TRAUMA AND MEMORY

Clinical and Legal Controversies

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Neuroanatomical Correlates of the Effects of Stress on Memory: Relevance to the Validity of Memories of Childhood Abuse

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The recent controversy surrounding the validity of memories of childhood abuse has centered on the question of whether memories of abuse can remain dormant for many years before they come to the surface in the form of delayed recall. Authors on one side of the controversy suggest that memories of abuse can be not available to conscious recall secondary to a mechanism described clinically as amnesia or "repression."[1,2] The other side of the controversy claims that psychotherapists practicing a form of psychotherapy known as *recovered memory therapy* have suggested episodes of abuse to their patients which never in fact occurred, through leading questions or excessive insisting.[3]

The fact that many individuals forget episodes of childhood abuse is well established. As many as 38% of individuals who experienced abuse severe enough to result in a visit to the hospital emergency room had no memory of the event 20 or more years later.[1,4] An important question is whether there are special mechanisms involved in the loss of memory for episodes of extreme childhood abuse in traumatized patients that are not normally operative.[5,6]

Findings from studies of the neurobiology of memory may provide insight into questions about delayed recall of childhood abuse. Traumatic stress has been shown in animal studies to result in long-term changes in brain regions involved in memory.[7,8]

Neuromodulators released during stress have both strengthening and diminishing effects on memory traces, depending on the dose and the particular type of neuromodulator. Dissociative amnesia, defined as gaps in memory that are not due to ordinary forgetting, is associated clinically with traumatic stress, amd empirical studies have shown an increase in this symptom in patients with posttraumatic stress disorder (PTSD).[9] Changes in brain regions involved in memory may underlie many of the symptoms of stress-related psychiatric disorders, including symptoms of amnesia. This chapter will review the controversy surrounding the validity of childhood memories of abuse from the standpoint of the neurobiology of memory. We feel that this approach may shed some light on the controversy surrounding the so-called false memory syndrome.

Are Normal Memories Subject to Modification?

There has been considerable interest in the potential vulnerability of memory traces to modification. In a typical example of a study addressing this question, 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. The authors of this study concluded that misleading information led to an "overwriting" of the original memory trace.[10] Memory can also involve a shift in recall towards facts that fits one's expectations. For example, in a story in which the Six Million Dollar Man is said to be too weak to carry a can of paint, children tested 3 weeks later had a shift in their memory toward a recall that was more congruous with their pre-testing knowledge.[11]

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 chances of getting the correct answer are less than that due to chance alone. In a study by McCloskey and Zaragoza,[12] subjects were assessed with a test in which they saw slides, which included one of a hammer, were then given misleading verbal information involving a screwdriver, and then a forced-choice test of what they had seen in the slides, the choice being between a hammer and an item to which they had previously not been exposed (a wrench). The authors argue that if there is a true overwriting phenomenon with misleading verbal material, then subjects exposed to misleading information should have a decrement in recall in comparison with subjects who have not been previously exposed to such information. They in fact found that there was no decrement in recall in this paradigm in subjects for whom the misleading item was not one of the possible choices in the forced-choice test of recall.[12] The effects of "source amnesia," or the forgetting of the location where the original memory was encoded, was examined in another study

by testing subjects for the source of their memories as well as for the recalled item. There was no difference in recall in this paradigm between subjects who had been exposed to misleading information versus controls[13] (although see Lindsay[14]). Suggestibility effects may be due to the forgetting of the source of the memory, rather than an overwriting phenomenon. Based on a review of these studies, there is not sufficient evidence to conclude that suggestive information does or does not result in the rewriting of memory.[14–16]

Effects of Stress on Memory in Normal Persons

Studies of normal memory may not be entirely applicable to those of memory for stressful events. John F. Kennedy's assassination raised the observation 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[17] that certain events that are surprising and consequential (emotionally charged), which they described as "flashbulb memories," lead to an enhancement of memory for personal circumstances surrounding the event. These include such facts as what the person was wearing and what they were doing at the time they received the news. Studies of the explosion on January 28, 1986, of the space shuttle *Challenger* have shown a relationship between emotional upsetness and recall of personal circumstances upon hearing the news[18,19] (but see Neisser and Harsch[20]). Experimental paradigms have also been used to examine differences in memory of details during stressful compared to nonstressful situations. Studies of subjects who experienced traumatic slides involving injury or threat have found a more enhanced recall of central details of the slide and a reduced recall of peripheral details, in comparison with the recall of details of neutral slides.[21–23]

Studies of the effects of stress on memory in children have focused on the visit to the doctor, since it entails the touching of private areas, or procedures such as blood-drawing or injections, all of which are routine events in a doctor's office, but which are also similar to the types of events occurring in childhood abuse. These studies have shown that small children are remarkably resistant to suggestion.[24–30] Children undergoing physical exam have been shown to be very reliable in the reporting of genital contact, in both open-ended and direct questioning; they answered questions about the genital exam with better recall than for the nongenital physical exam.[25,27] Most of the children did not report genital contact unless they were directly asked.[27] These studes have implications for clinical treatment of childhood abuse, in that it can be expected that the lack of direct questioning during the history-taking about abuse experiences will probably result in many unreported cases of abuse. Stressful events such as innoculation have been associated with an enhancement of memory and a resistance to misleading suggestions. The stress of innoculation was also associated with a relative enhancement of memory for central details related to the procedure.[24] In summary, the

findings are consistent with an enhancing effect of stress on memory, especially on recall of central details.

Brain Mechanisms Involved in Normal Memory Function

These studies have examined both the potential fallibility of memory and the effects of stress on memory in normal persons. Findings from these studies may not be applicable to situations in which there is severe childhood abuse. For many patients, childhood abuse may be associated with long-term alterations in brain systems involved in memory. We will now briefly review the mechanisms involved in normal memory function. This will serve as a background to a discussion about the effects of stress on memory.

Memory formation involves encoding, or the initial laying down of the memory trace, storage, or consolidation, and retrieval. Consolidation occurs over several weeks or more, during which time the memory trace is susceptible to modification.[31,32] Memory function can be divided into declarative, or *explicit* memory, and nondeclarative, or *implicit* or *procedural* memory.[33] 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.

Memory is mediated by several connected subcortical and cortical brain regions. The amygdala, hippocampus, and adjacent cortical areas, including perirhinal, entorhinal, and parahippocampal cortex; medial thalamus, fornix, and mammillary bodies have been shown to play an important role in memory. Other regions involved in memory are the prefrontal cortex, including what is known as the *dorsolateral prefrontal cortex* (middle frontal gyrus, principal sulcus region, or Area 46); orbital gyrus, and anteromedial prefrontal cortex (including the anterior cingulate cortex), as well as the parietal association cortex. In addition, memories are stored in the primary cortical sensory and motor areas that correspond to the particular sensory modality related to the memory. These brain regions interact with one another in the mediation of memory function.

