CHAPTER 6

THE NEUROBIOLOGY OF POSTTRAUMATIC STRESS DISORDER: AN INTEGRATION OF ANIMAL AND HUMAN RESEARCH

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I. PTSD: BIOLOGY AND PHENOMENOLOGY

Posttraumatic stress disorder (PTSD) is characterized by specific symptoms which develop following exposure to a "threat to the life of oneself or others" (Diagnostic and Statistical Manual-IV). An important point of this chapter is that symptoms of PTSD and other psychiatric disorders related to stress, such as the dissociative disorders, are a behavioral manifestation of stress-induced changes in brain structure and function. Animals exposed to severe stress (such as electric shock) show acute increases in stress-related neurotransmitters and neuropeptides, the chemical messengers of the brain, including corticotropin releasing factor (CRF), norepinephrine, serotonin, dopamine, endogenous benzodiazepines, and endogenous opiates. Long-term alterations in behavior are seen in animals exposed to chronic stress, and are associated with changes in these neurotransmitters and neuropeptides. Each of these neurotransmitters and neuropeptides have specific sites, or receptors, located on neurons to which they bind in order to exert their effects, which are also affected by stress, leading to changes in receptor number or affinity (the "stickiness" of binding to neurotransmitters and neuropeptides). Alterations in neurotransmitters and neuroreceptors result in changes in neuronal function in specific brain areas which are involved in the stress response. Stress also results in changes in the structure of neurons in these regions, which can lead to changes in function. These effects combine to alter the neuronal inter-connections, which result in long-term changes in brain "circuits" involved in the stress response.

Brain regions involved in stress also play a role in memory and emotion. It has been hypothesized that the symptoms of PTSD are mediated by abnormalities in these brain regions (Bremner, Krystal, Charney, & Southwick, 1996; Bremner, Krystal, Southwick, & Charney, 1995; Pitman, 1989). These include alterations in memory and emotion, as well as

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& Aghajanian, 1977; Korf, Bunney, & Aghajanian, 1974), benzodiazepines (Grant, Huang, & Redmond, 1980; Simson & Weiss, 1994), and serotonin (Akaoka & Aston-Jones, 1993; Aston-Jones, Akoaka, Charlety, & Chouvet, 1991).

The neuroanatomy of locus coeruleus is well suited to the role it plays in the stress response. The central nucleus of the amygdala, which is involved in the conditioned fear response (see section below, "The Amygdala"), has outputs to the lateral nucleus of the hypothalamus, which in turn mediates the increase in heart rate and blood pressure associated with fear. The nucleus paragigantocellularis (PGI), a major input to the locus coeruleus, also controls peripheral sympathetic activity. Stimulation of the PGI during stress could lead to parallel activation of central and sympathetic systems (Aston-Jones et al., 1985; Aston-Jones et al., 1991). The locus coeruleus responds to changes in the environment (e.g., physical sensations) or internal states (e.g., drop in blood pressure due to a loss of blood) through projections from sensory relay areas such as the nucleus tractus solitarius and the raphe to the locus coeruleus. The locus coeruleus represents a "central relay station" which responds to information from a variety of sources, and rapidly and globally activates neuronal function through simultaneous release of norepinephrine neurotransmitter throughout the brain. This release of transmitter leads to increased gene transcription and other secondary intracellular responses which are important in the stress response (Stone, 1987; Stone, John, Bing, & Zhang, 1992; Stone, Zhang, John, & Bing, 1991; Stone, Zhang, John, Filer, & Bing, 1993).

Stress results in a rapid and robust activation of the locus coeruleus/noradrenergic system. During states of rest, feeding, and grooming, locus coeruleus neurons discharge in a slow, phasic manner (Aghajanian, 1978; Aghajanian et al., 1977; Aston-Jones, 1985; Foote, Aston-Jones, & Bloom, 1980; Grant & Redmond, 1984). A variety of novel stimuli activate the locus coeruleus, including visual threats (Aston-Jones, 1985; Cedarbaum & Aghajanian, 1978; Foote, Aston-Jones, & Bloom, 1980; Grant et al., 1980; Grant & Redmond, 1984; Korf et al., 1974; Rasmussen & Jacobs, 1986). Novel stimuli-induced locus coeruleus activation is associated with an increase in heart rate and blood pressure, and plasma norepinephrine (Abercrombie & Jacobs, 1987a; Abercrombie & Jacobs, 1987b; Grant & Redmond, 1984). Behaviors which are characteristically seen during situations of stress and fear are associated with an increase in activation of the locus coeruleus/noradrenergic system. In the cat, exposure of stressors such as a dog results in increased locus coeruleus activity associated with defensive behaviors such as arched back, piloerection, flattened ears, increased heart rate and blood pressure, and mydriasis (Levine, Litto, & Jacobs, 1990), while behaviorally activating but nonstressful stimuli, such as seeing an inaccessible rat, have no effect (Abercrombie & Jacobs, 1987a; Rasmussen, Morilak, & Jacobs, 1986). Visual threat to monkeys also activates the locus coeruleus (Grant & Redmond, 1984). Infusion of norepinephrine into the hypothalamus of cats results in defensive/aggressive behaviors such as hissing, growling, and ear retraction (Barret, Shaikh, Edinger, & Siegel, 1987), while electrical stimulation of the locus coeruleus in monkeys results in similar fear-related behaviors (Redmond, Huang, Snyder, & Maas, 1976; Redmond & Huang, 1979). Administration of the alpha2 antagonists, yohimbine and piperoxane, which result in an increase in firing of the locus coeruleus (Rasmussen & Jacobs, 1986) and increased release of norepinephrine in target brain structures, produce behaviors consistent with anxiety or fear in several animal species (Blanchard, Taukulis, Rodgers, Magee, & Blanchard, 1993; Redmond, 1979). Agents which decrease firing in the locus coeruleus, including opiates, benzodiazepines (Drugan, Ryan, Minor, & Maier, 1984; Tanaka et al., 1990), ethanol (Shirao et al., 1988), and clonidine (Aghajanian, 1978; Aghajanian & Vandermaelen, 1982) have the opposite effect. These findings led to the hypothesis that increased noradrenergic activity is involved in the pathogenesis of anxiety and the stress response (Redmond et al., 1976).

Increases in locus coeruleus activity during stress are associated with an increase in regional turnover and release of norepinephrine in brain regions which are innervated by the locus coeruleus. We have recently reviewed in more depth the effects of stress on

norepinephrine metabolism and release in specific brain regions (Bremner, Krystal, Southwick, & Charney, 1996b). In summary, acute and chronic stress, including footshock, restraint, and forced swim, result in increased turnover and release of norepinephrine in several target brain regions of the locus coeruleus, including cerebral cortex, hippocampus, hypothalamus, and amygdala. Increased turnover of norepinephrine is manifested by an increased release of norepinephrine in these brain regions as measured by microdialysis, increased levels of the norepinephrine metabolite MHPG, decreased brain norepinephrine content (suggestive of increased utilization), and increased levels of the rate limiting enzyme of norepinephrine synthesis, tyrosine hydroxylase (Abercrombie, Keller, & Zigmond, 1988; Adell, Garcia-Marquez, Armario, & Gelpi, 1988; Anisman & Zacharko, 1985; Glavin et al., 1983; Irwin, Ahluwalia, & Anisman, 1986; Melia et al., 1992; Nissenbaum, Zigmond, Sved, & Abercrombie, 1991; Rossetti, Portas, Pani, Carboni, & Gessa, 1990; Shirao et al., 1988; Tanaka et al., 1982; Tanaka et al., 1983; Weiss et al., 1981; Yokoo et al., 1990). Animals with a prior history of exposure to chronic stress show an increase in norepinephrine release, MHPG, and tyrosine hydroxylase upon re-exposure to an acute stimulus, for several brain regions, including hippocampus, hypothalamus, and cortex. Re-exposure of animals with a history of prior footshock to the environment where footshock originally occurred results in an increased release of norepinephrine within the hypothalamus (Yokoo et al., 1990) and an increase in the norepinephrine metabolite, 3-methoxy-4-hydroxyphenylglycol (MHPG), in whole brain samples with associated fear-related behaviors such as increased defecation (Cassens, Roffman, Kuruc, & Schildkraut, 1980). These findings suggest that norepinephrine may be a chemical substrate for the conditioned fear responsiveness to complex spatial stimuli which is mediated by the hippocampus (described below in "The Hippocampus"). When synthesis is not able to keep up with demand, chronic stress results in a decrease in brain norepinephrine content with associated behavioral changes which have been termed "learned helplessness" (Petty, Kramer, Wilson, & Chae, 1993; Weiss, Stone, & Harrell, 1970; Weiss et al., 1981).

Chronic stress also results in an increased firing of the locus coeruleus (Korf, Aghajanian, & Roth, 1973; Pavcovich, Cancela, Volosin, Molina, & Ramirez, 1990; Simson & Weiss, 1988a; Simson & Weiss, 1988b). A decrease in density of alpha2 noradrenergic receptors specific to the hippocampus and amygdala, with an increase in affinity in the amygdala, has been associated with acute cold-restraint stress in the rat (Nukina, Glavin, & LaBella, 1987). In addition, chronic, but not acute, stress in rats blocks the reduction of locomotor activity normally associated with administration of the alpha2 agonist, clonidine, suggesting a decreased responsiveness of alpha2 receptors following chronic stress (Cancela, Volosin, & Molina, 1988). Administration of the alpha2 antagonist, idazoxan, results in increased locus coeruleus responsivity to external stimuli such as tail compression. Similarly, animals with a history of chronic stress have increased locus coeruleus responsivity to external stimuli, which has led to the idea of a "functional blockade" of alpha2 receptors with stress (Simson & Weiss, 1989; Simson & Weiss, 1994). Animals with a history of exposure to chronic stress have an increase in norepinephrine release in the hippocampus following administration of idazoxan (Nisenbaum & Abercrombie, 1993). An increase in locus coeruleus responsiveness and regional norepinephrine release with re-exposure to stressors in individuals with a prior history of stress exposure may explain clinical findings of stress sensitization in PTSD (Bremner, Southwick, Johnson, Yehuda, & Charney, 1993).

Studies in healthy human subjects are consistent with a relationship between stress and increased catecholaminergic function (reviewed in Bremner, Krystal, Southwick, & Charney, 1996b; reviewed in Weiner, 1984). Administration of catecholamines results in behaviors similar to those seen during stress. For instance, administration of norepinephrine to healthy subjects results in an increase in blood pressure, respiratory rate, and subjective sensations of anxiety, while administration of epinephrine causes increases in blood pressure, heart rate, cardiac output, respiratory rate, and subjective sensations of anxiety (Goodman & Gilman, 1985). The situation of an approaching parachute jump was associated with an increase in subjective fear and a steady increase in heart

rate (Fenz & Epstein, 1967; Fenz & Jones, 1972). Experimental induction of anger and fear in healthy subjects resulted in an increase in diastolic blood pressure and heart rate. Air Force pilots had an increase in both urinary norepinephrine and epinephrine during flight in comparison to ground activity (von Euler & Lundberg, 1954). During public speaking, plasma epinephrine levels increased two-fold, while during physical exercise, plasma norepinephrine levels increased three-fold (Dimsdale & Moss, 1980). Plasma epinephrine and norepinephrine levels increased over baseline in healthy subjects during cognitive stressors (mental arithmetic), physical stressors (knee bends), pain stressors (cold pressor and venipuncture) (Ward, Mefford, & Parker, 1983), public speaking (Taggart, Carruthers, & Sommerville, 1973), and race car driving (Taggart & Carruthers, 1971). The norepinephrine metabolite, plasma MHPG, was found to increase in healthy subjects during emotional stress (Lader, 1974; Buchsbaum, Muscettola, & Goodwin, 1981). Urinary MHPG increased in naval aviators after landings of aircraft on aircraft carriers (Rubin, Miller, & Clark, 1970). Plasma MHPG was correlated with state anxiety in healthy subjects exposed to the anticipatory stress of receiving an electric shock, while there was no such correlation in the absence of the electric shock threat (Uhde et al., 1982; Uhde et al., 1984). Significant within-individual correlations between changes in urinary MHPG and changes in state anxiety have been found in healthy human subjects (Sweeney, Maas, & Heninger, 1978). These studies are consistent with a relationship between norepinephrine and stress in healthy human subjects.

