extinction, and modulation of memory traces during and after encoding by neurotransmitters and neuropeptides that are released in high levels during stress, provide potential explanations for delayed recall of memories of childhood abuse. These mechanisms are probably applicable only to patients with disorders such as PTSD secondary to abuse, and not to the entire range of individuals who are exposed to childhood abuse, including those who do not develop abuse-related psychiatric disorders.

Studies to date have provided only an incomplete picture of how biological mechanisms may explain phenomena such as delayed recall of childhood abuse and dissociative amnesia (124). We do not mean to imply that definitive biological mechanisms have been elucidated that could explain these phenomena. Rather, this paper was intended as a critical review of the current status of the topic and as a reminder that dissociative amnesia is an important part of the constellation of symptoms related to traumatic stress, as John Nemiah and others reminded us in 1989.

REFERENCES

1. Williams LM: Recall of childhood trauma: a prospective study of women's memories of child sexual abuse. J Consult Clin Psychol 1994; 62:1167–1176
2. Loftus EF, Polonsky S, Fullilove MT: Memories of childhood sexual abuse: remembering and repressing. Psychology of Women Quarterly 1994; 18:67–84
3. Williams LM: What does it mean to forget child sexual abuse? a reply to Loftus, Garry, and Feldman (1994). J Consult Clin Psychol 1994; 62:1182–1186

4. Loftus EF, Garry M, Feldman J: Forgetting sexual trauma: what does it mean when 38% forget? J Consult Clin Psychol 1994; 62:1177–1181
5. Loftus EF, Loftus GR: On the permanence of stored information in the human brain. Am Psychol 1980; 35:409–420
6. Pitman RK: Posttraumatic stress disorder, hormones, and memory (editorial). Biol Psychiatry 1989; 26:221–223
7. Bremner JD, Krystal JH, Southwick SM, Charney DS: Functional neuroanatomical correlates of the effects of stress on memory. J Trauma Stress 1995; 8:527–554
8. Schacter D: Implicit memory: a new frontier for cognitive neuroscience, in The Cognitive Neurosciences. Edited by Gazzaniga MS. Cambridge, Mass, MIT Press, 1995, pp 815–819
9. Kihlstrom JF: The cognitive unconscious. Science 1987; 237: 1445–1451
10. Nemiah JC: Janet redivivus: the centenary of *L'automatisme psychologique*. Am J Psychiatry 1989; 146:1527–1529
11. Putnam FW: Pierre Janet and modern views of dissociation. J Trauma Stress 1989; 2:413–429
12. van der Kolk BA, van der Hart O: Pierre Janet and the breakdown of adaptation in psychological trauma. Am J Psychiatry 1989; 146:1530–1540
13. Bremner JD, Steinberg M, Southwick SM, Johnson DR, Charney DS: Use of the Structured Clinical Interview for DSM-IV Dissociative Disorders for systematic assessment of dissociative symptoms in posttraumatic stress disorder. Am J Psychiatry 1993; 150:1011–1014
14. Charney DS, Deutch AY, Krystal JH, Southwick SM, Davis M: Psychobiologic mechanisms of posttraumatic stress disorder. Arch Gen Psychiatry 1993; 50:294–299
15. McGaugh JL, Herz MJ: Memory Consolidation. San Francisco, Albion, 1972
16. Squire LR, Slater PC, Chace PM: Retrograde amnesia: temporal gradient in very long term memory following electroconvulsive therapy. Science 1975; 187:77–79
17. Kihlstrom JF: Hypnosis, delayed recall, and the principles of memory. Int J Clin Exp Hypn 1994; 42:337–345
18. Squire LR, Zola-Morgan S: The medial temporal lobe memory system. Science 1991; 253:1380–1386
