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Neurobiology of disaster exposure: fear, anxiety, trauma, and resilience

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Introduction

To date, clinical and research approaches to disaster mental health have focused primarily on the psychological experience of disaster survivors, and the development and effectiveness of psychological treatments. While these studies have contributed greatly to our understanding of the human response to disaster, it has become clear in recent years that, in addition to psychological approaches, neurobiological approaches to disaster-related psychopathology and resilience are also potentially informative.

Multiple neurobiological systems are involved in the human response to threat. Simultaneous activation of various brain regions and neurotransmitter systems allows the organism to assess and appropriately respond to potential dangers. This dynamic process contributes to the development of anxiety, fear, and the "fight or flight" response that allows the organism to protect itself by either fleeing from, or actively confronting, danger. Fear triggers the familiar "fight or flight" response, characterized by acute increased heart rate, breathing, and muscle tension, which facilitate escape from danger or defense against danger (e.g., predator). Based on a complex process of recognition and appraisal of internal and external stimuli, the brain regulates the strength and duration of this coping mechanism, and generally turns it off when it is appropriate to do so. Malfunction of regulatory systems, however, can lead to excessive fear, anxiety disorders such as post-traumatic stress disorder (PTSD) and significant impairment and disability in vulnerable individuals.

Most neurobiological research in PTSD as well as in the neurobiology of resilience has been concentrated on two systems that are critical for survival: the sympathetic nervous system (SNS) and the hypothalamic–pituitary–adrenal (HPA) axis. In this chapter, we will begin by reviewing the findings of human and animal studies which have characterized normal function in the SNS and the HPA axis, and then briefly describe PTSD-associated abnormalities seen in each system. We will then present several evolving models of PTSD, which attempt to explain abnormalities in these two systems. Next, we will review three key neuroanatomic structures/regions involved in the fear response: the amygdala, the hippocampus, and the prefrontal cortex. We will then describe neuroimaging findings associated with PTSD-related changes in structure and function in these three areas. Data on the genetics of risk for PTSD will also be discussed briefly. Finally, the focus on pathology will be supplemented by a brief review of recent findings, elucidating some of the key neural circuits and neurochemical systems that may underlie human resilience in the face of uncontrollable stress.

Although the current review focuses on the noradrenergic system and the HPA axis, it is important to emphasize that numerous neurobiological systems, such as the serotonin system, the opiate

Table 5.1 Sympathetic nervous system and hypothalamic–pituitary–adrenal (HPA) axis

- Psychophysiologic reactivity
- Increased epinephrine and norepinephrine
- Propranolol
- Sensitization
- Fear conditioning

system, and sex steroidal systems, are also involved in pathological and protective responses to stress, although less is known about their involvement in the genesis of PTSD and other disaster-related psychopathology. While a full discussion of these systems is beyond the scope of this chapter, several other relevant neurotransmitters, neuropeptides, and neurohormones will also be mentioned.

The sympathetic nervous system

Within the central nervous system, noradrenergic neural circuitry serves as one of the brain's principal general alarm systems (Gold & Chrousos, 2002) (see Table 5.1). The highest concentration of noradrenergic cell bodies in the brain is found in the locus ceruleus (LC), located in the mid pons. A single LC neuron can have as many as 100 000 nerve terminals and can innervate cells in multiple structures in the brain (Gold & Chrousos, 2002). The LC is activated by a host of different stressors, both intrinsic (decreased blood volume, hypoglycemia, decreased blood pressure, distension of the colon or bladder) and extrinsic (fear, threat, environmental stress). It has been suggested that the LC is critical in determining the organism's overall state of arousal and attention (Abercrombie & Zigmond, 1995; Robbins & Everitt, 1995). Under conditions of extreme stress, the LC–*norepinephrine* (NE) system operates to privilege instinctual responses, such as the "fight or flight" response, by dampening the functioning of the prefrontal cortex, the seat of higher order complex functioning. During the "fight or flight" response, the SNS increases blood flow to muscles and vital organs, limits blood loss, and mobilizes energy for use by large muscle groups.