Considerable interest has been focused on the relationship between norepinephrine and PTSD (Bremner, Krystal, Southwick, & Charney, 1996a; Bremner, Krystal, Southwick, & Charney, 1996b; Murberg, 1994) (Table 6.1). Kardiner noted in 1941 that veterans with psychiatric conditions related to their war experiences exhibited what appeared to be a hyperresponsiveness of the sympathetic system, manifested by increases in heart rate, blood pressure, sweatiness, irritability, palpitations, vertigo, dizziness, nausea, and syncope. Kolb hypothesized that the central disturbance of PTSD consisted of the

TABLE 6.1 Evidence for Altered Catecholaminergic Function in Posttraumatic Stress Disorder

Increased resting heart rate and blood pressure	+/-
Increased heart rate and blood pressure response to traumatic reminders	+++
Increased resting urinary NA and Epi	+
Increased resting urinary dopamine	+++
Increased resting plasma NA	-
Increased plasma NA in response to traumatic reminders	+
Increased MHPG with exercise	+
Increased orthostatic heart rate response to exercise	+
Decreased binding to platelet alpha2 receptors	+
Relative decrease in alpha2 receptors on platelets with epinephrine administration	+/-
Altered growth hormone response to desipramine (alpha2 probe)	-
Decrease in basal and stimulated activity of cAMP	+/-
Decrease in platelet MAO activity	+
Increased symptoms, heart rate, and plasma MHPG with yohimbine	+
Increased startle response with yohimbine	+
Differential brain metabolic response to yohimbine	+
Altered sleep function (suggestive of NA dysfunction)	+++
Alterations in event-related potentials (suggestive of NA dysfunction)	+

- One or more studies did not support this finding (with no positive studies), or the majority of studies do not support this finding;

+/- An equal number of studies supported this finding as studies that did not support this finding;

+ At least one study supports this finding with no studies not supporting the finding, or the majority of studies support the finding;

++ Two or more studies support this finding, with no studies conducted that do not support the finding;

+++ Three or more studies support this finding, with no studies that do not support the finding.

"conditioned emotional response" to the original traumatic event which resulted in a heightened physiological response, mediated through adrenergic systems, to subsequent events which were reminiscent of the original trauma (Kolb, 1984).

Since the time of Kardiner the psychophysiology technique has been used extensively to study conditioned emotional responding and sympathetic correlates of exposure to traumatic reminders in PTSD. Physiological variables which are recorded typically include heart rate, systolic and diastolic blood pressure, skin conductance, electromyographic (EMG) activity of the frontalis, corrugator, zygomaticus or orbicularis oculi muscles, and skin temperature. These variables reflect in part activity of the peripheral sympathetic nervous system. Exposure to traumatic reminders and neutral scenes utilized in the psychophysiology paradigm include slides (with or without accompanying sounds) of scenes similar to the original trauma or reading scripts which are descriptions of what actually happened during the original trauma. Comparisons are then made between exposure to trauma-related material and both the baseline and/or the neutral exposures. Wenger (1948) noted that veterans of the Second World War with stress-related symptoms had increased heart rate and skin conductance at baseline in comparison to patients with other psychiatric disorders and healthy control subjects. Dodds & Wilson (1960) first described increased heart rate and blood pressure responses in combat veterans with and without stress-related pathology who were exposed to combat slides and sounds in comparison to healthy controls. They also found increased heart rate at baseline in both the combat veterans with stress-related pathology and combat veterans without pathology in comparison to the healthy controls.

A number of investigators have utilized the psychophysiology paradigm since the time of these original studies. Conflicting results have been obtained with regard to baseline heart rate and blood pressure in patients with PTSD, which may be largely related to acclimatization to the testing environment. An increase in reactivity to traumatic reminders has been a consistent finding in patients with PTSD. An increase in heart rate in response to auditory reminders of trauma (such as tapes of the sound of gunfire) has been found in Vietnam combat veterans with PTSD in comparison to healthy nonveteran controls (Blanchard, Kolb, Pallmeyer, & Gerardi, 1982) and Vietnam combat veterans without PTSD (Blanchard, Kolb, Gerardi, Ryan, & Pallmeyer, 1986). No increase in heart rate in response to the stressor of mental arithmetic was found in any of these studies. An increase in heart rate following exposure to combined combat slides and sounds has been found in Vietnam combat veterans with PTSD in comparison to Vietnam combat veterans without PTSD (Keane, Wolfe, & Taylor, 1987; Malloy, Fairbank, & Keane, 1983; McFall, Murburg, Ko, & Veith, 1990). Hearing scripts of the individual's traumatic experiences resulted in an increase in heart rate in Vietnam combat veterans with PTSD in comparison to Vietnam combat veterans without PTSD (Pitman, Orr, Forgue, de Jong, & Claiborn, 1987; Pitman, van der Kolk, Orr, & Greenburg, 1990). An increase in heart rate with traumatic scripts has also been found in WWII and Korean veterans with PTSD in comparison to those without PTSD (Orr, Pitman, Lasko, & Herz, 1993) and in patients with civilian trauma-related PTSD in comparison to controls (Shalev, Orr, Peri, Schreiber, & Pitman, 1992). Prins, Kaloupek, and Keane (1995) have more completely summarized scientific findings from this area and Kaloupek and Bremner (1996) have outlined methodological issues relevant to the psychophysiology study paradigm.

Alterations in sleep function may also be secondary to altered pontine function and noradrenergic dysregulation in PTSD. PTSD patients have been found to have an increase in phasic rapid eye movement (REM) activity (Ross et al., 1994), decreased total sleep time, and increased "micro-awakenings" (Mellman, Kulick-Bell, Ashlock, & Nolan, 1995) relative to controls. These abnormalities may play a role in nightmares in PTSD patients (Ross, Ball, Sullivan, & Caroff, 1989). Ross et al. (1989) have reviewed in detail the literature related to sleep dysfunction in PTSD.

Event-related potentials (ERP) have been used as a method for studying central brain processes which are felt to be reflective of noradrenergic function. A study in patients with combat-related PTSD found a delayed N2 and attenuated P3 that failed to differentiate target from distractor tones, indicating that the

patients had difficulty distinguishing task stimuli of different relevance. The authors interpreted this result as consistent with an impairment in the ability of PTSD patients to attend to relevant stimuli and process information normally, which may be secondary to alterations in noradrenergic function in the hippocampal formation (McFarlane, Weber, & Clark, 1993).

Several groups have examined peripheral measures of noradrenergic function in PTSD. An increase in norepinephrine and epinephrine has been found in 24-hour urines of combat-related PTSD patients in comparison to patients with other psychiatric disorders (Kosten, Mason, Ostroff, & Harkness, 1987). An increase in the norepinephrine/cortisol ratio has been found to more specifically differentiate patients with PTSD from these patient groups (Mason, Giller, Kosten, & Harkness, 1988). Severity of PTSD symptoms in combat veterans was correlated with level of urinary norepinephrine (Yehuda, Southwick, Giller, Ma, & Mason, 1992). Women with sexual abuse-related PTSD were found to have elevated levels of urinary norepinephrine and epinephrine, which correlated with PTSD symptoms as measured with the Impact of Events (IES) Scale (but no difference in norepinephrine/cortisol ratio) relative to abused controls and normal women (Lemieux & Coe, 1995). Other investigators, however, have found no difference in urinary levels of norepinephrine, epinephrine, MHPG or cortisol in patients with combat-related PTSD in comparison to Vietnam veterans without PTSD (Pitman & Orr, 1990), or in plasma levels of norepinephrine at baseline in Vietnam veterans with PTSD in comparison to healthy controls (Blanchard, Kolb, Prins, Gates, & McCoy, 1991; McFall, Veith, & Murburg, 1992; Murberg, 1994). An increase in plasma epinephrine (McFall et al., 1990) and norepinephrine (Blanchard et al., 1991) with exposure to traumatic reminders, and increased MHPG with physical exercise (Hamner, Diamond, & Hitri, 1994) has been found in Vietnam veterans with PTSD in comparison to healthy subjects. Children with PTSD were found to have increased orthostatic heart rate response, suggesting noradrenergic dysregulation (Perry, 1994). Another study of sexually abused girls (the majority of whom did not meet criteria for PTSD) compared to healthy girls demonstrated elevated levels of catecholamine synthesis (sum of epinephrine, norepinephrine, dopamine, and their metabolites), which showed only a trend toward significance after adjusting for differences in height between the sexually abused girls and controls ($p = .1$) (DeBellis, Lefter, Trickett, & Putnam, 1994). Although these studies do not consistently support an increase in basal sympathetic function in PTSD, they do suggest that patients with PTSD may have an increased responsiveness of the sympathoadrenal system.

Studies of peripheral norepinephrine receptor function have had mixed results. A decrease in platelet adrenergic alpha2 receptor number as measured by total binding sites for the alpha2 antagonist [3H]rauwolscine was found in patients with combat-related PTSD (Perry, Giller, & Southwick, 1987). Some studies (Perry, Southwick, & Giller, 1991; Perry, 1994) found a significantly greater reduction in number of platelet alpha2 receptors after exposure to agonist (epinephrine) in PTSD patients in comparison to healthy controls. Other studies (Kohn, Newman, Lerer, Orr, & Pitman, 1995) did not find a difference between patients and controls in the effects of epinephrine on forskolin-stimulated adenylate cyclase activity (a probe of alpha2 receptor function), while Weizmann et al. (1994) found a trend for this parameter to be decreased in PTSD ($p = .057$).

Probes of the beta-adrenergic receptor-mediated cyclic adenosine 3',5'-monophosphate (cAMP) system have been developed. The beta-receptor-associated adenylate cyclase unit consists of three components: the receptor to which transmitter binds, a guanyl nucleotide binding unit, and a catalytic unit. Isoproterenol and prostaglandin (PGE-1) probes the receptor binding component, aluminum chloride plus sodium fluoride probes the guanyl nucleotide binding unit, and forskolin acts on the catalytic unit. cAMP signal transduction can therefore be tested using a combination of these probes. In an initial study, a decrease was found in lymphocyte basal, isoproterenol, and forskolin-stimulated cAMP signal transduction, and platelet basal, forskolin, PGE-1, and aluminum chloride plus sodium fluoride stimulated adenylate cyclase levels (Lerer, Ebstein, Shestatsky, Shemesh, & Greenberg, 1987). A replication study showed lower platelet basal and forskolin-stimulated activity in PTSD, but

no difference in aluminum chloride plus sodium fluoride or PGE-1-stimulated adenylate cyclase activity (Lerer, Bleich, Bennett, Ebstein, & Balkin, 1990). Two replication studies did not find a difference between patients with PTSD and controls in platelet basal, PGE-1, aluminum chloride plus sodium fluoride, or forskolin-stimulated adenylate cyclase activity (Kohn et al., 1995; Weizmann et al., 1994). One study found a decrease in basal platelet monoamine oxidase (MAO) activity (Davidson, Lipper, Kilts, Mahorney, & Hammett, 1985) in patients with combat-related PTSD in comparison to controls. In summary, results are mixed regarding alterations in noradrenergic receptor function in PTSD, and findings to date do not specifically support the hypothesis of alteration in the beta-adrenergic cAMP system.