The hippocampus plays an important role in explicit memory. Hippocampal lesions impair acquisition of spatial information as measured by a number of tasks, for instance, the ability of rats to learn to swim to a submerged water platform.[34,35] Lesion studies have been performed in monkeys in order to reproduce the anterograde explicit memory impairment seen in individuals with surgical resection of the medial temporal lobes.[33] Lesions occurring within the hippocampal formation (dentate gyrus, hippocampus proper, subicular complex, and entorhinal cortex), amygdala, and surrounding

perirhinal and parahippocampal cortices have been termed the *H + A + lesion,* where *H* refers to the hippocampus, *A* to the amygdala, and + to the surrounding areas. Monkeys with H + A + lesions have been shown to be severely impaired in delayed matching to sample memory tasks (a test of the working-memory type of explicit memory function), during which the animal has to remember where an object is located after a time delay, but is normal in acquiring and retaining motor skills.[36] Monkeys with the H + lesion were also found to have impaired explicit memory, although not to the degree of the H + A + monkeys. Furthermore, damage to the amygdala alone was not associated with declarative memory impairment,[37] whereas damage to the cortical areas adjacent to the amygdala, including the perirhinal cortex and parahippocampal gyrus (which has important efferent and afferent connections with the hippocampus), was associated with pronounced explicit memory impairment.[38,39] These studies suggest that the explicit memory impairment associated with the H + A + lesion is due to damage to the hippocampal region (dentate, hippocampus proper, subicular complex, and entorhinal cortex) and to the adjacent perirhinal cortex and parahippocampal gyrus. In addition to mediating the working-memory type of explicit memory function involved in the delayed matching to sample task, the hippocampus, but not the amygdala, plays an important role in the memory of where an object is located in space.[40]

Findings in human subjects are consistent with those in monkeys, which demonstrate a role for the hippocampus and adjacent cortex in explicit recall. Case studies, such as the famous case of H.M., have shown a relationship between severe deficits in explicit memory measured with free verbal recall and bilateral resection of the medial temporal lobes (i.e., hippocampus and adjacent structures).[41] Patients with Korsakoff's amnesia, in which damage occurs specifically to the hippocampus and dorsal-medial nucleus of the thalamus because of a thiamine deficiency, exhibit a specific and severe deficit in explicit memory measured by free verbal recall. In addition, in patients with hypoxic encephalopathy following cardiac arrest, which is associated with glutamate toxicity to the brain, the most common cognitive impairment is a deficit in explicit memory function measured by free verbal recall. Following the interruption of oxygen to the brain that occurs with a cardiac arrest, the brain region that is most susceptible to damage is the CA1 region of the hippocampus. Positron emission tomography (PET) studies of cerebral blood flow with $[^{15}O]H_2O$ also indicate a role for the hippocampus in explicit memory with the finding of an increase in right hippocampal blood flow during a stem-completion explicit memory task.[42] In summary, several lines of evidence from preclinical and clinical studies have demonstrated a role for the hippocampus and adjacent structures in explicit recall.

The thalamus is a gateway for sensory information relayed to multiple brain areas, including the amygdala and primary sensory neocortical areas.[43,44] A portion of the thalamus, the dorsal-medial nucleus, also plays a role in explicit memory tasks of free verbal recall. In one case, the patient N.A. received a fencing injury to the mediodorsal thalamic nucleus. He showed normal intelligence and general cognitive abilities, could remember events from before the accident, and was able to converse normally. How-

ever, he was unable to learn the names of new people or learn new information. These findings show that the medial thalamus is involved in explicit memory.

The amygdala is an important mediator of emotional memory. Monkeys with amygdala lesions have been shown to be less fearful than normal (i.e., they have alterations in emotional memory) but are without impairment in explicit (cognitive) memory, whereas monkeys with lesions of the hippocampus or adjacent cortex had normal fear responses (i.e., abnormal emotional memory) but severe impairments in explicit (cognitive) memory.[45] The paradigm of conditioned fear has been used as an animal model for stress-induced abnormalities of emotional memory.[46,47] Noise bursts elicit the acoustic startle response, which is used in the measurement of the conditioned fear response. In the fear-potentiated startle paradigm, 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 an increase in the startle response (referred to as *fear-potentiated startle*). The shock in this example is termed the *unconditioned stimulus,* because no training was required for it to have the effect of potentiating startle; the light is referred to as the *conditioned stimulus,* because the training trials pairing it with the shock were required for it to develop the capacity for potentiating the startle response.[46,47]

The neuroanatomy and neurophysiology of conditioned fear responses in animals have been well characterized (see Davis[46,47]). Lesions of the central nucleus of the amygdala have been shown to completely block fear-potentiated startle,[48,49] whereas electrical stimulation of the central nucleus increases acoustic startle.[50] The central nucleus of the amygdala projects to a variety of brain structures via the stria terminalis and the ventral amygdalofugal pathway. One pathway is from the central nucleus to the brainstem startle reflex circuit (nucleus reticularis pontis caudalis).[51] Lesions of this pathway at any point (caudal lateral hypothalamus-subthalamic area, substantia nigra, central tegmental field) block the development of fear-potentiated startle, whereas lesions of fibers which project outward from the central nucleus of the amygdala to sites other than the brainstem startle circuit have no effect.[52] The excitatory neurotransmitters play an important role in fear conditioning mediated by the amygdala, as demonstrated by the fact that antagonists of the N-methyl-D-aspartate (NMDA) receptor infused into the amygdala block the acquisition (but not the expression) of the fear-potentiated startle response.[53,54]

Considerable evidence suggests that the dorsolateral prefrontal cortex (principal sulcus, or middle frontal gyrus) is involved in the working memory type of explicit memory function.[55] In nonhuman primates, working memory is assessed by delayed-response tasks, in which monkeys perform tasks based on previously received information after a short time delay. These tasks typically involve learning a "set of rules," which is considered an important component of the memory function mediated by the dorsolateral prefrontal cortex. Lesions of the dorsolateral prefrontal cortex result in

deficits in working memory tasks, but explicit memory for features of the stimuli remain unaffected.[55] PET $[^{15}O]H_2O$ studies of cerebral blood flow in normal human subjects also demonstrate a role for the dorsolateral prefrontal cortex in both the encoding and retrieval of explicit memory traces[42,56,57,58] and attention.[59]