Norepinephrine is also involved in the organism's ability to focus, and to selectively attend to meaningful stimuli. By selectively enhancing strong excitatory or inhibitory input, NE facilitates the processing of relevant stimuli. In related work by Waterhouse and others, NE has been shown to "gate" postsynaptic activity in target neurons (Waterhouse *et al.*, 1988). Thus, target neurons that fail to respond to a particular stimulus become responsive to that same stimulus if sufficient NE is present. Norepinephrine-enhanced responsivity to both excitatory and inhibitory inputs has been reported to occur in the same neocortical cells.

Stressful stimuli of many types produce significant increases in brain noradrenergic activity. Stress produces regional increases in NE turnover in the LC, limbic regions (hypothalamus, hippocampus, and amygdala), and the cerebral cortex. These changes can be produced in animals by subjecting them to immobilization stress, foot shock, or conditioned fear. Repeated exposure to stressors from which the animal cannot escape results in behavioral deficits described as learned helplessness. The learned helplessness state is associated with depletion of NE, probably reflecting the point at which synthesis cannot keep up with demand.

Sympathetic nervous system alterations in PTSD

Findings from clinical physiological, receptor binding, and pharmacologic challenge studies have provided evidence for noradrenergic hyper-reactivity in traumatized individuals with PTSD (Orr *et al.*, 1990; Southwick & Friedman, 2001; Southwick *et al.*, 1999). This exaggerated activity is generally not present under baseline or resting conditions but instead is evident during stress, especially stress associated with traumatic reminders.

Numerous psychophysiological studies have documented heightened SNS arousal in combat veterans who suffer from PTSD (Orr *et al.*, 1990;

Prins *et al.*, 1995). Psychophysiological studies typically measure biological parameters such as heart rate, blood pressure, skin conductance, and electromyographic activity of facial muscles at baseline and in response to various trauma-relevant stimuli, generic stressors, and neutral stimuli.

Script-driven imagery of personally experienced traumas as well as generic visual or auditory reminders of traumas similar to the one experienced by the participant are examples of potential trauma-related stimuli.

Trauma victims with PTSD respond with greater psychophysiological reactivity (particularly heart rate) to trauma-relevant stimuli than do comparison groups such as trauma victims without PTSD and nontraumatized controls. Although some studies have reported a higher baseline resting heart rate in PTSD compared with control groups, most studies have found no differences (Orr *et al.*, 1990; Prins *et al.*, 1995). In addition, response to generic stressors has typically been the same in groups with and without PTSD (Pitman *et al.*, 1990). In summary, trauma survivors with PTSD appear to have normal resting SNS activity as reflected by heart rate and blood pressure that becomes abnormally reactive in response to specific reminders of a personally experienced trauma but not in response to generic stressors (Murburg, 1994; Prins *et al.*, 1995).

Biochemical correlates of this heightened SNS activation in veterans and civilians with PTSD include increased excretion of epinephrine and NE in urine collected over a 24-h period (Davidson & Baum, 1986; Kosten *et al.*, 1987; Yehuda *et al.*, 1992), and decreased numbers of alpha-2 adrenergic receptors on the surface of platelets (Perry, 1994; Perry *et al.*, 1987). Laboratory research suggests that chronically elevated levels of circulating epinephrine and NE may lead to a decrease in the number of adrenergic receptors. In a study designed to assess dynamic functioning of alpha-2 receptors, Perry (1994) incubated intact platelets with high levels of epinephrine and found a greater and more rapid loss in receptor number among subjects with PTSD as compared to controls, suggesting that alpha-2 adrenergic receptors in subjects with PTSD were particularly sensitive to stimulation by the agonist epinephrine (Perry, 1994).

These increases in epinephrine and NE may not be present during resting states. However, compared with healthy controls, it appears that PTSD subjects, as a group, respond to a variety of stressors with exaggerated increases in catecholamines (McFall *et al.*, 1990; Murburg, 1994; Southwick *et al.*, 1995). For example, greater increases in epinephrine have been observed in veterans with war-related PTSD compared with controls during and after viewing a combat film, but not in response to a film of an automobile accident (McFall *et al.*, 1990). Auditory reminders of trauma have also been used as in vivo nonpharmacologic probes of noradrenergic responsivity in combat veterans with PTSD. In a study of 15 combat veterans with PTSD compared to 6 combat veterans without a mental disorder, Blanchard *et al.* (1991) sampled plasma NE before and after exposure to combat-related auditory stimuli. The PTSD group showed a 30% increase in plasma NE compared to no change in the combat control comparison group. The PTSD group also showed a concomitant increase in heart rate (Blanchard *et al.*, 1991).