Pharmacological studies have also been performed to examine noradrenergic function in patients with PTSD. One study did not find a difference in growth hormone response to desipramine (a probe of central alpha$_2$ receptor function) between women with sexual assault-related PTSD and controls (Dinan, Barry, Yatham, Mobayed, & Brown, 1990). Administration of the alpha2 antagonist, yohimbine, which results in an increase of release of norepinephrine in the brain, results in flashbacks in 40 percent and panic attacks in 70 percent of Vietnam veterans with combat-related PTSD. PTSD patients report an increase in PTSD-specific symptomatology, including intrusive memories, emotional numbing, and hyperarousal with yohimbine. Yohimbine administration also results in increased MHPG, blood pressure, and heart rate response in patients with PTSD in comparison to normal healthy controls (Southwick et al., 1993). Administration of yohimbine resulted in an increase in the acoustic startle response in Vietnam combat veterans with PTSD relative to combat veterans without PTSD (Morgan et al., 1995). The alpha2 agonist, clonidine, which results in decreased noradrenergic activity, has been shown to be efficacious in civilians with PTSD in open trials (Kinzie & Leung, 1989).

Alterations in noradrenergic function may be associated with changes in central brain function in patients with PTSD. Preclinical studies have shown that high-dose yohimbine administration results in a decrease in brain metabolism in neocortical areas, including temporal, parietal, prefrontal and orbitofrontal cortex, as well as caudate. Other pharmacological studies suggest that norepinephrine has a dose-response effect on neuronal activity (which is associated with metabolism), so that while high levels of norepinephrine release result in a decrease in neuronal activity, low levels of norepinephrine release are associated with an increase in neuronal activity (reviewed in Bremner, Krystal, Southwick, & Charney, 1996a). Positron emission tomography (PET) studies measuring brain glucose metabolism with [18F]2-fluoro-2-deoxyglucose (FDG) examined brain metabolic response in patients with combat-related PTSD (N = 10) and controls (N = 10) following administration of yohimbine and placebo. Yohimbine was associated with a differential effect on brain metabolism in neocortical areas, including orbitofrontal, temporal, prefrontal, and parietal cortex, with metabolism having a tendency to increase in the controls and decrease in the patients (Bremner, Innis, et al., 1997).

There are several possible explanations for our PET yohimbine findings in PTSD. Previous studies support the idea of a dose response curve for norepinephrine, where low levels of norepinephrine release result in increased metabolism, and high levels of norepinephrine release result in decreased metabolism in neocortical areas of the brain. One possibility is that yohimbine administration results in relatively greater norepinephrine release in PTSD patients than controls, leading to decreased metabolism in PTSD and increased metabolism in controls. It is also possible that differences in pre- or post-synaptic sensitivity between PTSD and controls accounts for our findings. Blockade of pre-synaptic alpha2 receptors at the level of the locus coeruleus leads to an increase in firing of noradrenergic neurons, with increased release of norepinephrine at the level of cortical neurons. This may result in a decrease in cortical neuronal activity and metabolism. On the other hand, post-synaptic alpha2 receptors have an inhibitory effect on cortical neuronal activity, which means that blockade of these receptors leads to an enhancement of neuronal activity and metabolism. Following this model, yohimbine may be having a primary effect on presynaptic alpha2 neurons in PTSD patients, and a primary effect on post-synaptic alpha2 neurons in normal

controls. In summary, the findings are consistent with our previous hypotheses of alterations in noradrenergic brain function in PTSD (Bremner, Krystal, Southwick, & Charney, 1996b), and are suggestive of enhanced noradrenergic activity in these patients. Consistent with this, we recently used PET $H_2[^{15}O]$ to show increased activation during exposure to traumatic reminders in the area of the locus coeruleus in combat veterans with PTSD relative to those without PTSD (Bremner, Innis, et al., 1997).

Dopamine

The three major dopaminergic neuronal systems include the nigrostriatal, mesolimbic, and mesocortical projection systems. Nigrostriatal systems involve dopaminergic projections from the substantia nigra to the striatum, mesolimbic systems are comprised of projections from the midbrain to the nucleus accumbens, and mesocortical involve projections from midbrain to medial prefrontal cortex. Mesocortical dopaminergic systems are the most sensitive neural system to mild stressors: mild and brief stress in the form of footshock results in a selective increase in dopamine release (Abercrombie, Keefe, DiFrischia, & Zigmond, 1989; Deutch, Tam, & Roth, 1985; Imperato, Puglisi-Allegra, Casolini, & Angelucci, 1991; Inoue, Tsuchiya, & Koyama, 1994) and metabolism (Abercrombie et al., 1989; Imperato et al., 1991; Kalivas & Duffy, 1989) in the medial prefrontal cortex. Chronic stress also resulted in an increased release of dopamine (Finlay, Zigmond, & Abercombie, 1994) and dopamine metabolism (Sudha & Pradhan, 1995) in medial prefrontal cortex. Higher levels of stress can also result in increased dopamine release in nucleus accumbens (Abercrombie et al., 1989; Imperato et al., 1991; Roth, Tam, Ida, Yang, & Deutch, 1988) and striatum (Abercrombie et al., 1989; Keefe, Stricker, Zigmond, & Abercrombie, 1990) and dopamine metabolism in nucleus accumbens (Imperato et al., 1991) and striatum (Abercrombie et al., 1989; Keefe et al., 1990) as well as in medial prefrontal cortex. Following lesions of the prefrontal cortex, footshock results in significant increases in dopamine levels in the nucleus accumbens (Deutch, Clark, & Roth, 1990), suggesting that stress results in a preferential increase in mesoprefrontal cortical dopamine release. Administration of dopamine D2 receptor agonist (pramipexole) resulted in a reversal of stress-induced behavioral deficits (Willner, Lappas, Cheeta, & Muscat, 1994).

Stress-induced increases in mesoprefrontal cortical dopamine release is susceptible to modulation by several neurotransmitter systems. N-methyl-D-aspartate (NMDA) and opiate receptor blockade in the ventral tegmental area (VTA) prevents stress-induced activation of the cortical dopamine system (Kalivas & Abhold, 1987). In addition, pre-administration of benzodiazepines prevents attenuation of stress-induced activation of dopamine neurotransmission (Roth et al., 1988).

Studies of the effects of stress on dopaminergic systems may be relevant to PTSD. Intracranial self-stimulation for mesocortical and mesolimbic dopaminergic systems has been used as a model for anhedonia, or a decreased ability to take pleasure in activities. Uncontrollable stress was shown to lead to a decrease in intracranial stimulation for mesocortical and mesolimbic systems (Zacharko, Bowers, Kokkinidis, & Anisman, 1983; Zacharko, Gilmore, MacNeil, Kasian, & Anisman, 1990). These studies suggest that symptoms of emotional numbing, decreased interest in things, and being cut off from others may be related to alterations in mesocortical and mesolimbic dopaminergic systems. Administration of cocaine and amphetamine, which both stimulate endogenous dopamine release, results in an increase in paranoid and vigilance behaviors. One could speculate that alterations in dopamine systems may also play a role in the pathophysiology of these particular symptoms in patients with PTSD.

Although little work has been done to examine dopaminergic function in PTSD, one study in patients with combat-related PTSD found elevations in urinary dopamine relative to controls, which correlated with PTSD symptom severity (Yehuda et al., 1992), while women with sexual abuse-related PTSD were found to have elevated urinary dopamine relative to controls (Lemieux & Coe, 1995). Another study in sexually abused girls (most of whom did not meet criteria for PTSD) showed elevations of the dopamine metabolite, homovanillic acid (HVA), relative to nor-

mal girls (DeBellis et al., 1994). In summary, clinical studies to date, although preliminary, are consistent with increased dopamine release and metabolism in PTSD.

Corticotropin Releasing Factor/Hypothalamic-Pituitary-Adrenal Systems

The corticotropin releasing factor (CRF)/hypothalamic-pituitary-adrenal (HPA) axis system plays an important role in the stress response. Exposure to stressful situations is associated with a marked increase in cortisol release from the adrenal. Cortisol is important in effecting many of the expressions of the stress response, such as increased gluconeogenesis, inhibition of growth and reproductive systems, and containment of inflammatory responses. Cortisol release from the adrenal is regulated by adrenocorticotropin releasing hormone (ACTH) release from the pituitary, which in turn is primarily regulated by CRF release from the paraventricular nucleus (PVN) of the hypothalamus.

CRF is distributed in several brain areas, in addition to the PVN, which have been implicated in the behavioral and physiological responses to stress, including the central nucleus of the amygdala, hippocampus, prefrontal and cingulate cortices, locus coeruleus, thalamus, periacqueductal gray, and cerebellum (reviewed in Schatzberg & Nemeroff, 1988). Intraventricular injection of CRF results in a series of physiological and behavioral responses which are adaptive during stress and which are considered to be characteristic of anxiety responses. These behaviors include increased locomotion and grooming in an open field environment, a decrease in punished responding and time spent on the open arms of an elevated plus maze. CRF injected into the central nucleus of the amygdala results in an increase in the magnitude of the startle response and significantly improves retention of the inhibitory avoidance response, a measure of learning and memory (reviewed in Dunn & Berridge, 1990).

The CRF/HPA axis and norepinephrine systems are involved in a mutually inter-regulatory network. CRF-containing neurons from the paraventricular nucleus of the hypothalamus project to the locus coeruleus, and noradrenergic neurons from the locus coeruleus project to the paraventricular nucleus. Increases in CRF result in an increase in discharge rate of locus coeruleus neurons (Valentino et al., 1991), and conversely, emerging evidence suggests that brain norepinephrine systems stimulate CRF release at the level of the PVN (reviewed in Dunn & Berridge, 1990).

Stressors early in life may have long-term effects on the CRF/HPA axis. Both prenatal (light and noise) (Fride, Dan, Feldon, Halevy, & Weinstock, 1986) and early maternal deprivation stress (Stanton, Gutierrez, & Levine, 1988; Levine, Weiner, & Coe, 1993) and early manipulation stress (Levine, 1962) resulted in increased glucocorticoid response to subsequent stressors. Prenatal stress was associated with a failure of habituation of glucocorticoid responsiveness to novel stimuli (Fride et al., 1986). Increased glucocorticoid responsivity to ACTH challenge in maternal deprivation stress suggested an increase in adrenocortical responsivity with early stress (Stanton et al., 1988). Daily handling within the first few weeks of life (picking up rat pups and then returning them to their mother) resulted in increased Type II glucocorticoid receptor binding which persisted throughout life. This was associated with increased feedback sensitivity to glucocorticoids, and reduced glucocorticoid-mediated hippocampal damage in later life (Meaney, Aitken, van Berkel, Bhatnager, & Sapolsky, 1988; Meaney, Aitken, Sharma, & Sarrieau, 1989) (see below, "The Hippocampus"). It is not clear, however, whether early handling in these experiments represents a form of "stress innoculation" or is a form of early stressor. These hormonal systems have profound effects on neuronal development, which means that stress-induced alterations could have profound effects on development of the brain.