The anteromedial (or ventromedial) prefrontal cortex includes the anterior cingulate gyrus and is functionally and anatomically distinct from the dorsolateral prefrontal cortex. In the late nineteenth century the famous patient named Phineas Gage had a projectile metal spike pass through his frontal cortex, with damage specifically to the anterior cingulate, anteromedial prefrontal cortex, and parts of the orbitofrontal cortex. After the accident, the patient had normal memory recall and cognitive function, but his behavior deteriorated to irresponsibility, profanity, and a lack of social conventions, which indicated a deficit in the planning and execution of socially suitable behavior. This case suggests that the anteromedial frontal cortex (including the anterior cingulate) is responsible for socially appropriate behavior and the processing of emotionally related stimuli.[60] PET $[^{15}O]H_2O$ studies show an activation of the anterior cingulate occurring along with visual and verbal association tasks[56] and the Stroop paradigm.[59]

The orbitofrontal cortex is another frontal cortical area important to the effects of stress on memory. The orbitofrontal cortex is the primary sensory cortical area for smell. It also plays a role in the fear response, extinction, and certain types of memory. Lesions of the orbitofrontal cortex result in deficits in explicit memory of visual features of objects, but not in explicit memory for delayed-response tasks (i.e., working memory), which functionally differentiates it from the dorsolateral prefrontal cortex.[55] Studies of rats, however, in which olfaction is the primary stimulus, have shown deficits in delayed-response tasks in association with lesions of the orbitofrontal cortex.[61] Lesions of the medial orbitofrontal cortex in rats result in a significant delay in extinction to conditioned stimuli in the tone–footshock pairing paradigm, which suggests that this region plays a role in extinction of conditioned stimuli.[62]

Parietal cortex has been demonstrated to play an important role in spatial memory and attention. Single-cell recordings from alert monkeys have shown an activation of the parietal cortex when monkeys are required to attend to a visual location.[63] In PET $[^{15}O]H_2O$ studies of sustained vigilance and attention in healthy volunteers, subjects were asked to perform tasks of sustained visual attention (maintaining passive visual fixation on a mark on a screen while detecting pauses) and somatosensory attention (maintaining attention on their great toe while detecting pauses in a series of touches). Regardless of modality of sensory input, sustained attention was associated with increases in blood flow in the right prefrontal and superior parietal cortex.[64] Tasks of working memory have also shown activation of the right parietal cortex.[58]

In addition to the hippocampus and other subcortical structures, explicit memory storage also takes place in sensory brain areas in which an event is first experienced.[65]

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. PET $[^{15}O]H_2O$ studies of word presentation have shown an activation of the striate (primary visual) and extrastriate cortex (visual association cortex) in association with visual word presentation, and activation of the middle temporal gyrus (primary auditory cortex), temporal-parietal cortex, and inferior cingulate cortex along with explicit memory tasks involving verbal word presentation.[56]

Explicit memory formation is not instantaneous. After the laying down of the original memory trace, a process that can take from weeks to months occurs, called *consolidation,* during which the stored memory is subject to modification or deletion. Studies of rats suggest that explicit memory formation can be affected for weeks after the laying down of the original memory trace. Electroconvulsive treatments (ECT) after training sessions impair memory for the training experience. As the interval between the ECT and the training session increases, the severity of memory impairment decreases.[66] 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 of recall of television programs occurring 1 to 2 years before the administration of ECT, while memory of older programs is normal.[67] 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 intact hippocampus exhibited a pattern of remembering recently learned objects more than they did objects learned in the past. Monkeys with lesions of the hippocampus were impaired in the recall of recently learned objects, although their recall of objects learned in the distant past was normal.[68] The evidence is consistent with the fact that memories are stored in the primary neocortical sensory and motor areas and later evoked in those same cortical areas.[69] It has been hypothesized[68] 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 neocortex may also play a role in some types of implicit memory function. Patients with anterograde amnesia (i.e., deficits in explicit memory, or the recall of things such as names and facts) do not necessarily lose all aspects of short-term memory function. These patients show evidence of intact 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 amnesic patients. Priming effects require only the intactness of the cortical sensory area in which the memory was originally stored.[65]

Effects of Stress on Brain Regions Involved in Memory

Efficient recall of memories associated with previous stressors is crucial for survival. For instance, if one encounters a dangerous animal, the rapid recall of the memory of a previous encounter with a dangerous animal of the same type may be life saving. Brain regions involved in the recall of memory simultaneously activate the body's stress response system, leading to increased release of stress-related neurotransmitters and neuropeptides. These in turn modulate the encoding of memory, which results in a type of feedback loop of the body's stress response system on memory storage.

Brain regions involved in memory also play a prominent role in the execution of the stress response. In the early part of this century the observation was made that, with the removal of the cerebral cortex, a hyperexcitability of anger developed, which was termed *sham rage*.[69,70] Animals in the sham-rage state were quick to attack, and behaved as if they were experiencing a profoundly threatening situation. Papez[71] proposed that the hypothalamus, thalamus, hippocampus, and cingulate are responsible for the behaviors of the decorticate cat. Kluver and Bucy[72,73] noted that removal of the temporal lobe (including hippocampus and amygdala) resulted in "psychic blindness," or the absence of anger and fear. These observations led to the development of the concept of the limbic brain, in which the brain regions listed above (and others, including the orbitofrontal cortex) mediate the stress response.[74] The circuits constructed by these authors are no longer valid, based on the current evidence, although the individual brain regions described above as being part of the limbic system play an important role in the effects of stress on memory function. There is considerable literature claiming that stress also results in alterations in memory function. Therefore, the brain regions that are responsible for memory function and the stress response are in turn affected by exposure to traumatic stress. We review below the effects of stress on brain regions involved in memory.

Stress has effects on the hippocampus, which leads to both changes in its cytoarchitecture as well as to deficits in explicit recall.[75] Twenty-one days of restraint stress has been shown to be associated with deficits in spatial memory as measured by the radial arm maze.[76] A release of glucocorticoids follows exposure to stress, and the hippocampus is a major target organ for glucocorticoids in the brain. In addition, the hippocampus appears to play an important role in the pituitary–adrenocortical response to stress.[77] Studies of monkeys who died spontaneously following exposure to severe stress from improper caging and overcrowding were found on autopsy to have multiple gastric ulcers, which is consistent with exposure to chronic stress, and hyperplastic adrenal cortices, which is consistent with sustained glucocorticoid release.[78] They also suffered damage to the CA2 and CA3 subfields of the hippocampus. Follow-up studies suggested that hippocampal damage was associated with direct exposure of glucocorticoids to the hippocampus.[79] Studies in a variety of animal species[80,81] have

shown that direct glucocorticoid exposure results in a loss of pyramidal neurons[82,78] and dendritic branching[83,84] which are steroid- and tissue-specific.[85,86] Glucocorticoids appear to exert their effect by increasing the vulnerability of hippocampal neurons to endogenously released excitatory amino acids.[87–90] The same paradigm of stress exposure which increases glucocorticoids and causes loss of apical dendritic branching in the CA3 region of the hippocampus[84] is associated with deficits in spatial memory.[76] This suggests that the effects of glucocorticoids on the hippocampus have functional implications.