Pharmacologic provocation studies have also revealed exaggerated catecholamine responses in patients with PTSD as compared to healthy controls without PTSD. To more directly assess adrenergic responsivity of both the peripheral and central nervous system, one study administered intravenous yohimbine to 20 Vietnam combat veterans with PTSD and 18 healthy controls (Southwick *et al.*, 1993). Yohimbine is an alpha-2 adrenergic receptor antagonist that activates noradrenergic neurons by blocking the alpha-2 adrenergic autoreceptor, thereby increasing the release of endogenous NE. Yohimbine caused a marked increase in anxiety and PTSD-specific symptoms, as 70% of combat veterans with PTSD experienced yohimbine-induced panic attacks, and 40% had flashbacks. There were no panic attacks and one flashback in response to placebo. Subjects with PTSD also had significantly greater increases in heart rate and a greater than two

fold increase in plasma 3-methoxy-4-hydroxy phenylglycol (MHPG), which is a breakdown product of NE. In the above-cited study, the yohimbine-induced increase in catecholamine activity may have produced a biological context that resembled the biological state at the time of traumatic memory encoding, which then facilitated the retrieval of traumatic memories, a phenomenon known as "state-dependent recall."

To date, interventions designed to suppress noradrenergic hyper-reactivity directly in trauma survivors with PTSD have been limited to open pharmacologic trials with the antiadrenergic agents clonidine (Kinzie & Leung, 1989), guanfacine (Horrigan, 1996), prazosin (Raskind *et al.*, 2002), and propranolol (Pitman *et al.*, 2002). In a randomized double-blind study, Pitman *et al.* administered propranolol 40 mg four times daily vs. placebo to survivors of car accidents within 6 h of the accident. Treatment lasted for 10 days. The study's ability to detect a difference between treatment and control was diminished by bias in loss to follow-up. Although PTSD symptom scores at 1 and 3 months post trauma did not differ significantly between the two groups, at 3 months the propranolol group demonstrated significantly less psychophysiologic reactivity (heart rate, skin conductance, corrugator electromyogram) to mental imagery that symbolized or resembled the index trauma. Positive results with propranolol have also been reported in accident victims presenting to an emergency room with tachycardia (Vaiva *et al.*, 2003). In a recent case report of a woman with PTSD in remission, Taylor and Cahill (2002) described the successful use of propranolol (within 48 h of a new trauma) to treat re-emergent symptoms of PTSD. Those reports are consistent with data in healthy humans, where Southwick *et al.* (1995) found a positive association between enhanced noradrenergic activity and enhanced long-term memory, and Cahill and colleagues reported that propranolol blocked enhanced memory for an arousing story (Cahill *et al.*, 1994). However, it is important to note that preclinical evidence has shown that propranolol can block extinction of fear-related memories (Cain *et al.*, 2004).

Taken together, the above evidence suggests that at least a subgroup of individuals with PTSD has increased responsivity of the SNS that is most clearly evident when the individual is re-stressed (Southwick *et al.*, 1995).

Hypothalamic–pituitary–adrenal (HPA) axis

Whereas the SNS prepares the organism to react to stressful stimuli, the HPA axis appears to serve a catabolic, restorative role (Yehuda, 1997b). When an organism is stressed, the hypothalamus releases corticotropin-releasing hormone (CRH) which then stimulates the release of adrenocorticotropic hormone (ACTH) from the pituitary gland. ACTH in turn stimulates the adrenal gland to release cortisol. Cortisol serves to mobilize and replenish energy stores, and contributes to increased arousal, vigilance, focused attention and memory formation, as well as inhibition of the growth and reproductive systems and containment of the immune response. It also helps to terminate a variety of neurobiological reactions that have been set in motion by stressful stimuli.