Studies in human subjects have validated the important role of cortisol in the stress response. Underwater demolition team training (Rubin, Rahe, Arthur, & Clark, 1969), landing aircraft on aircraft carriers (Miller, Rubin, Clark, Crawford, & Arthur, 1970), and other highly stressful experiences (reviewed in Miller, 1968) resulted in elevations in serum cortisol relative to background levels. The exact relationship between stress and cortisol in human subjects, however, is

complex, and is highly dependent on psychological factors. For instance, in one study measuring levels of urinary cortisol in helicopter ambulance medics, there was no difference between ground time and time flying on combat missions with the threat of death. Overall, the medics had lower cortisol levels than expected from normal samples. The authors noted that psychological factors, such as feelings of being in control, invulnerability, and downplaying the threat of death, probably played an important role in the findings (Bourne, Rose, & Mason, 1967). Consistent with this, combat veterans under threat of an impending attack in Vietnam showed differing levels of cortisol depending on their role. The officers and the radioman, who were actively planning the response, had elevated levels, while the enlisted men, who had no part in the preparation, had lowered levels (Bourne, Rose, & Mason, 1968). Miller (1968) summarized this literature and concluded that psychological factors, including feelings of control and competency, play an important role in the cortisol response to stress.

Several clinical studies suggest that alterations in HPA axis function may be associated with PTSD (Table 6.2). A large increase in urinary cortisol was found during the stress of bombardment in veterans of the Korean War (Howard et al., 1955). A decrease in urinary cortisol levels has been found in Vietnam veterans with chronic PTSD in comparison to controls and patieders in some studies (Mason, Giller, Kosten, Ostroff, & Podd, 1986; Yehuda, Southwick, Nussbaum, Giller, & Mason, 1991; Yehuda, Boisoneau, Mason, & Giller, 1993) but not others (Pitman & Orr, 1990), while decreased plasma cortisol was found in 24-hour sampling in patients with combat-related PTSD relative to healthy controls and patients with depression (Yehuda, Teicher, Levengood, Trestman, & Siever, 1994). On the other hand, women with a history of childhood sexual abuse-related PTSD (Lemieux & Cole, 1995) and patients with PTSD related to a natural disaster (Baum, Cohen, & Hall, 1993) had elevated levels of urinary cortisol relative to controls. Male patients with combat-related PTSD (Kosten, Wahby, & Giller, 1990; Kudler, Davidson, Meador, Lipper, & Ely, 1987; Olivera & Fero, 1990) and female patients with sexual assault-related PTSD (Dinan et al., 1990) have been shown to suppress normally with the standard 1 mg dexamethasone suppression test (DST). Studies utilizing lower doses of DST (0.5 mg) suggest that PTSD may be associated with a super-suppression of the cortisol response in comparison to normal controls (Yehuda, Southwick, et al., 1993), which appears to be the opposite of patients with major depression who are non-suppressers with the standard 1 mg DST test. PTSD patients have also been found to have a significantly lower ("blunted") adrenocorticotropin hormone (ACTH) response to corticotropin releasing factor (CRF) than controls, suggesting an increased release of neuronal CRF (Smith et al., 1989). Consis-

TABLE 6.2 Evidence for Alterations in CRF/HPA Axis Function in PTSD

Alterations in urinary cortisol	+/-*
Decreased plasma cortisol with 24-hour sampling	+
Super-suppression with DST	+
Blunted ACTH response to CRF	+
Elevated CRF in CSF	+
Increased lymphocyte glucocorticoid receptors	++

-	One or more studies did not support this finding (with no positive studies), or the majority of studies do not support this finding;
+/-	An equal number of studies supported this finding as studies that did not support this finding;
+	At least one study supports this finding with no studies not supporting the finding, or the majority of studies support the finding;
++	Two or more studies support this finding, with no studies conducted that do not support the finding;
+++	Three or more studies support this finding, with no studies that do not support the finding.

*Findings of decreased urinary cortisol in older male combat veterans and holocaust survivors, and increased cortisol in younger female abuse survivors, may be explainable by differences in gender, age, trauma type, or developmental epoch at the time of the trauma.

tent with this are findings of elevated levels of CRF in the cerebrospinal fluid of Vietnam combat veterans with PTSD relative to healthy subjects (Bremner, Licinio, et al., 1997). Other studies showed that patients with combat-related PTSD had an increase in lymphocyte glucocorticoid receptors in comparison to healthy subjects, nonPTSD combat veterans and patients with other psychiatric disorders (Yehuda, Lowy, Southwick, Shaffer, & Giller, 1991; Yehuda, Boisoneau, Lowy, & Giller, 1995). These studies demonstrate that alterations in cortisol and HPA axis function are associated with PTSD. One possible explanation of clinical findings to date is an increase in neuronal CRF release, with resultant blunting of ACTH response to CRF, increased central glucocorticoid receptor responsiveness, and resultant low levels of peripheral cortisol due to enhanced negative feedback. Interestingly, nonhuman primates with variable foraging mothers (a model for early-life stress) had elevated CSF CRF and decreased CSF cortisol levels in adulthood, a picture that is closer to PTSD than depression (Coplan et al., 1996).

Benzodiazepine Systems

Benzodiazepine receptors are present throughout the brain (Mohler & Okada, 1977), with the highest concentration in cortical grey matter (Hirsch, Garrett, & Beer, 1985). Benzodiazepines potentiate and prolong the synaptic actions of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA). Central benzodiazepine receptors and GABAa receptors are part of the same macromolecular complex. These receptors have distinct binding sites, although they are functionally coupled and regulate each other in an allosteric manner. A correlation has also been found between the efficacy of the benzodiazepines and their potency at displacing [3H]diazepam binding, which suggests that these compounds are physiologically relevant (Mohler & Okada, 1977; Squires & Braestrup, 1977). The hypothesis that alterations in benzodiazepine receptor function play a role in the pathophysiology of stress-related psychiatric disorders such as PTSD is supported by several lines of preclinical evidence (reviewed by Guidotti, Baraldi, Leon, & Costa, 1990).

Administration of inverse agonists of benzodiazepine receptors, such as beta-carboline-3-carboxylic acid ethyl ester (beta-CCE), result in behavioral and biological effects similar to those seen in anxiety and stress, including increases in heart rate, blood pressure, plasma cortisol, and catecholamines (Braestrup, Smiechen, Neef, Nielsen, & Petersen, 1982). Administration of N-methyl-beta-carboline-3-carboxamide results in the development of an inability to learn maze escape behaviors, as is seen in the learned helplessness paradigm (Drugan, Maier, Skolnick, Paul, & Crawley, 1985). Administration of the beta-carboline FG 7142 also results in an increase in local cerebral glucose utilization in brain structures involved in memory, including lateral septal nucleus, mammillary bodies, and anterior thalamic nuclei (Ableitner & Herz, 1987). The effects of the beta-carbolines are blocked by administration of benzodiazepines (Ninan et al., 1982), or pretreatment with the benzodiazepine antagonist flumazenil (Drugan et al., 1985).

Studies using the animal model of uncontrollable stress, a model for stress-related psychiatric disorders such as PTSD, suggest alterations in benzodiazepine receptor function associated with uncontrollable stress (reviewed in Bremner, Davis, Southwick, Krystal, & Charney, 1993; Charney, Deutch, Krystal, Southwick, & Davis, 1993). Multiple studies have found that animals exposed to acute or chronic inescapable stress in the form of cold swim or footshock (but not defeat stress) (Miller et al., 1987) develop a decrease in benzodiazepine receptor binding (Bmax) (but not typically KD) in frontal cortex, but not other regions, including pons, striatum, or thalamus (Braestrup, Nielsen, Nielsen, & Lyon, 1979; Drugan et al., 1989; Medina, Novas, & De Robertis, 1983; Medina, Novas, Wolfman, De Stein, & De Robertis, 1983; Weizman et al., 1990). Some studies (Drugan, Basile, Crawley, Paul, & Skolnick, 1986; Drugan et al., 1989; Medina, Novas, & De Robertis, 1983; Medina, Novas, Wolfman, et al., 1983; Weizman et al., 1990) but not others (Braestrup et al., 1979; Havoundjian, Paul, & Skolnick, 1986; LeFur, Guilloux, Mitrani, Mizoule, & Uzan, 1979; Skerritt, Trisdikoon, & Johnston, 1981) showed decreases in cerebral cortex. Some studies showed decreases in hippocampus (Drugan et al., 1989; Weizman et al.,

1990), and hypothalamus (Drugan et al., 1989; Lippa et al., 1987), but other studies did not replicate these results (Braestrup et al., 1979; LeFur et al., 1979; Medina, Novas, & De Robertis, 1983; Skerritt et al., 1981). Differences in findings between different groups may be related to types of stressors, stressor duration, animal species strain, and ligand used to measure benzodiazepine receptor binding. Decreases in benzodiazepine receptor binding are associated with alterations in memory manifested by deficits in maze escape behaviors (Weizman et al., 1989; Drugan et al., 1989). Changes in benzodiazepine receptor function appear to be specific to uncontrollable stress, as opposed to controllable stress, and are prevented by pre-administration of benzodiazepines (Drugan et al., 1984). In addition, animals exposed to inescapable stress exhibit decreases in binding of the benzodiazepine receptor antagonist flumazenil (formerly designated Ro-15-1788) (Drugan et al., 1989), which are associated with deficits in learning, and decreased depolarization-induced release of GABA relative to controls (Petty & Sherman, 1981). These studies suggest that acute and chronic stress are associated with specific decreases in benzodiazepine receptor binding in frontal cortex.

A decrease in benzodiazepine receptor binding (Bmax) has been demonstrated in the so-called Maudsley genetically fearful strain of rat in comparison to non-fearful rats in several brain structures including the hippocampus (Robertson, Martin, & Candy, 1978).

Evidence from clinical studies performed to date suggests a possible role for alterations in benzodiazepine receptor function in PTSD. Healthy subjects exposed to the stress of war were found to have a decrease in binding of benzodiazepine receptors on peripheral mitochondria during the stressful period before and during war relative to the period after the war, which was correlated with an improvement of anxiety after the end of the war (Weizman, Laor, et al., 1994). No difference was found in anxiety response to the benzodiazepine receptor antagonist, flumazenil, between patients with combat-related PTSD and controls (Randall et al., 1995). Flumazenil, however, has no effect on the receptor per se: future studies are required with other agents, such as inverse agonists, which have an effect on the benzodiazepine receptor. Perhaps the most convincing piece of evidence linking benzodiazepine receptor function to the pathophysiology of PTSD is the efficacy of the benzodiazepines in their treatment (reviewed in Bremner & Charney, 1994). PTSD patients specifically report an improvement in intrusive and hyperarousal symptoms with benzodiazepines (Bremner, Southwick, Darnell, & Charney, 1996).