19. Loftus EF, Palmer JC: Reconstruction of automobile destruction: an example of the interaction between language and memory. J Verbal Learning and Verbal Behavior 1974; 13:585–589
20. Loftus EF, Miller DG, Burns HJ: Semantic integration of verbal information into a visual memory. J Exp Psychol Hum Learn Mem 1978; 4:19–31
21. Roediger HL, McDermont KB: Creating false memories: remembering words not presented in lists. J Exp Psychol Learn Mem Cogn 1995; 21:803–814
22. Ceci SJ, Caves RD, Howe MJA: Children's long-term memory for information that is incongruous with their prior knowledge. Br J Psychol 1981; 72:443–450
23. Loftus EF, Loftus GR, Messo J: Some facts about "weapon focus." Law and Human Behavior 1987; 11:55–62
24. McCloskey M, Zaragoza M: Misleading postevent information and memory for events: arguments and evidence against memory impairment hypotheses. J Exp Psychol Gen 1985; 114:1–16
25. Lindsay DS, Johnson MK: The eyewitness suggestibility effect and memory for source. Mem Cogn 1989; 17:349–358
26. Lindsay DS: Misleading suggestions can impair eyewitnesses' ability to remember event details. J Exp Psychol Learn Mem Cogn 1990; 16:1077–1083
27. Loftus EF, Schooler J, Wagenaar W: The fate of memory: comment on McCloskey and Zaragoza. J Exp Psychol Gen 1985; 114:375–380
28. McCloskey M, Zaragoza M: Postevent information and memory: reply to Loftus, Schooler and Wagenaar. J Exp Psychol Gen 1985; 114:381–387
29. Brown R, Kulik J: Flashbulb memories. Cognition 1977; 5:73–99
30. Pillemer D: Flashbulb memories of the assassination attempt on President Reagan. Cognition 1984; 16:63–80
31. Bohannon JN III, Symons VL: Flashbulb memories: confidence, consistency and quantity, in Affect and Accuracy in Recall: Studies in "Flashbulb Memories." Edited by Winograd E, Neisser U. New York, Cambridge University Press, 1992, pp 65–94
32. Bohannon JN: Flashbulb memories for the space shuttle disaster: a tale of two theories. Cognition 1988; 29:179–196
33. Neisser U, Harsch N: Phantom flashbulbs: false recollections of hearing the news about *Challenger*, in Affect and Accuracy in Recall: Studies in "Flashbulb Memories." Edited by Winograd E, Neisser U. New York, Cambridge University Press, 1992, pp 9–31
34. Rubin DC, Kozin M: Vivid memories. Cognition 1984; 16:81–95
35. Loftus EF, Burns TE: Mental shock can produce retrograde amnesia. Mem Cogn 1982; 10:318–323
36. Christianson S, Nilsson L: Functional amnesia as induced by psychological trauma. Mem Cogn 1984; 12:142–155
37. Christianson S, Loftus EF: Memory for traumatic events. Applied Cognitive Psychol 1987; 1:225–239
38. Christianson SA, Loftus EF: Remembering emotional events: the fate of detailed information. Cognition and Emotion 1991; 5:81–108
39. Christianson SA, Loftus EF, Hoffman H, Loftus GR: Eye fixations and memory for emotional events. J Exp Psychol Learn Mem Cogn 1991; 17:693–701
40. Ornstein PA, Gordon BN, Larus D: Children's memory for a personally experienced event: implications for testimony. Applied Cognitive Psychol 1992; 6:49–60
41. Goodman GS, Hirschman JE, Hepps JE, Rudy L: Children's memory for stressful events. Merrill-Palmer Quarterly 1991; 37:109–158
42. Saywitz KJ, Goodman GS, Nicholas E, Moan SF: Children's memories of a physical examination involving genital touch: implications for reports of child sexual abuse. J Consult Clin Psychol 1991; 59:682–691
43. Ceci SJ, Ross DF, Toglia MP: Suggestibility of children's memory: psycholegal implications. J Exp Psychol Gen 1987; 116:38–49