The hippocampus also plays an important role in emotional memory of the context of a fear-inducing situation. In conditioned fear response experiments where a tone (conditioned stimulus) is paired with an electric footshock (unconditioned stimulus), reexposure of the animal to the tone will result in conditioned fear responses (increase in "freezing" responses, which is characteristic of fear), even in the absence of the shock. In addition, reintroduction to the context of the shock, or the environment where the shock took place (the testing box), even in the absence of the shock or the tone, will result in conditioned fear responses. Lesions of the amygdala before fear conditioning block fear responses to both simple stimuli (tone) and to the context of the footshock. 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.[91] Lesions of the hippocampus 1 day after fear conditioning (but not as much as 28 days after fear conditioning) also abolish context-related fear responses, but not the fear response related to the cue (tone), while lesions of the amygdala block fear responses to both the cue and the context.[92] These studies suggest that the hippocampus has a time-limited role in fear responses to complex phenomena with stimuli from multiple sensory modalities, but not to stimuli from simple sensory stimuli.

Stress also has effects on amygdala function. The amygdala integrates information necessary for the proper execution of the stress response, including (internal) emotion and information from the external environment.[93–95] Information from the environment that has emotional significance is transmitted through the dorsal thalamus to sensory cortical receiving areas, and from there to the amygdala.[96] Emotional responses to auditory stimuli are also mediated by direct projections from the medial geniculate in the thalamus to the amygdala, which suggests that the cerebral cortex is not necessary for emotional responses to stimuli.[97] Evidence suggests that the lateral nucleus of the amygdala is the site of convergence of stimuli from multiple sensory modalities, including somatosensory and auditory stimuli. This suggests that this region may be the site where information from unconditioned stimuli (footshock) and conditioned stimuli (tone) converge, and are translated into a final common pathway of the conditioned emotional response.[98] The amygdala then activates the peripheral sympathetic system, which plays a key role in the stress response, through the lateral nucleus of the hypothalamus and the central gray, leading to increased heart rate and blood pressure, as well as activating other aspects of the body's stress response system. Projections from

the central nucleus of the amygdala to brainstem regions, including the parabrachial nucleus, dorsal motor vagal complex, and nucleus of the solitary tract, mediate the cardiovascular response to stress (increased heart rate and blood pressure).[99] Repeated exposure to stress can result in an exaggerated startle response, which indicates an increased sensitivity of amygdala function.

Very little is known about the effects of stress on dorsolateral prefrontal cortical function. Studies are currently underway using the Wisconsin Card Sort Test, which is felt to represent a measure of dorsolateral prefrontal cortical function, in PTSD patients and controls (R. Yehuda, personal communication, 1994). We have found a differential effect of yohimbine on dorsolateral prefrontal cortex metabolism in patients with PTSD in comparison with controls.

Studies have demonstrated that the anteromedial prefrontal cortex (including the anterior cingulate) plays an important role in the stress response. Lesions of the anteromedial prefrontal cortex (including the anterior cingulate) in the rat interfere with conditioned emotional responses to fear-eliciting stimuli. Specifically, these lesions result in a decrease in freezing behaviors and conditioned cardiovascular responses (increased heart rate) with fear-inducing stimuli. Lesions of the cingulate gyrus increase plasma levels of adrenocorticotropin (ACTH) and corticosterone in response to restraint stress. This suggests that this area is a target site for the negative feedback effects of glucocorticoids on stress-induced hypothalamic–pituitary–adrenal (HPA) activity. In other words, the cingulate has a braking effect on the HPA axis system response to stress.[100]

Little is known about the effects of stress on parietal cortex function. Since the parietal cortex is involved in attention, it is reasonable to predict that the increase in focused attention which occurs during stressful situations is associated with activation of the parietal cortex. As reviewed above, studies in normal human subjects have found differences in recall during stressful as compared with nonstressful situations, with an increase of focused attention on central details of stressful situations.

Stress-Induced Neuromodulation of Memory Traces

Neurotransmitters and neuropeptides released during stress have a modulatory effect on memory function. Several neurotransmitters and neuropeptides are released during stress which have an effect on learning and memory, including norepinephrine, epinephrine, adrenocorticotropic hormone (ACTH), glucocorticoids, corticotropin-releasing factor (CRF), opioid peptides, endogenous benzodiazepines, dopamine, vasopressin, and oxytocin.[101] 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 footshock 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, which is the site of most of the body's epinephrine, results in a blocking of passive avoidance behavior, which is restored by the administration of adequate amounts of epinephrine.[102] Post-training administration of epinephrine after a learning task influences retention, the rate of which resembles an inverted U-shaped curve: retention is enhanced at moderate doses and impaired at high doses.[103–105] Low-dose (0.2 μg) injections of norepinephrine into the amygdala facilitate memory function in an inhibitory avoidance task, while higher doses (0.5 μg) impair memory function.[106] Depletion of norepinephrine with DSP-4 has no effect on acquisition of place-learning, although it does have a significant effect on retention.[107] Stimulation of the locus coeruleus, site of most of the noradrenergic cell bodies in the brain, produces a significant improvement in performance of acquisition and extinction of a reinforced task, whereas lesions of the locus coeruleus suppress this effect.[108] Other studies have shown an impairment in acquisition of fear-conditioned learning[109] with noradrenergic depletion. The acetylcholine antagonist, scopolamine, impairs memory as measured by acquisition and retention of an inhibitory avoidance task, as well as by place-learning.[107] The combined blockade of the cholinergic and noradrenergic systems with scopolamine and propranolol, respectively, which only had effect when administered in combination, profoundly impaired inhibitory avoidance as well as spatial learning.[110] In summary, epinephrine and norepinephrine released during stress act to enhance the formation of memory traces.[37,111]