Stress-related HPA activation results in transient elevation of plasma cortisol during and shortly after the cessation of the stressful stimulus. It is key, however, that the stress-induced increase in cortisol ultimately be constrained through an elaborate negative feedback system involving glucocorticoid (GC) and mineralocorticoid (MR) receptors. Excessive sustained cortisol secretion can have adverse effects, including hypertension, osteoporosis, immunosuppression, insulin resistance, dyslipidemia, dyscoagulation, and, ultimately, atherosclerosis and cardiovascular disease.

CRH cell bodies and receptors are found in high concentrations in the hypothalamus and throughout the brain, including the prefrontal and cingulate cortices, the central nucleus of the amygdala, as well as the LC. CRH is one of the most important mediators of the stress response, coordinating the adaptive behavioral and physiological changes that

occur during stress (Grammatopoulos & Chrousos, 2002). Moreover, intraventricular administration of CRH can produce a variety of behavioral effects that show a striking similarity to those seen following a natural stressor. Given the important role of the amygdala in fear and anxiety it is not surprising that many effects of CRH given intraventricularly may result from actions in the amygdala or closely related structures. In general, these effects are not eliminated by adrenalectomy or hypophysectomy, indicating that they result from direct actions in the brain.

HPA axis alterations in PTSD

The facts that cortisol levels are increased during stress and that the magnitude of the stress response is associated with the magnitude of increases in cortisol led to the hypothesis that cortisol should be increased in PTSD. However, 20 years ago, the first report of cortisol in PTSD yielded counterintuitive results: the mean 24-h urinary excretion of cortisol was lower in patients with PTSD when compared with other psychiatric patients (Mason *et al.*, 1986). Ambiguity has persisted in the literature regarding the direction of any PTSD-associated change in cortisol levels, as some investigators have reported increased urinary cortisol excretion in PTSD. Yehuda (2002) noted that PTSD is associated with a dysregulation of the cortisol response, rather than a clear-cut directional response (cortisol levels that are "too low" or "too high") as would be found in an endocrinopathy.

Present evidence supports the hypothesis that preexisting low cortisol is associated with increased risk for PTSD. Several recent studies have found that trauma victims who develop PTSD have lower initial cortisol responses to a traumatic event than trauma victims who do not develop PTSD (McFarlane *et al.*, 1997; Resnick *et al.*, 1997). And in combat veterans with chronic PTSD, low plasma levels of cortisol have been recorded throughout the day and night, especially in the early morning and late evening (Yehuda, 2002). Finally, in a randomized double-blind placebo-controlled study, Schelling *et al.* (2001) assessed the effect of hydrocortisone versus placebo administered during septic shock. Physiologic stress doses of hydrocortisone did have a moderate protective effect against PTSD (Schelling *et al.*, 2001).

Receptor binding studies have found an increased number of GC receptors in subjects with PTSD compared with controls without PTSD (Yehuda, 1997a; Yehuda *et al.*, 1995a). An increased number of receptors would enhance sensitivity by providing more binding sites for cortisol. Consistent with increased receptor number and sensitivity is the finding that subjects with PTSD hyper-respond to administration of dexamethasone, a synthetic GC that acts like cortisol (Yehuda, 1997a; Yehuda *et al.*, 2004). Normally, when dexamethasone is administered to healthy individuals, it engages GC receptors that serve as part of a negative feedback mechanism. When engaged, these receptors signal the hypothalamus and pituitary to decrease the release of CRH and ACTH, which in turn results in decreased stimulation of the adrenal gland and diminished release of endogenous cortisol. In several different populations of trauma survivors with PTSD, dexamethasone has had an exaggerated effect, with the result that endogenous cortisol release is reduced to a greater degree than in normal controls. These HPA axis findings in PTSD differ markedly from findings in studies of major depressive disorder, where cortisol tends to be elevated, and the cortisol response to dexamethasone administration is reduced.