44. Ceci SJ, Bruck M: Suggestibility of the child witness: a historical review and synthesis. Psychol Bull 1993; 113:403–439
45. Goodman GS, Aman C: Children's use of anatomically detailed dolls to recount an event. Child Dev 1990; 61:1859–1871
46. Rudy L, Goodman GS: Effects of participation on children's reports: implications for children's testimony. Developmental Psychol 1991; 27:527–538
47. Oates K, Shrimpton S: Children's memories for stressful and non-stressful events. Med Sci Law 1991; 31:4–10
48. Torrie A: Psychosomatic casualties in the Middle East. Lancet 1944; 29:139–143
49. Spiegel D, Hunt T, Dondershine HE: Dissociation and hypnotizability in posttraumatic stress disorder. Am J Psychiatry 1988; 145:301–305
50. Bremner JD, Southwick S, Brett E, Fontana A, Rosenheck R, Charney DS: Dissociation and posttraumatic stress disorder in Vietnam combat veterans. Am J Psychiatry 1992; 149:328–332
51. Loewenstein RJ, Putnam F: A comparison study of dissociative symptoms in patients with partial-complex seizures, MPD, and PTSD. Dissociation 1988; 1:17–23
52. Carlson EB, Rosser-Hogan R: Trauma experiences, posttraumatic stress, dissociation, and depression in Cambodian refugees. Am J Psychiatry 1991; 148:1548–1551
53. Cardeña E, Spiegel D: Dissociative reactions to the San Francisco Bay Area earthquake of 1989. Am J Psychiatry 1993; 150: 474–478
54. Koopman C, Classen C, Spiegel D: Predictors of posttraumatic stress symptoms among survivors of the Oakland/Berkeley, Calif, firestorm. Am J Psychiatry 1994; 151:888–894
55. Marmar CR, Weiss DS, Schlenger WE, Fairbank JA, Jordan BK, Kulka RA, Hough RL: Peritraumatic dissociation and posttraumatic stress in male Vietnam theater veterans. Am J Psychiatry 1994; 151:902–907
56. Helweg-Larsen P, Hoffmeyer H, Kieler J, Thaysen EH, Thaysen JH, Thygesen P, Wulff MH: Famine disease in German concentration camps: complications and sequels. Acta Med Scand 1952; 274:235–460
57. Thygesen P, Hermann K, Willanger R: Concentration camp sur-

vivors in Denmark: persecution, disease, disability, compensation. Dan Med Bull 1970; 17:65–108
58. Sutker PB, Galina ZH, West JA, Allain AN: Trauma-induced weight loss and cognitive deficits among former prisoners of war. J Consult Clin Psychol 1990; 58:323–328
59. Sutker PB, Winstead DK, Galina ZH, Allain AN: Cognitive deficits and psychopathology among former prisoners of war and combat veterans of the Korean conflict. Am J Psychiatry 1991; 148:67–72
60. Bremner JD, Scott TM, Delaney RC, Southwick SM, Mason JW, Johnson DR, Innis RB, McCarthy G, Charney DS: Deficits in short-term memory in posttraumatic stress disorder. Am J Psychiatry 1993; 150:1015–1019
61. Uddo M, Vasterling JJ, Brailey K, Sutker PB: Memory and attention in combat-related post-traumatic stress disorder (PTSD). J Psychopathology and Behavioral Assessment 1993; 15:43–52
62. Yehuda R, Keefe RSE, Harvey PD, Levengood RA, Gerber DK, Geni J, Siever LJ: Learning and memory in combat veterans with posttraumatic stress disorder. Am J Psychiatry 1995; 152:137–139
63. McNally RJ, Shin LM: Association of intelligence with severity of posttraumatic stress disorder symptoms in Vietnam combat veterans. Am J Psychiatry 1995; 152:936–938
64. Zeitlin SB, McNally RJ: Implicit and explicit memory bias for threat in posttraumatic stress disorder. Behav Res Ther 1991; 29:451–457
65. Mishkin M: Memory in monkeys severely impaired by combined but not separate removal of amygdala and hippocampus. Nature 1978; 173:297–298