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.[103] The effects of ACTH on learning and memory have also been tested through the measurement of its effect on the acquisition of conditioned fear responses. As reviewed above, animals are exposed to a conditioned stimulus (a tone) and an unconditioned stimulus (footshock). The animal must learn to exit from a box when the conditioned stimulus (the tone) comes on. ACTH enhances the acquisition of learning in this paradigm. ACTH also delays extinction of the avoidance response, i.e., it takes longer for the animal to realize after the association between the tone and the shock is ended that it does not have to exit the box when the tone comes on to avoid the shock.[112] The effects of ACTH on learning and memory are mediated through the hippocampus and amygdala.[113] Glucocorticoids, in contrast, enhance extinction in the conditioned fear paradigm.[112] The neuropeptide CRF, which stimulates release of ACTH from the pituitary and hence, glucocorticoids from the adrenal, has anxiogenic effects when administered into the cerebral ventricles.[114]

Other neurotransmitters and neuropeptides released during stress have effects on learning and memory. Both the dopamine and acetylcholine brain systems play a role in

enhancing memory formation.[115] When administered after training in a learning task opiate receptor agonists impair retention, whereas opiate receptor antagonists, such as naloxone, enhance retention.[116] Opiate antagonists (naloxone) enhance retention of recently acquired information when injected into the amygdala.[117] Vasopressin injected 3 hours before or after a new learning paradigm 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,[118] while oxytocin has the opposite effect. Gamma-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, whereas GABA agonists have the opposite effect.[119] The GABA antagonist picrotoxicin enhances the extinction of conditioned fear.[105]

Recent studies have begun to address the question of neuromodulation of memory function with stress in human subjects. In one recent study, the β-adrenergic antagonist, propranolol, or placebo, was administered 1 hour before a neutral or an emotionally arousing (stress-related) story in healthy human subjects. Propranolol, but not placebo, interfered with the recall of the emotionally arousing story, but not the neutral story. This study suggests that activation of β-adrenergic receptors in the brain enhances the encoding of emotionally arousing memories.[120]

Findings related to neuromodulation of memory function are of importance for understanding the symptomatology of PTSD. The 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 in the enhancement of specific traumatic memories, which is part of the clinical presentation of PTSD. 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.[121] We have reviewed above how neuromodulators may be involved in the mechanisms of stress sensitization and the pathological retrieval of traumatic memories in patients with PTSD. We hope that 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.[6,8,122]

Stress-related Alterations in Brain Memory Systems in Patients with Stress-related Psychiatric Disorders

There is emerging evidence that stress has effects on explicit memory function in humans which involve deficits in both encoding and retrieval. Patients with a history of exposure to stressors such as childhood abuse exhibit alterations in memory, including

nightmares, flashbacks, intrusive memories, and amnesia of the traumatic event(s). Studies of war veterans have documented incidents of alterations in memory function on the battlefield, such as the forgetting of one's name or identity and the forgetting of events that has just taken place during the previous battle.[123,124] In one study it was found that immediately after a major campaign, about 5% of the soldiers who had been combatants had no memory for the events that had just occurred.[125] Follow-up studies of WW II combat veterans have found that many veterans continue to suffer from "blackouts" or loss of memory many years after their period of service.[126] We have reported an increase in the dissociative symptom of amnesia (in addition to increased depersonalization, derealization, and identity disturbance) as measured with the SCID-D (Structured Clinical Interview for DSMIIIR–Dissociative Disorders) in Vietnam combat veterans with PTSD in comparison with Vietnam combat veterans without PTSD.[9] Episodes of amnesia in these patients took the form of gaps in memory which lasted from minutes to hours or days. Individual patients reported a range of experiences, from driving on the highway and suddenly noticing that three hours had passed, to walking down a street in Boston and then finding themselves in a motel room in Texas, with no idea of how they got there.

Physiological or emotional states may trigger recall of certain memories. For instance, one patient who was a Vietnam veteran with PTSD was involved 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 all he could say was "got to get them out, got to get them out!". This case illustrates how particular physiological or emotional states may facilitate recall of events for which there previously was amnesia, in a manner similar to state-dependent learning.[127] It also illustrates how traumatic recall often occurs in dissociated states that are reminiscent of the state in which the event originally was experienced, as we review below. In a similar fashion, victims of childhood sexual abuse may have no recall of their abuse until they are subsequently victimized as adults by rape. The emotional state which this involves is similar to the emotional state at the time of the original victimization; this emotional state may be associated with a triggering of recall of the original episode of childhood abuse. It may be that during states of arousal, release of neuromodulators such as norepinephrine leads to pathological recall of traumatic memories for which the patient may have been previously amnestic.

Evidence from other studies of traumatized patients is also consistent with that of abnormalities of explicit memory function involving encoding. Studies of concentration camp survivors from the Second World War have found high rates of impairment in explicit memory function.[128] In one group of 321 Danish survivors of WW II concentration camps who experienced high levels of psychiatric symptomatology and were seeking compensation for disability, 87% of the individuals complained of memory impairment suggestive of deficits in explicit recall 10 or more years after release from

internment. Severe intellectual impairment was also found upon testing in 61% of the group.[129] Korean prisoners of war have been found to have an impairment of explicit memory tasks of free verbal recall as measured by the Logical Memory component of the Wechsler Memory Scale (WMS), whereas Korean veterans without a history of containment were not impaired.[130] We have measured explicit memory function with the WMS-Logical (for verbal memory) and WMS-Figural (for 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 a significant decrease in 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.[131] PTSD patients also had deficits in explicit recall as measured by the Selective Reminding Test (SRT) for both verbal and visual components. We have subsequently found deficits in explicit memory tasks of free verbal recall as measured by the WMS-Logical component in adult survivors of childhood abuse seeking treatment for psychiatric disorders.[132] Studies have found deficits in explicit short-term memory as assessed by the Auditory Verbal Learning Test (AVLT) in Vietnam combat veterans with PTSD, whereas such deficits were not found in National Guard veterans without PTSD.[133] The California New Learning Test also revealed these deficits in Vietnam veterans with combat-related PTSD in comparison with controls.[134] Studies of female Vietnam combat nurses with PTSD are currently in progress (J. Wolfe personal communication, 1994). Deficits in academic performance have also been shown in Beirut adolescents with PTSD in comparison with Beirut adolescents without PTSD (P. Saigh, personal communication, 1994). These studies suggest deficits in encoding on explicit memory tasks. However, other studies of patients with PTSD have shown enhanced explicit recall of trauma-related words relative to neutral words in comparison with controls.[135] In summary, these findings show deficits in encoding on explicit memory tasks, deficits in retrieval, as well as enhanced encoding or retrieval of specific trauma-related material.