Additional findings in subjects with PTSD include elevated CRH levels in cerebrospinal fluid (Baker *et al.*, 1997; Bremner *et al.*, 1997), blunted ACTH response to CRH infusion (Smith *et al.*, 1989), and increased ACTH response to metyrapone (Yehuda *et al.*, 2004). These findings are consistent with preclinical studies in primates that have experienced early life stress (Coplan *et al.*, 1996). Animal data assessing the effects of a nonpeptide CRH receptor 1 antagonist (antalarmin) that penetrates the blood–brain barrier has found that it blocks the development, consolidation, and expression of conditioned fear (Deak *et al.*, 1999). Recent studies in rhesus macaques also show that oral administration of antalarmin significantly inhibits stress-induced increases in plasma NE, cortisol and anxiety-related

behaviors (Habib *et al.*, 2000). If applicable to humans, these data suggest that a CRH antagonist could be helpful after an acute traumatic event, or in preventing harmful CNS changes that occur during chronic stress (Gold *et al.*, 2005).

In summary, most PTSD studies demonstrate alterations consistent with enhanced feedback inhibition of the HPA axis and increased HPA reactivity. The degree to which these abnormalities represent predisposing neurobiological risk factors for the development of PTSD versus consequences of trauma and/or living with PTSD is not yet clear (Yehuda, 2002).

It is also important to note that stressors experienced within critical periods of neurodevelopment may exert long-term effects on HPA axis function. Early postnatal experiences such as maternal separation are associated with long-term alterations in basal concentrations of hypothalamic CRH mRNA, hippocampal glucocorticoid mRNA and the magnitude of the stress-induced release of CRH, corticosterone, and ACTH (Heim & Nemeroff, 2001). Thus, early stress experiences can have long-term consequences on HPA axis responsivity to future stressors.

Stress sensitization

The alterations in both the SNS and the HPA axis that are found in patients with PTSD suggest that sensitization of both systems may contribute to PTSD. Sensitization refers to a stressor-induced increase in behavioral or physiological responsiveness following exposure to subsequent stressors of the same or lesser magnitude (Post, 1992; Post *et al.*, 1995; Prasad *et al.*, 1995). When a neurobiological system becomes sensitized, its behavioral, physiological, and biochemical responses to a given stressor gradually increase in intensity over time. The time interval between the initial stressors appears to be an important factor in the development of sensitization. In some cases, a single stressful stimulus may be capable of initiating behavior sensitization if sufficient time has passed between the initial stressor and subsequent stressors. Because the organism may be better prepared for future dangers, the capacity to respond more readily to stressors may be adaptive and increase the possibility of survival (Post *et al.*, 1995; Prasad *et al.*, 1995). However, sensitization might also leave the organism in a hyper-responsive state, where it may exhibit exaggerated responses to minor stressors. The organism may become hypervigilant and continue to act biologically as if a danger exists when, in fact, minimal or no threat is present (Southwick *et al.*, 1995).

Evidence characterizing the neurochemical and neuroanatomic systems mediating sensitization is as yet incomplete. The most extensively studied systems in the development and maintenance of stress-induced sensitization in mammals have been catecholamine systems (especially dopamine and NE). Evidence for sensitization of catecholamine systems in humans comes from an earlier cited study where equivalent doses of yohimbine caused significantly greater increases in heart rate, plasma MHPG, anxiety, vigilance, and intrusive memories in combat veterans with PTSD, compared with health controls. Recent genetic studies also suggest that alpha-2 adrenoreceptor gene polymorphisms play a role in baseline catecholamine levels, intensity of stress-induced SNS activation, and rate of catecholamine return to baseline after stress. In a study of healthy subjects, homozygous carriers for the alpha-2 cDel322–325-AR polymorphism had exaggerated total-body noradrenergic spillover at baseline, exaggerated yohimbine-induced increases in anxiety and total-body noradrenergic spillover, and a slower than normal return of total body noradrenergic spillover to baseline after yohimbine infusion (Neumeister *et al.*, 2005). It is possible that such individuals may be more vulnerable to stress-related psychiatric disorders such as PTSD and depression.