66. Murray EA, Mishkin M: Visual recognition in monkeys following rhinal cortical ablations combined with either amygdalectomy or hippocampectomy. J Neurosci 1986; 6:1991–2003
67. Zola-Morgan S, Squire LR, Amaral DG, Suzuki WA: Lesions of perirhinal and parahippocampal cortex that spare the amygdala and hippocampal formation produce severe memory impairment. J Neurosci 1989; 9:4355–4370
68. Goldman-Rakic PS: Topography of cognition: parallel distributed networks in primate association cortex. Annu Rev Neurosci 1988; 11:137–156
69. Save E, Poucet B, Foreman N, Buhot M-C: Object exploration and reactions to spatial and nonspatial changes in hooded rats following damage to parietal cortex or hippocampal formation. Behav Neurosci 1992; 106:447–456
70. Posner MI, Petersen SE, Fox PT, Raichle ME: Localization of cognitive operations in the human brain. Science 1988; 240: 1627–1631
71. Zola-Morgan SM, Squire LR: The primate hippocampal formation: evidence for a time-limited role in memory storage. Science 1990; 250:288–290
72. Davis M: The role of the amygdala in fear and anxiety. Annu Rev Neurosci 1992; 15:353–375
73. Hitchcock JM, Davis M: Lesions of the amygdala, but not of the cerebellum or red nucleus, block conditioned fear as measured with the potentiated startle paradigm. Behav Neurosci 1986; 100:11–22
74. Hitchcock JM, Sananes CB, Davis M: Sensitization of the startle reflex by footshock: blockade by lesions of the central nucleus of the amygdala or its efferent pathway to the brainstem. Behav Neurosci 1989; 103:509–518
75. Rosen JB, Davis M: Enhancement of acoustic startle by electrical stimulation of the amygdala. Behav Neurosci 1988; 102: 195–202
76. Parent MB, Tomaz C, McGaugh JL: Increased training in an aversively motivated task attenuates the memory-impairing effects of posttraining N-methyl-D-aspartate-induced amygdala lesions. Behav Neurosci 1992; 106:789–797
77. Uno H, Tarara R, Else JG, Suleman MA, Sapolsky RM: Hippocampal damage associated with prolonged and fatal stress in primates. J Neurosci 1989; 9:1705–1711
78. Sapolsky R, Krey L, McEwen B: Prolonged glucocorticoid exposure reduces hippocampal neuron number: implications for aging. J Neurosci 1985; 5:1221–1226
79. Sapolsky RM, Uno H, Rebert CS, Finch CE: Hippocampal damage associated with prolonged glucocorticoid exposure in primates. J Neurosci 1990; 10:2897–2902
80. Watanabe Y, Gould E, McEwen BS: Stress induces atrophy of apical dendrites of hippocampal CA3 pyramidal neurons. Brain Res 1992; 588:341–345
81. Wooley CS, Gould E, McEwen BS: Exposure to excess glucocorticoids alters dendritic morphology of adult hippocampal pyramidal neurons. Brain Res 1990; 531:225–231
82. McEwen BS, Gould EA, Sakai RR: The vulnerability of the hippocampus to protective and destructive effects of glucocorticoids in relation to stress. Br J Psychiatry 1992; 160:18–24
83. Luine V, Villegas M, Martinez C, McEwen BS: Repeated stress causes reversible impairments of spatial memory performance. Brain Res 1994; 639:167–170
84. Phillips RG, LeDoux JE: Differential contribution of amygdala and hippocampus to cued and contextual fear conditioning. Behav Neurosci 1992; 106:274–285
85. Kim JJ, Fanselow MS: Modality-specific retrograde amnesia of fear. Science 1992; 256:675–677
86. Holstege G, Meiners L, Tan K: Projections of the bed nucleus of the stria terminalis to the mesencephalon, pons and medulla oblongata in the cat. Exp Brain Res 1985; 58:379–391