Studies using neuroimaging techniques have found that stress in humans may be associated with changes in brain structure, including the morphology of the hippocampus. As reviewed above, increased circulating glucocorticoids appear to be toxic to the hippocampus. An increase in glucocorticoids has been shown in soldiers undergoing the stress of bombardment.[136] Studies using computed tomography (CT) and magnetic resonance imaging (MRI) in human subjects suggest that a history of exposure to therapy, or depression may be associated with changes in brain structure.[137–140] Studies of concentration camp survivors from World War II seeking compensation for disability utilized pneumoencephalography and reported "[cerebral] atrophy of varying degrees . . . in the majority [of the individuals]."[129] Other authors who have used pneumoencephalography to measure brain structure in concentration camp survivors reported "diffuse encephalopathy" in 81% of cases (reviewed in Thygesen et al.[129]).

We compared hippocampal volume measured with MRI in Vietnam combat veterans

with PTSD ($N = 26$) and in healthy subjects ($N = 22$) who were matched for factors that 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 with controls ($p < 0.05$) (Fig. 3-1), but no significant decrease in volume of comparison structures, including the 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 decreased right hippocampal volume in the PTSD patients ($r = 0.64$; $p < 0.05$). 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).[141] We recently have analyzed data which shows a statistically significant 12% decrease in left hippocampal volume in 17 patients with a history of PTSD related to severe childhood physical and sexual abuse, as compared with 17 controls matched on a case-by-case basis with the patients (Bremner et al., unpublished data, 1996). In summary,

a

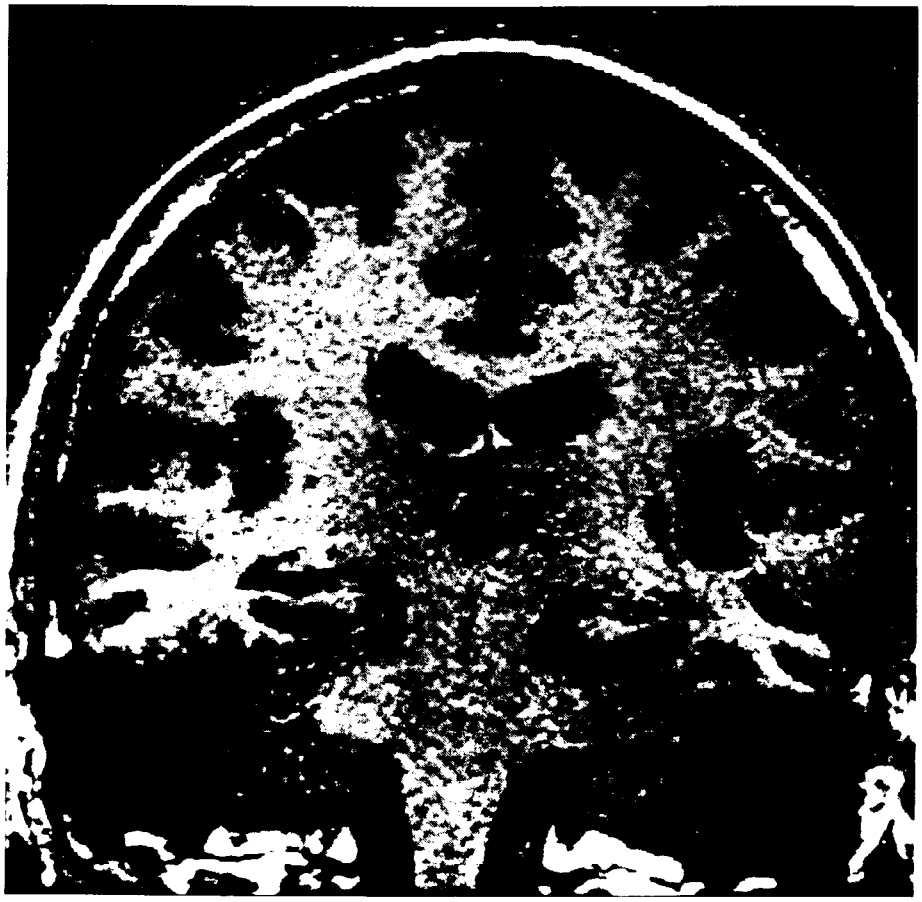

Figure 3–1. Coronal magnetic resonance imaging (MRI) scan in a patient with posttraumatic stress disorder (PTSD) (*a*) and a normal control (*b*). The hippocampus is visually smaller in the PTSD patient compared to the control.

this evidence is consistent with that of alterations in hippocampal morphology being associated with deficits in explicit memory function in patients with PTSD.

Other aspects of the alterations in memory function seen in PTSD may be mediated by the hippocampus. Electrical stimulation of the temporal lobe (including the hippocampus and adjacent cortical regions, parahippocampal gyrus, amygdala, and temporal lobe neocortex) in patients with epilepsy resulted in the subjective experience of a number of symptoms that are similar to those seen in PTSD. Eighteen out of 35 patients experienced symptoms of some kind. These included the subjective sensation of fear (7 patients), complex visual hallucinations (flashbacks) (5 patients), memory recall (5 patients), deja vu (4 patients), and emotional distress (3 patients).[142] In another study, electrical stimulation of the hippocampus and amygdala in epileptic patients was also associated with visual and auditory hallucinations, and dream-like and memory-like hallucinations, which are descriptively similar to flashbacks reported by patients with PTSD.[143] We have found an increase in dissociative symptomatology and disruption of delayed word recall in normal subjects following intravenous administration of keta-

b

hydrochloride, a noncompetitive antagonist of the NMDA receptor.[144] The NMDA receptor, which is highly concentrated in the hippocampus, is involved in memory function at the molecular level (i.e., long-term potentiation [LTP]).

The neurophysiology of the thalamus is of interest from the standpoint of trauma-related symptomatology such as dissociation.[145] During slow-wave sleep, thalamic nuclei exhibit slow spindle oscillations that disrupt transmission of sensory information to cortical and limbic structures, while in wakefulness, the thalamus fires in a relay mode that facilitates transmission of sensory information to cortical regions. During rapid eye movement (REM) sleep (the sleep stage during which dreaming occurs), there is a phasic enhancement of thalamocortical cells,[146] which suggests that dreams (and other internally generated experiences) may arise as a result of thalamocortical projections that bypass the slow spindle oscillations of the thalamus blocking transmission of sensory information from the outside to the cortex.[147] Consistent with this process is the fact that patients with paramedian thalamic infarcts have a profound sense of detachment, reduced responsivity to external stimuli, and sleep-like posturing without the electrophysiological correlates of non-REM sleep. Dissociative states such as flashbacks in PTSD patients, which are also characterized by a feeling of unreality and detachment, may be due to alterations in thalamic function that result in a blocking of the transmission of sensory information from the outside. This is combined with the generation of internal images derived from recalled memories which have the unreal quality typical of dream or dissociative states.