The HPA axis may also be sensitized in patients with PTSD. As noted above, in subjects with PTSD compared to controls, researchers have reported elevated levels of CSF CRH, exaggerated suppression of cortisol in response to dexamethasone, and greater CRF-induced increases in ACTH and cortisol. Further, in a study using a personalized trauma script

in abused women with and without PTSD, Elzinga *et al.* (2003) reported increased cortisol levels in patients with PTSD as compared with controls.

Fear conditioning

Several investigators have noted that the behavioral and physiological responses of veterans with war neuroses or PTSD (Kardiner & Spiegel, 1947; Kolb, 1987) are similar to the effects of fear conditioning in animals. "Fear conditioning" refers to the process through which a previously innocuous stimulus (unconditioned stimulus or US) is paired with a fear-provoking stimulus and as a result transformed into a fear-conditioned stimulus (CS) that is capable of evoking fear, and related responses, in its own right (Blair *et al.*, 2001).

Fear conditioning can be adaptive. The individual who can predict a threat by responding to conditioned contextual cues can rapidly engage in appropriate defensive behaviors. Clinically, specific environmental stimuli (CS) may be linked to a traumatic event, a spontaneous panic attack, or an embarrassing social situation (US), such that exposure to a similar cue produces a recurrence of symptoms of anxiety and fear. For example, to survivors of the terrorist attacks on the World Trade Center, the sound of an airplane flying overhead may no longer be a neutral stimulus, and, instead, may now serve as a CS that is capable of evoking fear and fear-based behaviors.

Fear conditioning occurs outside of conscious awareness (LeDoux, 1996). A traumatized disaster survivor may not be consciously aware that a formerly neutral stimulus has become frightening because it has been transformed into a fear-conditioned stimulus. Clinically, this means that a traumatized individual, when exposed to a fear-conditioned cue, may become frightened, anxious or irritable for reasons that he or she does not understand.

Fear-conditioned responses, once they are established, can persist for long periods. Theoretically, once a conditioned-fear stimulus is no longer associated with an aversive outcome, the conditioned-fear response should extinguish. However, recent evidence suggests that extinction is an active process that may involve new learning, and that the old fear-conditioned association may persist indefinitely and under the right circumstances become reactivated (Bouton & Nelson, 1994).

While the neurobiological underpinnings of fear conditioning are not completely understood, it is clear that the amygdala plays a pivotal role in both unconditioned and conditioned fear (Aggleton, 1992; Blanchard & Blanchard, 1972).

The amygdala and the hippocampus: key neuroanatomic structures involved in fear and anxiety states

The amygdala, a small almond-shaped structure in the anterior temporal lobe, is a crucial node in a neural network that mediates both conditioned and unconditioned fear (see Table 5.2). Ledoux proposed a cellular-molecular model to explain how the lateral amygdala mobilizes long-term potentiation (LTP), such as changes that permit long-term storage of memories during fear conditioning. The formation of short-term memories requires calcium entry through the *N*-methyl-D-aspartate (NMDA) receptor (LeDoux, 1996). However, in order to consolidate synaptic changes into long-term memory, in addition to the calcium entry through NMDA receptors, an influx of calcium through voltage-gated calcium channels is required (Blair *et al.*, 2001). In addition to its role in threat and fear conditioning, recent research demonstrates that the amygdala is involved in both the encoding of reward learning (Gottfried *et al.*, 2003) and translating the perception of potential benefit as well as potential harm.

Table 5.2 Neuroanatomy

- Amygdala
- Hippocampus
- Medial prefrontal cortex
- Locus ceruleus

The amygdala is comprised of several separately functioning clusters of cell bodies or nuclei. Key among these nuclei are the basolateral complex and the central nucleus. The basolateral complex receives input from sensory systems and is necessary for acquisition of fear conditioning. The central nucleus is the main output for the basolateral complex and is involved in emotional arousal. Projections from the basolateral complex activate the hypothalamus, the SNS, the reticular nucleus for increased reflexes, the trigeminal nerve and facial nerve for facial expressions of fear, and the ventral tegmental area, LC, and laterodorsal tegmental nucleus for activation of dopamine, NE, and epinephrine systems. The amygdala reacts to dangerous situations by erring on the side of excessive safety – "false positives" and "false alarms."