Opiates

Endogenous opiate systems play a role in the stress response (Grossman, 1988). Exposure to stress results in an increased release of opiate peptides and the development of an analgesia to pain known as stress-induced analgesia (Helmstetter & Fanselow, 1987; Maier et al., 1981). Stress-induced analgesia can be blocked by administration of the opiate receptor antagonist naltrexone (Helmstetter & Fanselow, 1987; Maier et al., 1981). In rats with a history of inescapable stress, re-exposure to the environment where the shock took place is sufficient to reinvoke stress-induced analgesia (Hemingway & Reigle, 1987). Rats exposed to inescapable stress develop decreased binding of the mu-opiate receptor agonist DAGO in the midbrain (Stuckey, Marra, Minor, & Insel, 1989). Perhaps one of the most important functions of the endogenous opiate system is a counter-regulatory one, serving to decrease activity of other major stress axes, such as CRF and norepinephrine (Grossman, 1988). For instance, preadministration of morphine to rats exposed to inescapable stress attenuated the stress-induced release of norepinephrine in hypothalamus, hippocampus, amygdala, midbrain, and thalamus (Tanaka et al., 1983). Opiates cause a decrease in firing from the locus coeruleus; this provides an explanation for the favorable response of hyperarousal symptoms of PTSD to opiates such as heroin (Bremner, Southwick, et al., 1996).

Endogenous opiates may play an important role in responses to early stress. Stress in the first few weeks of life results in a decrease in levels of ornithine decarboxylase, a key regulator of cell growth. Administration of beta-endorphin also results in a decrease in ornithine decarboxylase, suggesting that

beta-endorphin may mediate the effects of early stress on activity of this enzyme (and therefore cell growth) (Bartolome, Johnston, & Schanberg, 1994). These findings suggest that endogenous opiates are involved in the stress response at all stages of development.

Several lines of evidence suggest that alterations in endogenous opiate systems may be associated with the clinical symptomatology of patients with PTSD. Since the time of World War II, surgeons working on the battlefield have noted that wounded soldiers have a reduced need for opiate analgesic medication, suggesting that the stress of combat is associated with an increase in endogenous opiate release (Howard et al., 1955). PTSD patients have been shown to have high rates of heroin abuse and dependence (Kulka et al., 1990). In one study, PTSD patients reported an improvement in symptoms of hyperarousal and intrusive symptomatology with heroin administration. This was in contrast to other substances of abuse, such as cocaine (Bremner, Southwick, et al., 1996). Vietnam veterans with PTSD had a reduced sensitivity to pain during exposure to traumatic reminders in the form of a videotape with combat-related scenes (van der Kolk, Greenburg, Orr, & Pitman, 1989). This analgesia to pain is reversible with the opiate antagonist, naloxone, which prompted the authors to point out the parallel between their finding and the stress-induced analgesia response in animals (Pitman, van der Kolk, et al., 1990). PTSD patients have been found to have a relative increase in plasma beta-endorphin levels in response to exercise, with no difference in baseline levels, in comparison to healthy controls (Hamner & Hitri, 1992). These studies are interesting, and suggest that additional studies should be performed in this area in the future.

Serotonin

The serotonin system is involved in the stress response. Acute electric shock resulted in increased metabolism of serotonin in medial prefrontal cortex, nucleus accumbens, amygdala, and lateral hypothalamus (Inoue et al., 1994). Conditioned fear stress resulted in a preferential increase in serotonin metabolism in medial prefrontal cortex (Inoue et al., 1994). Chronic electric shock resulted in a decrease in serotonin (5HT) release in frontal cortex which are associated with stress-induced behavioral deficits ("learned helplessness") (Petty, Kramer, & Wilson, 1992). Preadministration of benzodiazepines or tricyclic antidepressants prevents stress-induced decreases in serotonin and the acquisition of behavioral deficits (Petty et al., 1992), while injection of serotonin (5HT) into the frontal cortex after stress exposure reverses behavioral deficits (Sherman & Petty, 1982). Chronic restraint stress results in a decrease in 5HT1A binding in the hippocampus (Mendelson & McEwen, 1991; Watanabe, Sakai, McEwen, & Mendelson, 1993). Animals exposed to social stress had a decrease in binding of 5HT1A receptors in hippocampus and dentate gyrus, and a decrease in 5HT2 binding in parietal cortex (McKittrick, Blanchard, Blanchard, McEwen, & Sakai, 1995). Administration of 5HT1A agonists such as buspirone result in a reversal of stress-induced behavioral deficits (Drugan, Crawley, Paul, & Skolnick, 1987; Przegalinski, Moryl, & Papp, 1995).

There is some preliminary evidence to support alterations in serotonin reuptake site function in PTSD. Patients with combat-related PTSD had reduced paroxetine binding sites (lower Bmax and Kd) in platelets (evidence of reduced serotonin reuptake site function) (Arora, Fichtner, O'Connor, & Crayton, 1993), with decreases in Bmax significantly correlated with PTSD, anxiety, and depressive symptoms (Fichtner, O'Connor, Yeoh, Arora, & Crayton, 1995). Lower pretreatment Kd values predicted positive response to treatment with serotonin reuptake inhibitors, and there was a trend toward lower Bmax values predicting treatment response (Fichtner, Arora, O'Connor, & Crayton, 1994). Another study found no difference in platelet serotonin levels or uptake relative to controls (Mellman & Kumar, 1994). Studies of 5HT1A function have not been suggestive of abnormality. One study in women with sexual assault-related PTSD did not find a difference in prolactin response to buspirone (a probe of 5HT1A function) between women with sexual assault-related PTSD and controls (Dinan et al., 1990). A study in victims of SCUD missile attacks with PTSD did not find an effect of serotonin on forskolin-stimulated adenylate cyclase activity in platelets (a putative probe of 5HT1A) (Weizman, et al., 1994). Further research is

necessary to clarify the role of serotonin dysfunction in PTSD. Perhaps the best clinical evidence for serotonergic involvement in PTSD is the responsiveness of patients with abuse-related PTSD to the serotonin reuptake inhibitor, fluoxetine, in controlled clinical trials (van der Kolk et al., 1994).

Other Neuropeptides and Neurotransmitters

Other neurotransmitter and neuropeptide systems are involved in stress (Table 6.3). Thyroid releasing hormone (TRH) released from the hypothalamus causes release of thyroid stimulating hormone (TSH) from the pituitary, which in turn stimulates thyroid hormone (thyroxine, or T4) release from the thyroid gland. TRH prevented the acquisition of stress-induced behavioral effects (Drago, Pulvirenti, Spadaro, & Pennisi, 1990). Stress is associated with an increase in plasma thyroid levels (Groscolas & LeLoup, 1989; Langer, Vigas, Kvetnansky, Foldes, & Culman, 1983). Studies in monkeys showed that stress results in a slow increase in plasma thyroid hormone, with a peak at greater than 24 hours after the stressor (Mason, Mougey, Brady, & Tolliver, 1968).

In humans, a relationship between stress and thyroid disease was first pointed out many years ago. Patients with hyperthyroidism exhibit symptoms of anxiety and hyperarousal, which has prompted many clinicians to routinely screen psychiatric patients for thyroid disorders. Recently, patients with combat-related PTSD were found to have increased baseline plasma levels of thyroid hormone compared to controls (Mason et al., 1994). PTSD patients also had a pattern of increased thyrotropin stimulating hormone (TSH) response to thyrotropin releasing hormone (TRH) relative to normal controls and patients with depression (Kosten et al., 1990).

Stress is associated with increases in acetylcholine release and metabolism in the hippocampus (Imperato et al., 1991) and glutamate release in the frontal cortex (Moghaddam, 1993). Preclinical studies show that somatostatin is involved in the stress response and modulation of corticotropin releasing factor release. Recent clinical studies in Vietnam combat veterans with PTSD showed increased somatostatin levels in cerebrospinal fluid relative to controls. Increased somatostatin levels were significantly correlated with increased CRF levels in the PTSD patients, but not the controls (Bremner, Licinio, et al., 1997).

TABLE 6.3 Evidence for Alterations in Other Neurotransmitter and Neuropeptidal Systems in PTSD

Benzodiazepine	
Increased symptomatology with benzodiazepine antagonist	-
Opiate	
Naloxone-reversible analgesia	+
Increased plasma beta-endorphin response to exercise	+
Serotonin	
Decreased serotonin reuptake site binding in platelets	++
Decreased serotonin transmitter in platelets	-
Blunted prolactin response to buspirone (5HT1A probe)	-
Altered serotonin effect on cAMP in platelets (5HT1A probe)	-
Thyroid	
Increased baseline thyroxine	+
Increased TSH response to TRH	+
Somatostatin	
Increased somatostatin levels at baseline in CSF	+

-	One or more studies did not support this finding (with no positive studies), or the majority of studies do not support this finding;
+/-	An equal number of studies supported this finding as studies that did not support this finding;
+	At least one study supports this finding with no studies not supporting the finding, or the majority of studies support the finding;
++	Two or more studies support this finding, with no studies conducted that do not support the finding;
+++	Three or more studies support this finding, with no studies that do not support the finding.

IV. EFFECTS OF STRESS ON THE NEUROBIOLOGY OF LEARNING AND MEMORY

Recently there has been considerable interest in alterations in memory function in PTSD (Journal of Traumatic Stress, 1995, Volume 8). Memory alterations in PTSD take the form of deficits in both short-term memory as well as potentiation of recall of traumatic experiences and dissociative flashbacks (Pitman, 1989; Bremner, Krystal, et al., 1995; Bremner, Krystal, Charney, & Southwick, 1996). PTSD patients also demonstrate alterations in emotion-related learning, such as conditioned fear responses, increased startle, and failure of extinction. Studies in animals show that exposure to extreme stress results in alterations in memory function with associated long-term changes in brain regions involved in memory, including amygdala, hippocampus, parahippocampus, orbitofrontal cortex, cingulate, and thalamus. Other brain regions involved in memory and attention, such as parietal cortex and cerebellum, also probably play a role in stress-related symptoms.

Memory formation involves encoding (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. A number of schema have been formulated to describe memory function. Many authors make the distinction between declarative ("explicit") and nondeclarative ("implicit" or "procedural") memory (Squire & Zola-Morgan, 1991; Schacter, 1995). 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 have been shown to play an important role in memory. Other regions involved in memory include the prefrontal cortex, including what is known as the dorsolateral prefrontal cortex (middle frontal gyrus, principal sulcus region, or Area 46), orbital gyrus, anteromedial prefrontal cortex (including anterior cingulate cortex), cerebellum, and parietal association cortex. In addition, memories are stored in the primary cortical sensory and motor areas which correspond to the particular sensory modality related to the memory. These brain regions interact with one another in the mediation of memory function.

It has long been hypothesized that brain regions involved in memory also play a role in stress and the fear response. Early neuroanatomical studies showed that removal of the cerebral cortex of the cat, which left only subcortical regions including amygdala, thalamus, hippocampus, and hypothalamus, resulted in accentuated fearful responses to potentially threatening or novel stimuli, accompanied by signs of diffuse sympathetic activation such as increased blood pressure, sweating, piloerection, and increased secretion of epinephrine from the adrenal medulla (Cannon, 1927). This behavioral response became termed as "sham rage," and led to the original hypothesis that subcortical brain structures above the level of the midbrain, such as the hypothalamus, hippocampus, cingulate, entorhinal cortex, and thalamus, may be involved in emotional responses such as fear (Kluver & Bucy, 1937, 1939; Papez, 1937; reviewed in LeDoux, 1977). MacLean (1949) later added the amygdala to the "Papez Circuit" of "limbic" brain structures, so called because of their relationship to olfaction in evolution, which were hypothesized to play a role in fear and anxiety. These early neuroanatomical investigations were valuable in showing that brain regions involved in memory also play an important role both in fear-related behaviors seen naturally in the wild, and in manifestations of increased catecholaminergic activity. Below, brain regions involved in memory are outlined, with a review of normal function and stress-induced changes in function, followed by a discussion of possible correlates with PTSD (Figure 6.2).