Evidence from preclinical investigations indicates that the amygdala is involved in abnormalities of emotional memory manifested by, for instance, conditioned emotional responses, which are prominent in the clinical presentation of patients with PTSD. 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.[148] Amygdala stimulation of human subjects is also accompanied by activation of the stress response system, as manifested by increases in peripheral catecholamines, a phenomenon that is also seen in animals during conditioned fear responses.[149] Exaggerated startle response (which has been demonstrated to be mediated by the amygdala in animals) is an important feature of the clinical presentation of patients with PTSD, and empirical investigations have shown alterations of startle to be associated with PTSD.[150] We have not found a difference in amygdala volume measured with MRI between patients with combat-related PTSD and healthy controls (Bremner et al., unpublished data, 1996).

Investigations have also addressed alterations in emotional memory as demonstrated by conditioned emotional responses in patients with PTSD. The conditioned emotional response can be studied in humans in the laboratory by using the psychophysiology paradigm. Lawrence Kolb[151] noted that patients with PTSD have a heightened physiological responsiveness to reminders of the original trauma that resemble conditioned responses. These conditioned responses to cues related to the original trauma (combat

films and sounds, scripts of traumatic events) parallel those seen in the conditioned fear paradigm in animals. Studies have used measurements of heart rate and blood pressure as indexes of sympathetic function (the psychophysiology paradigm) to examine the relationship between traumatic reminders, subjective experience, and physiological reactivity.[152] Increases in heart rate and systolic blood pressure following exposure to combat sounds have been found in Vietnam veterans with combat-related PTSD but not in non-veteran healthy subjects, non-PTSD combat veterans,[153,154] and Vietnam veterans with other psychiatric disorders.[154] Increases in plasma epinephrine, pulse, blood pressure, and subjective distress following combat stimuli have been reported in PTSD patients but not in healthy controls.[155] PTSD patients have also been found to have a higher heart rate, skin conductance, and frontalis electromyogram than controls after hearing "scripts" of the subjects's combat experiences read to them.[156] An increase in heart rate responses and skin conductance following exposure to loud tones is also seen in patients with PTSD, but not in healthy controls, patients with other anxiety disorders, and patients without PTSD but with a history of past traumatic experiences.[157] This heightened responsiveness to reminders of the original trauma, or conditioned emotional stimuli, is probably mediated by the amygdala.

Abnormalities in the Stroop test, which are associated with activation of the cingulate cortex, have been associated with PTSD. Delays in color-naming PTSD-related words such as "body-bag" are involuntary, and such delays 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 to color-name obsessive, positive, or neutral words; this delay was correlated with severity of PTSD symptomatology as measured by the Mississippi Scale.[158] Stroop interference has also been shown in patients with PTSD that is related to the trauma of rape.[159,160] These studies therefore make Stroop interference one of the more replicated findings in PTSD.

The anterior cingulate is also involved in abnormalities of emotional memory. Inducing fear by increasing the number of dangerous animals in a word list presented to human subjects results in an increase in blood flow in the anterior cingulate.[64] Studies of human patients with brain lesions have shown that damage to the anterior one-third of the frontal cortex often results in seizures during which the individual experiences intense feelings of fear or anguish. This suggests that the anteromedial prefrontal cortex plays a role in fear-related behavior. In addition, some patients have been observed to experience visual hallucinations during seizures,[161] which are reminiscent of the flashbacks seen in victims of trauma.

The orbitofrontal cortex may be involved in abnormalities of emotional memory that are seen in patients with a history of childhood abuse. Studies of human patients with brain lesions have shown that lesions of the orbitofrontal cortex also result in symptoms of intense fear during seizures. Some case reports have described a relationship between damage to the orbitofrontal cortex and visual hallucinations that appear to be similar to the flashbacks which are characteristic of PTSD.[162] Yohimbine is an alpha-2

noradrenergic antagonist which causes an increase in brain norepinephrine release and increased symptoms of PTSD.[163] Through assessment by PET [^{18}F]2-fluoro-2-deoxyglucose (FDG), we have found a differential response of cerebral metabolism in PTSD patients and controls after the administration of yohimbine.[164] The greatest magnitude of difference was seen in the orbitofrontal cortex. Differences were also seen in the prefrontal, temporal, and parietal cortex. The orbitofrontal cortex as well as other brain regions are involved in implicit memory function. Patients with PTSD have been shown to have a more enhanced implicit recall (i.e., recall following priming) of trauma-related words than of neutral words in comparison with controls.[135] These findings may have implications for the greater intrusiveness of trauma-related memories over normal memories in patients with PTSD.

Extinction

Extinction is also relevant to understanding the effects of stress on memory in patients with PTSD. The mechanism of extinction involves cortical inhibition of amygdala function. Victims of childhood abuse clinically exhibit a failure of extinction to trauma-related stimuli. For instance, an individual who was locked in a closet may continue to show anxiety reactions when they are in a close space, even when there is no real threat of danger. The neocortex mediates extinction of emotional memory. For instance, the auditory neocortex suppresses conditioned fear responses mediated by the amygdala to stimuli that are not specific to the original conditioned stimulus (i.e., it prevents stimulus generalization).[165] The auditory cortex is also involved in extinction through the suppression of amygdala responsiveness.[166]

Stress Sensitization

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 in 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.[167] As reviewed above, 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 alteration in memory encoding and retrieval, which may have implications for understanding the mechanisms of traumatic recall in PTSD.

The mechanism of stress sensitization illustrates how the amygdala mediates the development of stress-induced abnormalities of emotional memory. In stress sensitization, repeated exposure to a stressor such as footshock results in the potentiation of the startle response with reexposure to a subsequent footshock. Enhanced release of neuro-

modulators in the amygdala that affect memory function, such as epinephrine or norepinephrine, may mediate the abnormalities of emotional memory that are seen following exposure to repeated stressors. Repeated exposure to stress will also potentiate responsiveness to cues associated with the original stressors, as well as the number of cues that can act as conditioned stimuli. This produces the phenomenon of stimulus generalization, in which a wide range of stimuli in the environment can result in conditioned responsiveness. As is seen both in animals in the laboratory model of conditioned fear as well as in patients with PTSD, avoidant behavior develops in an attempt to stay away from these stimuli in the environment, leading to conditioned responses.