The amygdala influences the focusing of cortical attention on stimuli that may be associated with threat, even if those stimuli are outside of conscious awareness. In return, these higher cortical structures and associated cortico-striato-thalamic circuits facilitate gating, organizing and bringing into awareness the information conveyed via the senses about the perceived threat. They also provide critical top-down control of the amygdala fear response, suppressing the response once danger has passed or when critical new information has changed the meaning of a potentially threatening situation. This capacity for modulating the "fight or flight" response in response to changes in the perceived meaning of a threat underlies the capacity for cognitive reframing. The ability to reframe threats as challenges or as opportunities for growth is a key component of resilience.

Stress, plasticity and the hippocampus

The hippocampus is instrumental in assessing the context of a threat. Dysfunction of the hippocampus may result in poor contextual stimulus discrimination and overgeneralization of fear responses, which are a cardinal feature of the anxiety disorders (Charney *et al.*, 1993).

Acute stress can suppress neurogenesis in the dentate gyrus (Cameron & Gould, 1996) and in the CA3 region of the hippocampus. Stress-induced increases in adrenal stress hormones and excitatory amino acid neurotransmitters can cause atrophy of dendrites and possibly cognitive impairment in short-term memory and visual-spatial ideational tasks (McEwen, 2002). When stress is severe and prolonged, it can result in actual neuronal loss. Because the hippocampus also exerts inhibitory control over ACTH, damage to the hippocampus can result in even greater increases in glucocorticoids, which in turn cause additional damage to the hippocampus.

Investigations of the hippocampus, using a combination of behavioral, morphological, molecular, and pharmacological approaches, have yielded evidence contrary to the historic view that the adult brain is unable to generate new neurons once they are damaged or lost. Evidence suggests that structural plasticity and neurogenesis in the hippocampus includes structural plasticity, neuronal replacement, remodeling of dendrites, and turnover of synapses. For example, one recent study involving post mortem brains of cancer patients found that the hippocampus retains the capacity for neurogenesis throughout human life (Eriksson *et al.*, 1998). Investigators found that post mortem brains of cancer patients, who had been given the nucleoside analog bromodeoxyuridine (BrdU) for diagnostic studies, still contained the BrdU even though the BrdU had been administered before death. Only dividing cells could have incorporated the BrdU and maintained it in the brain. This suggests that neurogenesis occurred in the hippocampus prior to the death.

Treatment with the serotonin releasing drug D-fenfluramine has been associated with the finding of increased neurogenesis (Gould, 1999) in the adult dentate gyrus. Blockade of serotonergic 5HT1A receptors had the opposite effect, and prevented the effect of D-fenfluramine treatment. Similarly, aerobic exercise has been shown to increase brain-derived neurotrophic factor (BDNF) in the hippocampus and to serve a protective role

by buffering against reductions in stress-associated reductions in BDNF.

Cortex and neural circuits

Of the many subcortical brain regions which are active in the stress and fear response, the amygdala and hippocampus have been the most widely studied, but they clearly operate in the context of multiple controls and inputs. One of the most important of these involves cortical circuitry particularly the medial frontal cortex, which provides higher order control over the stress- and fear-related responses of the amygdala and hippocampus.

Under normal conditions, the prefrontal cortex modulates the behavioral, affective, cognitive, and physiological responses typically set in motion by the amygdala during responses to stress. The prefrontal cortex plays key roles in complex problem solving, in part by sequentially switching attention between tasks (Smith & Jonides, 1999). The subgenual prefrontal cortex is involved in cognitively assessing whether a given situation is likely to produce punishment or reward, and in linking affect to changes in the environment (Gold & Chrousos, 2002). The ventral, prefrontal, and subgenual cortex also exert inhibition on the SNS and the HPA axis. Humans with lesions of the subgenual prefrontal cortex show exaggerated autonomic and endocrine responses to stress (Smith & Jonides, 1999).