87. Davis M, McNish K, Gewertz J: The role of the amygdala and bed nucleus of the stria terminalis in explicit cue conditioning and contextual fear conditioning using the fear-potentiated startle paradigm. Society of Neuroscience Abstracts (in press)
88. Bremner JD, Randall P, Scott TM, Bronen RA, Seibyl JP, Southwick SM, Delaney RC, McCarthy G, Charney DS, Innis RB: MRI-based measurement of hippocampal volume in combat-related posttraumatic stress disorder. Am J Psychiatry 1995; 152: 973–981
89. Southwick SM, Krystal JH, Morgan CA, Johnson D, Nagy LM, Nicolaou A, Heninger GR, Charney DS: Abnormal noradrenergic function in posttraumatic stress disorder. Arch Gen Psychiatry 1993; 50:266–274
90. Bremner JD, Ng CK, Staib L, Markey J, Duncan J, Zubal G, Krystal JH, Mazza S, Rich D, Southwick SM, Capelli S, Seibyl JP, Dey H, Soufer R, Charney DS, Innis RB: PET measurement of cerebral metabolism following a noradrenergic challenge in patients with posttraumatic stress disorder and in healthy subjects (abstract). J Nucl Med 1993; 34:205P–206P
91. De Wied D, Croiset G: Stress modulation of learning and memory processes. Methods Achiev Exp Pathol 1991; 15:167–199
92. Borrell J, De Kloet ER, Versteeg DHG, Bohus B: Inhibitory avoidance deficit following short-term adrenalectomy in the rat: the role of adrenal catecholamines. Behav Neural Biol 1983; 39:241–246
93. Gold PE, van Buskirk R: Facilitation of time-dependent memory processes with posttrial epinephrine injections. Behav Biol 1975; 13:145–153
94. Liang KC, Juler RG, McGaugh JL: Modulating effects of posttraining epinephrine on memory: involvement of the amygdala noradrenergic system. Brain Res 1986; 368:125–133
95. Liang KC, McGaugh JL, Yao HY: Involvement of amygdala pathways in the influence of post-training intra-amygdala norepinephrine and peripheral epinephrine on memory storage. Brain Res 1990; 508:225–233
96. McGaugh JL: Significance and remembrance: the role of neuromodulatory systems. Psychol Sci 1990; 1:15–25
97. De Wied D, Jolles J: Neuropeptides derived from pro-opiocortin: behavioral, physiological, and neurochemical effects. Physiol Rev 1982; 62:976–1059
98. Greidanus TB, De Wied D: Dorsal hippocampus: a site of action of neuropeptides on avoidance behavior? Pharmacol Biochem Behav 1976; 5(suppl 1):29–33
99. Greidanus TB, Croiset G, Bakker B, Bouman H: Amygdaloid lesions block the effect of neuropeptides (vasopressin, ACTH (4-10)) on avoidance behavior. Brain Res Bull 1979; 3:227
100. Dunn AJ, Berridge CW: Physiological and behavioral responses to corticotropin-releasing factor administration: is CRF a mediator of anxiety or stress responses? Brain Res Brain Res Rev 1990; 15:71–100

101. Gasbarri A, Introini-Collison IB, Packard MG, Pacitti C, McGaugh JL: Interaction of cholinergic-dopaminergic systems in the regulation of memory storage in aversively motivated learning tasks. Brain Res 1993; 627:72–78
102. Castellano C: Effects of morphine and heroin on discrimination learning and consolidation in mice. Psychopharmacology (Berl) 1975; 42:235–242
103. Introini-Collison IB, Nagahara AH, McGaugh JL: Memory-enhancement with intra-amygdala posttraining naloxone is blocked by concurrent administration of propranolol. Brain Res 1989; 476:94–101
104. Gaffori O, De Wied D: Time-related memory effects of vasopressin analogues in rats. Pharmacol Biochem Behav 1986; 25: 1125–1129