The Hippocampus

The hippocampus plays an important role in explicit memory. Case studies such as the famous case of H.M. found a relationship between severe deficits in

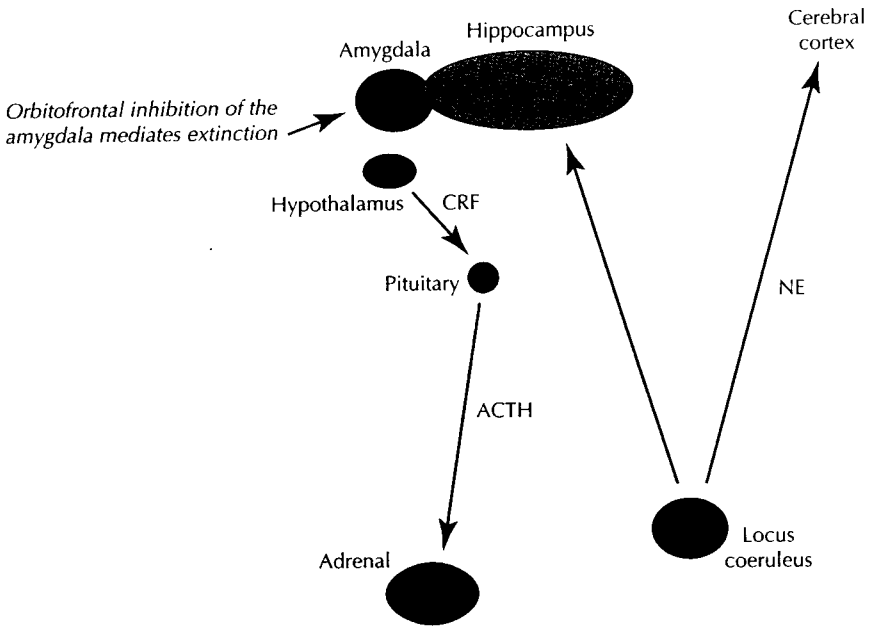


FIGURE 6.2 The Neuroanatomy of the Effects of Stress on Brain Regions Involved in Memory. Multiple brain areas mediate stress and fear responses, including amygdala, hippocampus, orbitofrontal cortex, cerebral cortex, hypothalamus, and the brain stem. These regions are functionally inter-related. Long-term changes in function and structure of these regions lead to symptoms of PTSD.

explicit memory measured with free verbal recall and lesions of the medial temporal lobes (i.e., hippocampus and adjacent structures). Lesions including the hippocampus and adjacent cortex (dentate gyrus, hippocampus proper, subicular complex, and entorhinal cortex), amygdala, and surrounding perirhinal and parahippocampal cortices in primates led to deficits in explicit memory measured with working memory tasks (Mishkin, 1978). Damage to the amygdala alone was not associated with declarative memory impairment (Zola-Morgan, Squire, & Amaral, 1989), while damage to the cortical areas adjacent to the amygdala, including perirhinal cortex and parahippocampal gyrus (which has important efferent and afferent connections with the hippocampus), was associated with pronounced explicit memory impairment (Murray & Mishkin, 1986; Zola-Morgan, Squire, Amaral, & Suzuki, 1989). These studies demonstrated that the hippocampal region (dentate, hippocampus proper, subicular complex, and entorhinal cortex) and the adjacent perirhinal cortex and parahippocampal gyrus are involved in explicit memory. Recent positron emission tomography (PET) studies of cerebral blood flow are also consistent with a role for the hippocampus in explicit memory (Grasby, Frith, Friston, Frackowiak, & Dolan, 1993; Squire et al., 1992).

The hippocampus has long been felt to be involved in the emotions of fear and anxiety (Gray, 1982). The hippocampus is also known to play an important role in placement of memory traces in space and time (Parkinson, Murray, & Mishkin, 1988),

including conditioned fear responses related to the context of a fear-inducing situation. In conditioned fear response experiments where a tone (conditioned stimulus) is paired with electric footshock (unconditioned stimulus), re-exposure 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 (i.e., 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 (Phillips & LeDoux, 1992). Lesions of the hippocampus one day after fear conditioning (but not as much as 28 days after fear conditioning) 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 (Kim & Fanselow, 1992). 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. The amygdala integrates information from multiple sensory modalities and effects the conditioned emotional response. The role of the hippocampus is to formulate conditioned responses to complex spatially related stimuli. It probably does this by integrating complex spatially related stimuli, and passing this information through the subiculum to the amygdala, which effects the stress response.

There is a wealth of evidence from studies in animals that stress results in long-term alterations in brain systems involved in memory (McEwen et al., 1992; Sapolsky, Uno, Rebert, & Finch, 1990). For instance, there is a considerable amount of evidence derived from research in animals which suggests that stress is associated with damage to hippocampal neurons. Monkeys who died spontaneously following exposure to severe stress were found on autopsy to have multiple gastric ulcers, consistent with exposure to chronic stress, and hyperplastic adrenal cortices, consistent with sustained glucocorticoid release. These monkeys also had damage to the CA3 subfield of the hippocampus (Uno, Tarara, Else, Suleman, & Sapolsky, 1989). Studies in a variety of animal species (Sapolsky, Packan, & Vale, 1988; Sapolsky et al., 1990) suggest that direct glucocorticoid exposure results in decreased dendritic branching in the hippocampus (Wooley, Gould, & McEwen, 1990) and a loss of neurons (Uno et al., 1989). Glucocorticoids appear to exert their effect by increasing the vulnerability of hippocampal neurons to insults such as excitatory amino acids (Sapolsky, 1986; Virgin et al., 1991). High levels of glucocorticoids seen with stress have also been associated with deficits in new learning (Luine, Villages, Martinex, & McEwen, 1994), with the magnitude of deficits in new learning behaviors correlated with the number of damaged cells in the CA3 region of the hippocampus. These studies suggested the possibility that high levels of cortisol released during stress could damage the hippocampus in humans with PTSD, leading to deficits in verbal memory function and decreased hippocampal volume.

Studies in clinical populations are consistent with deficits in verbal memory function. PTSD exhibit alterations in memory, including nightmares, flashbacks, intrusive memories, and amnesia for the traumatic event. We have reported an increase in the dissociative symptom of amnesia as measured with the SCID-D (Dissociative Disorders) in Vietnam combat veterans with PTSD in comparison to Vietnam combat veterans without PTSD (Bremner, Steinberg, Southwick, Johnson, & Charney, 1993). 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.

Evidence from other studies in traumatized patients are also consistent with abnormalities of explicit memory function. In one group of 321 Danish survivors of WWII concentration camps with high levels of psychiatric symptomatology who were seeking

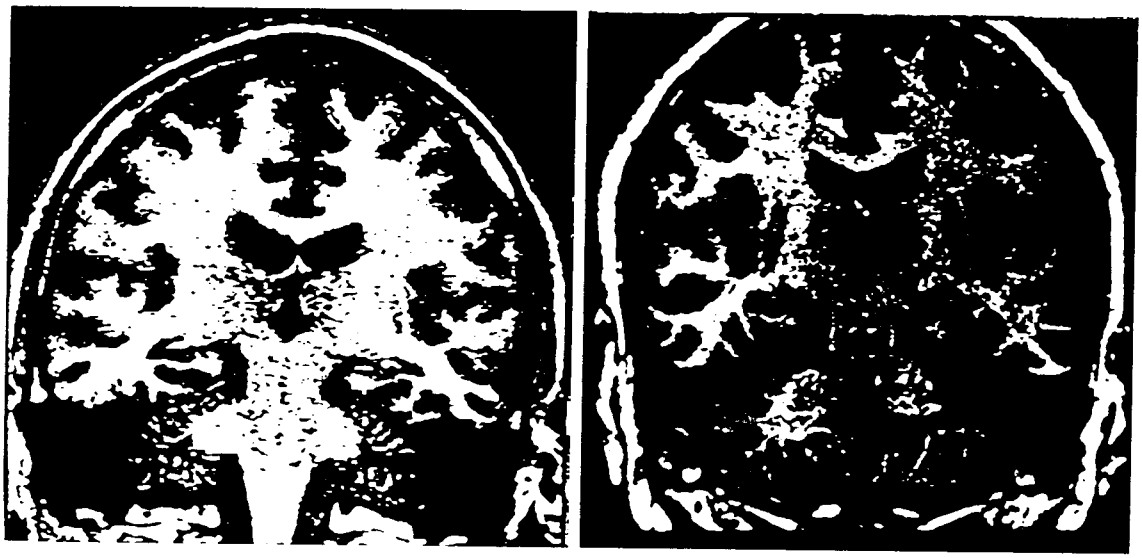
compensation for disability, there were complaints of memory impairment suggestive of deficits in explicit recall 10 or more years after release from internment in 87 percent of individuals. Severe intellectual impairment was also found on testing in 61 percent of cases (Thygesen, Hermann, & Willanger, 1970). Korean prisoners of war have been found to have an impairment on explicit memory tasks of free verbal recall measured with the Logical Memory component of the Wechsler Memory Scale in comparison to Korean veterans without a history of containment (Sutker, Winstead, Galina, & Allain, 1991). We found deficits in explicit verbal memory function as measured with the Wechsler Memory Scale (WMS)-Logical component and the Selective Reminding Test-verbal, in Vietnam combat veterans with PTSD (Bremner, Scott, et al., 1993) and adult survivors of childhood abuse (Bremner, Randall, Capellie, et al., 1995) without deficits in IQ as measured by the Wechsler Adult Intelligence Scale-Revised. Studies have found deficits in explicit short-term memory as assessed with the Auditory Verbal Learning Test (AVLT) in Vietnam combat veterans with PTSD in comparison to National Guard veterans without PTSD (Uddo, Vasterling, Brailey, & Sutker, 1993) and the California New Learning Test in Vietnam veterans with combat-related PTSD in comparison to controls (Yehuda, Keefer, et al., 1995). Deficits in academic performance have also been shown in Beirut adolescents with PTSD in comparison to Beirut adolescents without PTSD (Saigh, Mroueh, & Bremner, 1997).

Other aspects of cognitive function have been investigated in PTSD. Vietnam veterans with PTSD were found to have decreased IQ relative to controls, suggesting that low intelligence may be a risk factor for PTSD (McNally & Shin, 1995). Patients with combat-related PTSD were found to have deficits in autobiographical memory, characterized by an inability to retrieve specific memories, relative to controls (McNally, Lasko, Macklin, & Pitman, 1995; McNally, Litz, Prassas, Shin, & Weathers, 1994). PTSD patients showed a relative deficit in retrieval of specific autobiographical memories in response to positive cues (McNally et al., 1995), as well as a greater effect of negative emotional cues (combat slides and sounds) on decreasing specificity of retrieved autobiographical memories (McNally et al., 1994). Patients with combat-related PTSD have increased rates of childhood abuse (Bremner, Southwick, et al., 1993), and other studies have noted a relationship between childhood trauma and impairments in autobiographical memory (cited in McNally et al., 1994). Traumatic events during childhood may result in a disruption in development of the normal catalogue of memories which lead to a sense of identity and the "story of one's life," which explains findings of deficits in autobiographical memory in PTSD. Studies of implicit memory bias for trauma-relevant material showed no differences between PTSD patients and controls using a perceptual identification paradigm (identifying words on a computer screen) (McNally & Amir, 1996), although a significant implicit memory bias was found for combat-relevant sentences using a noise judgment task (PTSD subjects rated the volume of noise accompanying "old" trauma sentences as less loud than new sentences, whereas controls did not) (Amir, McNally, & Wiegartz, 1996).