Stress sensitization has clinical applications for PTSD. We have found that exposure to the stressor of childhood physical abuse increases the risk for the development of combat-related PTSD.[168] Israeli veterans with a history of previous combat-related acute stress reactions have also been found to be at increased risk for reactivation of combat-related stress reactions in comparison with combat veterans without a history of stress reaction in response to combat.[169] In addition, other clinical examples exist of how a history of exposure to prior stress increases the risk for stress-related symptomatology upon reexposure to stressors.[170]

A Working Model for the Neurobiology of Memory Alterations in Survivors of Childhood Abuse

A special mechanism of memory which explains delayed recall of episodes of childhood abuse may be found in amnesia. Dissociative amnesia is not typically a normal phenomenon of memory and has been found to be increased in patients with PTSD.[9] Amnestic symptoms in these patients ranged from gaps of memory lasting 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 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 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. 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 recent studies have documented the existence of dissociative amnesia in patients with PTSD.[171–176]

Based on 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 above, the hippo-

campus 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, an episode of sexual abuse is marked by the smell of the perpetrator, the sounds involved in the abuse, the visual appearance of the perpetrator and the scene where the abuse takes place, and the tactile sensations. All of these individual features are stored in the primary sensory cortical areas to which they correspond; for instance, smell is stored in the olfactory cortex. When a similar situation recurs, the hippocampus and adjacent cortex activate cortical areas and bring together the diverse sensory elements to recreate 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 abnormal intrusion of some traumatic memories into consciousness, the disintegration of dissociated traumatic memories, and the total lack of recall (amnesia) for other events.

Neuropeptides and neurotransmitters released during stress can modulate memory function (Fig. 3-2). These neuromodulators act at the level of the hippocampus, amygdala, and other brain regions involved in memory. Disorders such as PTSD may be associated with long-term alterations in the function of these neuromodulators, which would in turn be associated with alterations in memory in these patients that would not occur in normal persons. Exposure to subsequent stressors could also be associated with altered release of neuromodulators, resulting in altered memory recall in PTSD patients.

Mechanisms involving state-dependent recall may also be applicable to amnesia for abuse.[127] *State-dependent recall* refers to the phenomenon whereby an affective state similar to that at the time of encoding leads to a facilitation of memory retrieval. For instance, memories encoded during a state of sadness will have a facilitated retrieval during similar states of sadness. Similar situations can occur for other emotional states. To extend this concept to victims of abuse, it can be seen that particular emotions will predominate at the time of the original abuse, such as extreme fear or sadness. These emotional states occur infrequently during a routine adult life that is free of stressors. The recurrence of the extreme fear or sadness that occurred during the original abuse during psychotherapy or with exposure to a subsequent stressor may lead to a delayed recall of the original abuse experiences. A clinical example of this would be the victim of sexual abuse who has no recall of her experiences of sexual abuse until she is raped as an adult, which leads to a recall of the original trauma.

Concluding Remarks

We have examined the question of the validity of memories of childhood abuse as it relates to the current controversy surrounding the false memory syndrome from both theoretical and biological perspectives. Studies in cognitive psychology have provided evidence for an enhancement of central details related to stressful events and for the

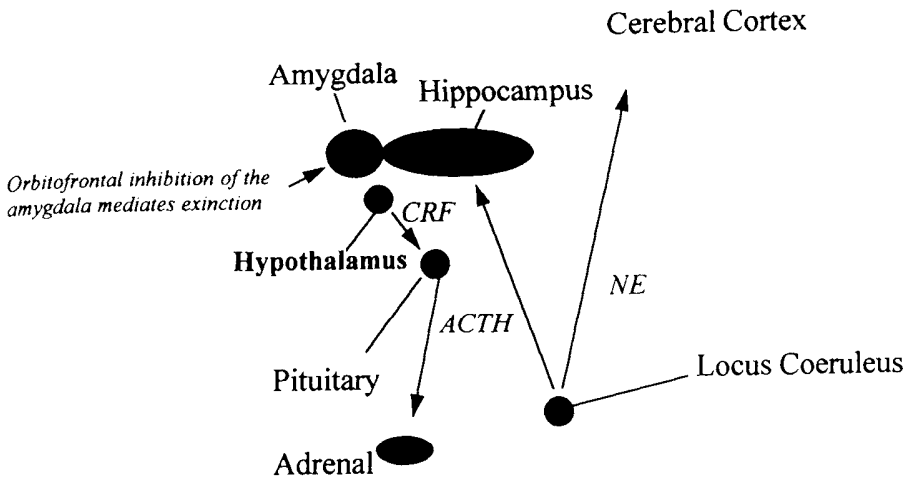

Figure 3–2. Diagrammatic representation of the effects of traumatic stress on brain regions and systems involved in memory. Input to the amygdala from orbitofrontal cortex and temporal cortex is involved in extinction of conditioned fear, which is mediated by the amygdala. Release of corticotropin releasing-factor (CRF) from the hypothalamus causes release of ACTH from the pituitary, which in turn results in release of cortisol from the adrenal. CRF and cortisol play an important role in the stress response, modulate memory function, and are altered in PTSD. The hippocampus is involved in short-term memory and fear responses for context. High levels of cortisol associated with stress may damage the hippocampus and lead to altered memory function in PTSD. Locus coeruleus, site of norepinephrine (NE) cell bodies, is also involved in stress. Alterations in NE function are associated with PTSD, and may underlie sensitization and alterations in memory in PTSD patients.

exclusion of peripheral details in normal human subjects. Much has been made in the popular press about the potential effects of suggestion on memory. However, a review of this literature does not support the conclusion that suggestions can lead to a rewriting of original memory traces.

Patients with PTSD have been shown to have an increase in self-reported dissociative amnesia, which is defined as gaps in memory not due to normal forgetting. Other aspects of memory function are deficient in PTSD patients, including verbal recall. Both preclinical and clinical studies support the idea that traumatic stress is associated with alterations in brain regions involved in memory, resulting in functional memory deficits. Other concepts such as state-dependent memory, stress sensitization, and modulation of memory traces during and after encoding by neurotransmitters and neuropeptides released at high levels during stress, provide potential explanations for delayed recall of memories of childhood abuse. These mechanisms are probably only applicable 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 dissocia-

tive amnesia. We do not mean to imply that definitive biological mechanisms have been elucidated which could explain these phenomena. Rather, this chapter is a critical review of the current status of the topic, and through it we have sought to raise awareness about how the neurobiology of the effects of stress on memory may be applicable to these questions. Future studies should shed additional light on the neurobiology of memory in individuals with a history of exposure to childhood abuse.

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