105. Brioni JD, Nagahara AH, McGaugh JL: Involvement of the amygdala GABAergic system in the modulation of memory storage. Brain Res 1989; 487:105–112
106. Cahill L, Prins B, Weber M, McGaugh JL: Beta-adrenergic activation and memory for emotional events. Nature 1994; 371: 702–704
107. Pitman RK, Orr SP, Lasko NB: Effects of intranasal vasopressin and oxytocin on physiologic responding during personal combat imagery in Vietnam veterans with posttraumatic stress disorder. Psychiatry Res 1993; 48:107–117
108. Abercrombie ED, Keller RW Jr, Zigmond MJ: Characterization of hippocampal norepinephrine release as measured by microdialysis perfusion: pharmacological and behavioral studies. Neuroscience 1988; 27:897–904
109. Bremner JD, Southwick SM, Johnson DR, Yehuda R, Charney DS: Childhood physical abuse and combat-related posttraumatic stress disorder in Vietnam veterans. Am J Psychiatry 1993; 150:235–239
110. Solomon Z, Garb R, Bleich A, Grupper D: Reactivation of combat-related posttraumatic stress disorder. Am J Psychiatry 1987; 144:51–55
111. Bremner JD, Southwick SM, Charney DS: Etiologic factors in the development of posttraumatic stress disorder, in Stress and Psychiatric Disorders. Edited by Mazure CM. Washington, DC, American Psychiatric Press, 1994, pp 149–186
112. Chapman WP, Schroeder HR, Guyer G, Brazier MAB, Fager C, Poppen JL, Solomon HC, Yakolev PI: Physiological evidence concerning the importance of the amygdaloid nuclear region in the integration of circulating functions and emotion in man. Science 1954; 129:949–950
113. Gunne LM, Reis DJ: Changes in brain catecholamines associated with electrical stimulation of amygdaloid nucleus. Life Sci 1963; 11:804–809
114. Butler RW, Braff DL, Rausch JL, Jenkins MA, Sprock J, Geyer MA: Physiological evidence of exaggerated startle response in a subgroup of Vietnam veterans with combat-related PTSD. Am J Psychiatry 1990; 147:1308–1312
115. McGaugh JL: Involvement of hormonal and neuromodulatory systems in the regulation of memory storage: endogenous modulation of memory storage. Annu Rev Neurosci 1989; 12: 255–287
116. Jarrell TW, Gentile CG, Romanski LM, McCabe PM, Schneiderman N: Involvement of cortical and thalamic auditory regions in retention of differential bradycardiac conditioning to acoustic conditioned stimuli in rabbits. Brain Res 1987; 412:285–294
117. LeDoux JE: Emotional memory: in search of systems and synapses. Ann NY Acad Sci 1993; 702:149–157
118. Morgan MA, LeDoux JE: Medial orbital lesions increase resistance to extinction but do not affect acquisition of fear conditioning (abstract). Proceedings of the Society of Neuroscience 1994; 2:1006
119. Bower GH: Mood and memory. Am Psychol 1981; 36:129–148
120. Kluft RP: Basic principles in conducting the treatment of multiple personality disorder, in Clinical Perspectives on Multiple Personality Disorder. Edited by Kluft RP, Fine CG. Washington, DC, American Psychiatric Press, 1993, pp 53–73
121. Fine CG: Treatment stabilization and crisis prevention: pacing the therapy of the multiple personality disorder patient. Psychiatr Clin North Am 1991; 14:661–675
122. Terr LC: Childhood trauma: an outline and overview. Am J Psychiatry 1991; 148:10–20
123. Herman JL, Schatzow E: Recovery and verification of memories of childhood sexual trauma. Psychoanal Psychol 1987; 4:1–14
124. Andreasen NC: Posttraumatic stress disorder: psychology, biology, and the Manichean warfare between false dichotomies (editorial). Am J Psychiatry 1995; 152:963–965

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