Studies utilizing neuroimaging techniques have found that stress in humans may be associated with changes in brain structure, including the morphology of the hippocampus. Studies in concentration camp survivors from World War II seeking compensation for disability utilized pneumoencephalography and reported "[cerebral] atrophy of varying degrees" and "diffuse encephalopathy" in up to 81 percent of cases (referenced in Thygesen et al., 1970). We compared hippocampal volume measured with MRI in Vietnam combat veterans with PTSD ($N = 26$) and healthy subjects ($N = 22$) matched for factors which could affect hippocampal volume, including age, sex, race, years of education, height, weight, handedness, and years of alcohol abuse. Patients with combat-related PTSD had an 8 percent decrease in right hippocampal volume in comparison to controls ($p < 0.05$), but no significant decrease in volume of comparison structures including temporal lobe and caudate. Deficits in free verbal recall (explicit memory) as measured by the Wechsler Memory Scale-Logical Component, percent retention, were associated with 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) (Bremner, Randall, Scott, et al., 1995). We also found a statistically significant 12 percent decrease in left hippocampal volume in 17 patients with a history of PTSD related to severe childhood physical and sexual abuse, in relationship to 17 controls matched on a case-by-case basis with the patients (Bremner, Randall, et al., 1997) (Figure 6.3). PET $H_2[^{15}O]$ studies of PTSD during exposure to traumatic reminders in the form of combat-related slides and sounds showed activation in right posterior parahippocampus relative to non-PTSD combat veterans (Bremner, Innis, et al., 1997).

Other aspects of the alterations in memory function seen in PTSD may be mediated by the hippocampus and adjacent cortex. Electrical stimulation of the temporal lobe (including 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 which 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 (i.e., flashbacks) (5), memory recall (5), deja vu (4), and emotional distress (3) (Gloor, Olivier, Quesney, Andermann, & Horowitz, 1982). In another study, electrical stimulation of the hippocampus and amygdala in epileptic patients was also associated with visual and auditory hallucinations, dream-like and memory-like hallucinations which descriptively are similar to flashbacks reported by patients with PTSD (Halgren, Walter, Cherlow, & Crandall, 1978). An increase in dissociative symptomatology and disruption of delayed word recall was found in normal subjects following intravenous administration of ketamine hydrochloride, a noncompetitive antagonist of the N-methyl-D-aspartate (NMDA) receptor (Krystal et al., 1994). The NMDA receptor, which is highly concentrated in the hippocampus, probably mediates memory function at the molecular level through mechanisms such as long-term potentiation (LTP) (reviewed in Krystal, Bennett, Bremner, Southwick, & Charney, 1995).



(a) PTSD (b) CONTROL

FIGURE 6.3 Magnetic resonance scan of a patient with PTSD and a normal comparison subject. There is visible atrophy of the hippocampus in the patient with PTSD relative to the comparison subject.

We have hypothesized that stress-induced hippocampal dysfunction may mediate many of the symptoms of PTSD which are related to memory dysregulation, including both explicit memory deficits as well as memory distortions similar to those seen with hippocampal stimulation, as reviewed above (Bremner, Krystal, Southwick, & Charney, 1995; Bremner, Krystal, Charney, & Southwick, 1996). The hippocampus and adjacent cortex plays an important role in binding together information from multiple sensory cortices into a single memory at the time of retrieval, and in locating a memory trace in space and time. 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 and the scene where the abuse takes place, tactile sensations, and the temporal relationship of the elements of memory to other aspects of the individual's life experiences. 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 activates cortical areas and brings together the diverse sensory elements in relevant spatiotemporal format in order to recreate the memory. Abnormalities of hippocampal function in PTSD may impair the ability of the hippocampus to recreate a normal memory. Traumatic memories may not be able to be placed in space and time, leading to fragmentation or amnesia. Traumatic memories may intrude into consciousness without any discernible reason, leading to the symptom of intrusive memories and flashbacks.

The Amygdala

The amygdala is involved in memory for the emotional valence of events. The paradigm of conditioned fear has been utilized as an animal model for stress-induced abnormalities of emotional memory (Davis, 1992). Noise bursts elicit the acoustic startle response, which is used in the measurement of the conditioned fear response. Fear conditioning (reviewed above in "The Hippocampus") results in an increase in the startle response. The neuroanatomy and neurophysiology of conditioned fear responses in animals have been well characterized (Davis, 1992). Lesions of the central nucleus of the amygdala have been shown to completely block fear-potentiated startle (Hitchcock & Davis, 1986; Hitchcock, Sananes, & Davis, 1989) while electrical stimulation of the central nucleus increases acoustic startle (Rosen & Davis, 1988). 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). Lesions of this pathway at any point (caudal lateral hypothalamus-subthalamic area, substantia nigra, central tegmental field) block the development of fear-potentiated startle, while lesions of fibers which project outward from the central nucleus of the amygdala to sites other than the brainstem startle circuit have no effect (Hitchcock & Davis, 1991). 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 (Miserendino, Sananes, Melia, & Davis, 1990). These findings demonstrate that the amygdala is involved in emotional memory, including conditioned fear responses, as well as effecting the stress response.

Pathways from the amygdala to the lateral hypothalamus effect peripheral sympathetic responses to stress (Iwata, LeDoux, Meeley, Arneric, & Reis, 1986). Electrical stimulation of the amygdala in cats resulted in peripheral signs of autonomic hyperactivity and fear-related behaviors seen in the wild when the animal is being attacked or is attacking, including alerting, chewing, salivation, piloerection, turning, facial twitching, arching of the back, hissing, and snarling (Hilton & Zbrozyna, 1963), which was associated with a depletion of norepinephrine in the brain and epinephrine and norepinephrine in the adrenal, suggesting an increase in catecholamine turnover.

Studies in human subjects support a role for the amygdala in emotion and the stress response. Studies in human subjects have demonstrated that the threat of electric shock results in an increase in startle response (Grillon, Ameli, Woods, Merikangas, & Davis,

1991). Patients with unilateral temporal lobectomy (including amygdala resection) showed impaired acquisition of fear conditioning relative to controls (LaBar, LeDoux, Spencer, & Phelps, 1995). These subjects, however, showed no difference in recall of emotional words relative to controls (Phelps, LaBar, & Spencer, 1997), suggesting that although the amygdala probably plays an important role in the specific paradigm of conditioned fear, it may not play a unique role in all facets of emotional experience in human subjects. Electrical stimulation of the amygdala in human subjects resulted in an increase in heart rate and blood pressure, increased muscle tension, and subjective sensations of fear or anxiety (Chapman et al., 1954). Amygdala stimulation of human subjects is also accompanied by activation of the stress response system, as manifested by increases in peripheral catecholamines, in a similar fashion to that seen in animals during conditioned fear responses (Gunne & Reis, 1963). We have not found a difference in amygdala volume measured with MRI between patients with combat-related PTSD (Bremner et al., unpublished data, 1/96) or abuse-related PTSD (Bremner, Randall, et al., 1997) and matched controls.

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 utilizing the psychophysiology paradigm, which is reviewed above in "Noradrenergic Systems." Lawrence Kolb (1984) noted that patients with PTSD have a heightened physiological responsiveness to reminders of the original trauma which resemble conditioned responses. These conditioned responses to cues related to the original trauma (combat films and sounds, scripts of traumatic events) are parallel to those seen with the conditioned fear paradigm in animals.

Studies have also found abnormalities of the startle response in patients with PTSD. Increased startle magnitude has been found in Vietnam combat veterans with PTSD in comparison to Vietnam combat veterans without PTSD in some studies (for 80 dB bursts of white noise) (for 95 and 100 dB noise—Butler et al., 1990) but not others (Paige, Reid, Allen, & Newton, 1990). One study showed increased baseline startle in PTSD relative to controls in an experimental setting where electric shock was to be delivered at some point during the experiment. PTSD patients did not demonstrate greater increases in startle, however, when explicitly told that they were now going to receive shock (Morgan, Grillon, Southwick, Davis, & Charney, 1995). No difference in trials to habituation of startle response between PTSD and controls was demonstrated in one study (Ross, Ball, Cohen, et al., 1989). An increase in heart rate and skin conductance during the startle paradigm was reported in patients with civilian PTSD in comparison to controls (Shalev et al., 1992). One study in children with PTSD found an absent normal inhibition of acoustic startle by nonstartling acoustic prestimulation (Ornitz & Pynoos, 1989). In summary, there is evidence for abnormalities in startle response in PTSD. The heightened responsiveness to reminders of the original trauma, or conditioned emotional stimuli, and abnormalities of the startle response are probably mediated by the amygdala, in addition to other brain regions reviewed within this chapter.

Prefrontal Cortex, Anterior Cingulate, and Orbitofrontal Cortex

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 (Goldman-Rakic, 1988). Working memory refers to the ability to store information in a visual or verbal buffer while performing a particular operation utilizing that information. In non-human primates, working memory is assessed by the 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, while explicit memory for features of the stimuli are unaffected. PET $H_2[^{15}O]$ studies of cerebral blood flow in normal human subjects are also consistent with a role for dorsolateral prefrontal cortex in both encoding and retrieval of

explicit memory traces and attention (reviewed in McCarthy, 1995). Deficits in explicit memory function (reviewed above) could therefore be consistent with abnormalities in dorsolateral prefrontal cortex function, in addition to hippocampal dysfunction. An increase in neurological soft signs in Vietnam combat veterans with PTSD could also be explainable by abnormalities in frontal lobe function (Gurvits et al., 1993).

The anteromedial (or ventromesial) 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. Following the accident the patient had normal memory recall and cognitive function, but his behavior deteriorated to irresponsibility, profanity, and 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 anterior cingulate) is responsible for socially appropriate behavior and the processing of emotionally related stimuli (Damasio, Grabowski, Frank, Galaburda, & Damasio, 1994). Symptoms such as feeling cut off from others and avoidance in PTSD patients may be related to dysfunction of anteromedial prefrontal cortex. Studies of human patients with brain lesions has shown that damage to the anterior one third of the frontal cortex (including anterior cingulate) often results in seizures in which the individual experiences intense feelings of fear or anguish as a symptom, suggesting that the anteromedial prefrontal cortex plays a role in fear-related behavior. In addition, some patients have been observed to experience visual hallucinations as well during seizures, which are reminiscent of the flashbacks seen in victims of trauma (Goldensohn, 1992). Studies in PTSD patients during exposure to reminders of their traumatic experiences have shown activation of anterior cingulate (Rauch et al., 1996) and mid-cingulate (Bremner, Innis, et al., 1997).

Abnormalities in the Stroop test, a marker of anterior cingulate function (Pardo, Pardo, Janer, & Raichle, 1990), have been associated with PTSD. Delays in color-naming with PTSD-related words such as "body-bag" are involuntary, and provide quantitative measures of the intrusive cognition which is an important part of PTSD. Vietnam combat veterans with PTSD have been found to take longer to color-name "PTSD" words than obsessive words, positive words, and neutral words, and this delay was correlated with severity of PTSD symptomatology as measured by the Mississippi Scale (McNally, Kaspi, Riemann, & Zeitlin, 1990; McNally, English, & Lipke, 1993). Stroop interference has also been shown in patients with PTSD related to the trauma of rape (Foa, Feske, Murdock, Kozak, & McCarthy, 1991; Cassiday, McNally, & Zeitlin, 1992). No difference was found when subliminal interference was compared to supraliminal interference with the Stroop task (McNally, Amir, & Lipke, 1996).

The orbitofrontal cortex is another frontal cortical area which is of importance from the standpoint of 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. The orbitofrontal cortex may be involved in abnormalities of emotional memory which are seen in patients with PTSD. Studies of human patients with brain lesions have shown that lesions of the orbitofrontal cortex result in symptoms of intense fear during seizures. In addition, some patients have been observed to experience visual hallucinations as well during seizures (Goldensohn, 1992). Some case reports have described a relationship between damage to the orbitofrontal cortex and visual hallucinations which appear to be similar to the flashbacks which are characteristic of PTSD (Fornazzari, Farcnik, Smith, Heasman, & Ichise, 1992).

Orbitofrontal cortex is also involved in the neural mechanism of extinction. As reviewed above, in the conditioned fear paradigm, repetitive pairing of a light (conditioned stimulus) and a shock (unconditioned stimulus) will result in a conditioned fear response to the light alone. Repeated exposure to the light alone will eventually lead to the loss of conditioned responding, a phenomenon known as extinction of the conditioned fear response. Lesions of the medial orbitofrontal cortex in extinction to condi-

tioned stimuli in this paradigm, suggesting that this region plays a role in extinction of conditioned stimuli (Morgan & LeDoux, 1994). Studies have shown that this extinction is due in fact to an inhibition by orbitofrontal cortex of subcortical brain structures (such as the amygdala) which mediate conditioned fear responding. A failure of extinction of conditioned emotional responding is a characteristic of patients with PTSD. For example, a veteran who has a conditioned fear response of becoming startled and agitated with the sound of a car backfiring, which is associated with the original aversive stimulus of gunfire in Vietnam, does not become less agitated with repeated exposures to cars backfiring. We have found the greatest differential response of cerebral metabolism measured with PET between PTSD patients and controls following administration of yohimbine in the orbitofrontal cortex, with a relative blunting of metabolism in this region with yohimbine in PTSD (Bremner, Innis, et al., 1997). Exposure of PTSD patients to traumatic cues resulted in a failure of orbitofrontal cortical activation as measured with PET $H_2[^{15}O]$ relative to combat-exposed controls (Bremner, Innis, et al., 1997). These findings are consistent with orbitofrontal dysfunction in PTSD, and suggest a neural mechanism for the failure of extinction which characterizes PTSD patients.

Neocortex

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. PET $H_2[^{15}O]$ studies during sustained attention showed increases in blood flow in the right prefrontal and superior parietal cortex (Posner, Peterson, Fox, & Raichle, 1988). PET $H_2[^{15}O]$ in patients with combat-related PTSD showed increased activation of parietal cortex with traumatic reminders relative to non-PTSD combat veterans (Bremner, Innis, et al., 1997). Other neocortical regions besides parietal cortex are involved in memory function. Explicit memory storage takes place in sensory brain areas in which an event is first experienced. For instance, visual information is stored in the occipital cortex, tactile information in the sensory cortex, auditory information in the middle temporal gyrus, olfactory information in the orbitofrontal cortex, and motor information in the motor cortex (precentral gyrus). The hippocampus has been hypothesized to bring together diverse memory elements in the correct spatiotemporal context at the time of memory retrieval (Zola-Morgan & Squire, 1990). PET $H_2[^{15}O]$ studies showed activation in insula, medial temporal cortex, sensorimotor cortex, and visual association cortex in PTSD patients during traumatic reminders relative to a control task (Rauch et al., 1996). We have found greater activation with traumatic reminders in combat veterans with PTSD relative to those without PTSD in motor cortex, in addition to other regions described above (Bremner, Innis, et al., 1997).

Stress-Induced Neuromodulation of Memory

Neurotransmitters and neuropeptides released during stress have a modulatory effect on memory function. These include norepinephrine, epinephrine, adrenocorticotropic hormone (ACTH), glucocorticoids, corticotropin releasing factor (CRF), opioid peptides, endogenous benzodiazepines, dopamine, vasopressin, and oxytocin (De Wied & Croiset, 1991). Brain regions involved in memory are richly innervated by these neurotransmitters and neuropeptides.

Removal of the adrenal medulla, site of most of the body's epinephrine, results in impairment in new learning and memory, which is restored by administration of adequate amounts of epinephrine (Borrell, De Kloet, Versteeg, & Bohus, 1983). Posttraining administration of epinephrine after a learning task influences retention with an inverted U-shaped curve: retention is enhanced at moderate doses and impaired at high doses (Gold & van Buskirk, 1975; Liang, Juler, & McGaugh, 1986; McGaugh, Castellano, & Brioni, 1990). Low dose (0.2 microgram) injections of norepinephrine into the amygdala facilitate memory function, while higher doses (0.5 microgram) impair memory function (Liang, McGaugh, & Yao, 1990). Lesions of the dorsal noradrenergic bundle result in an impairment in the learning and memory (reviewed in Robbins, Everitt, & Cole, 1985; Cole & Robbins,

1992) and acquisition of conditioned fear responding (Selden, Robbins, & Everitt, 1990). Activation of the noradrenergic system through electrical stimulation of the locus coeruleus (Velly, Kempf, Cardo, & Velley, 1985), administration of the alpha2 antagonist, yohimbine (Goldberg & Robertson, 1983) or amphetamine (Sara, 1985), (both of which stimulate brain norepinephrine release) enhance memory acquisition and storage. Norepinephrine increases neuronal firing in the hippocampus, suggesting a possible mechanism for enhancement of memory storage (Madison & Nicoll, 1982). The acetylcholine antagonist, scopolamine, impairs memory as measured by acquisition and retention of an inhibitory avoidance task as well as place learning (Decker & McGaugh, 1989). Combined blockade of both the cholinergic and noradrenergic systems with scopolamine and propranolol, respectively, at doses which had no effect individually, when administered in combination profoundly impaired inhibitory avoidance as well as spatial learning (Decker, Gill, & McGaugh, 1990). In summary, epinephrine and norepinephrine released during stress act to enhance the formation of memory traces (McGaugh, 1989, 1990).

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 (Gold & van Buskirk, 1975). ACTH enhanced the acquisition of learning in a conditioned fear paradigm (see above, "The Amygdala"). ACTH also delayed extinction of the avoidance response (see above, "Orbitofrontal Cortex") (De Wied & Jolles, 1982). The effects of ACTH on learning and memory are mediated through the hippocampus and amygdala (Van Wimersma Greidanus, Croiset, Bakker, & Bouman, 1979). Glucocorticoids, in contrast, enhance extinction in the conditioned fear paradigm (De Wied & Jolles, 1982). 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 (Britton, Koob, & Vale, 1982).

Other neurotransmitters and neuropeptides released during stress have effects on learning and memory. Opiate receptor agonists when administered after training in a learning task impair retention, while opiate receptor antagonists such as naloxone enhance retention (Castellano, 1975). Vasopressin injected three hours before or after a new learning paradigm increases resistance to extinction, possibly through effects on consolidation, as well as facilitating new learning, while oxytocin has the opposite effect (Gaffori & De Wied, 1986). Gamma-aminobutyric acid (GABA) antagonists such as bicuculline, which block the action of GABA, impair memory retention following administration into the amygdala, while GABA agonists have the opposite effect (Brioni, Nagahara, & McGaugh, 1989). Analogues of thyrotropin releasing hormone (TRH) also facilitate learning and memory (Drago et al., 1991).

Recent studies have begun to address the question of neuromodulation of memory function with stress in human subjects. In one recent study, the beta-adrenergic antagonist, propranolol, or placebo, was administered one hour before a neutral or an emotionally arousing (stress-related) story in healthy human subjects. Propranolol, but not placebo, interfered with recall of the emotionally arousing story, but not the neutral story, suggesting that activation of beta-adrenergic receptors in the brain enhanced the encoding of the emotionally arousing memories (Cahill, Prins, Weber, & McGaugh, 1994). The cortisol analogue, dexamethasone, impaired verbal recall in young (but not elderly) healthy subjects (Newcomer, Craft, Hershey, Askins, & Bardgett, 1994). The findings indicate that preclinical studies of neuromodulation are relevant to human subjects.

Findings related to neuromodulation of memory function are of importance for understanding the symptomatology of PTSD. Increased release of neurotransmitters and neuropeptides with modulatory actions on memory function during stress probably plays a role in deficits in encoding and retrieval, as well as the enhancement of specific traumatic memories, which is part of the clinical presentation of PTSD. 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 increase electromyographic responses during personal traumatic imagery, but not during generic traumatic slides, suggesting a facilitation of traumatic remembrance (Pitman, Orr, & Lasko, 1993).

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. Hopefully, an extension of preclinical findings on the effects of stress-related neuromodulators on memory function to clinical populations will enhance our understanding of memory alterations in PTSD.

Mechanisms involving state-dependent recall (Bower, 1981), which are applicable to memory alterations in PTSD, may be mediated by some of these neuromodulators described above. State-dependent recall refers to the phenomenon where a similar affective state to the time of encoding leads to a facilitation of memory retrieval. For instance, memories which 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. To extend this concept to PTSD, 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 routine adult life which is free of stressors. The recurrence of the state of extreme fear or sadness which 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 sexual abuse experiences until subsequent victimization by rape as an adult which leads to a recall of the original trauma.

V. CONCLUDING REMARKS

Multiple neurotransmitter and neuropeptide systems are involved in the stress response, including corticotropin releasing factor (CRF), norepinephrine, serotonin, dopamine, endogenous benzodiazepines, and endogenous opiates. These transmitters mutually regulate one another in the execution of the stress response. Chronic stress is associated with long-term alterations in these transmitters and peptides, which translate into changes in neuronal function, and structure. Preliminary clinical studies in patients with PTSD are beginning to replicate many of the findings from animal studies.

Brain regions in which there are the greatest changes with stress, including hippocampus and amygdala, are those which are involved in memory and emotion, as well as the stress response. Neurotransmitter and neuropeptidal systems involved in stress modulate behavior and memory function through direct actions on these brain regions. Chronic stress, probably through long-term alterations in these systems, can lead to long-term behavioral and memory disturbances. This may represent the mechanism for many of the symptoms of PTSD. Exposure to subsequent stressors is also associated with altered release of neuromodulators, resulting in altered memory recall in PTSD patients. Other concepts such as state-dependent memory, fear conditioning, stress sensitization, and failure of extinction are important models for understanding how changes in brain function translate into symptoms of PTSD.

Studies to date have provided only an incomplete picture of biological mechanisms in PTSD. The animal literature of stress is vast, and this chapter represents only a partial overview. This chapter was intended as a review of the current status of the topic, and to raise awareness about how the neurobiology of stress relates to PTSD, and to what extent these findings have been replicated in humans. Hopefully, increased understanding of the neurobiology of PTSD can lead to specific advances in treatment of this troubling disorder (Friedman, 1988, 1991).

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