In contrast to noradrenergic effects mediated by alpha-1 and beta-1 adrenergic receptors, stimulation of alpha-2 adrenoreceptors protects prefrontal cortex cognitive function during stress. Animal research in rodents and primates suggests that prefrontal cortical cognitive functioning is improved by moderate basal release of NE, through its preferential binding to postsynaptic alpha-2 receptors. Psychopharmacologic agents which act on the alpha-2 receptor have been shown to improve cortical functioning in monkeys whose NE has been depleted naturally or experimentally. For example, clonidine and guanfacine have been shown to improve performance on tasks that assess prefrontal function, whereas the alpha-2 adrenergic receptor antagonist yohimbine impairs performance. The alpha-2 agonist guanfacine is even more potent than clonidine in protecting against stress-induced prefrontal cortex dysfunction (Birnbaum *et al.*, 2000). However, under stressful conditions (particularly uncontrollable stress), when NE release is increased above basal levels in the prefrontal cortex, postsynaptic alpha-1 receptors become activated, resulting in a decline in prefrontal cortex functioning. It has been proposed that this inhibition of prefrontal cortex functioning during stressful or dangerous situations has value for survival by allowing the organism to employ rapid habitual subcortical modes of response (Arnsten & Goldman-Rakic, 1998; Birnbaum *et al.*, 1999). In this way, NE can act as a chemical switch, determining which brain structures have control over behavior. The intracellular signaling initiated by high levels of NE in the prefrontal cortex is the focus of intensive study.

Additionally, the medial prefrontal cortex is involved in fear extinction. In the short term, fear extinction is not just a forgetting or an erasure, but rather an inhibition of an autonomic nervous system response to a conditioned stimulus (Morgan *et al.*, 1993). The ability of firefighters to run into burning buildings demonstrates how cortical inputs can override the autonomic "fight or flight" responses normally associated with an aversive stimulus.

We now briefly review PTSD-related neuroimaging research findings which further characterize the normal structure and function of the amygdala, hippocampus and relevant cortical regions, as well as the abnormalities associated with PTSD.

Neuroimaging in fear and anxiety: focus on PTSD

Neurobiological models of the structure, function and neurochemistry of the brain have evolved significantly as a result of recent input from findings

of neuroimaging studies. In humans, neuroimaging studies of PTSD have primarily focused on the amygdala, the hippocampus, medial prefrontal cortex, and anterior cingulate cortex.

PTSD: findings from structural neuroimaging studies

Quantitative magnetic resonance imaging (MRI) studies allow visualization of gross structural abnormalities and provide a method for estimating brain structure volumes. Reduced hippocampal volume has been reported in a diverse population of adults with PTSD, both those with a history of childhood trauma and those who suffered trauma as adults. However, not all published studies report smaller hippocampal findings in subjects with PTSD (Bonne *et al.*, 2001). Possible explanations for discrepant findings of hippocampal volume in PTSD include variability in intensity and duration of trauma exposure, presence of comorbid psychiatric disorders, and differences in imaging methodology (Vythilingam *et al.*, 2005). There is also controversy about how long it may take volume-related changes to occur in trauma survivors with PTSD. Bonne and colleagues found that early after a traumatic event, at 1 week or at 6 months, subjects with PTSD did not have smaller hippocampal volume than subjects without PTSD, nor was there a reduction in hippocampal volume between 1 week and 6 months in these subjects (Bonne *et al.*, 2001). However, more recently, Wignall and colleagues (2004) evaluated 15 patients with PTSD on average 5 months after the trauma, finding significantly reduced right-sided hippocampal volume when compared to controls, after correcting for effects of age and whole-brain volume. Patients also had lower whole-brain volume.

There is also ambiguity in the literature about whether PTSD is associated with reduced hippocampal volume in children (De Bellis *et al.*, 2001). Recent studies suggest that traumatic stress in early development may have more diffuse effects on total brain volume, rather than only effects on hippocampal volume (De Bellis *et al.*, 2002a, 2002b). Additionally, hippocampal volume has been reported to be reduced in burns patients compared to controls. However, hippocampal volume did not differ between burns patients with and without PTSD, suggesting that the trauma associated with being severely burned, as opposed to PTSD per se, was most likely associated with smaller hippocampal volume (Winter & Irle, 2004).

The first study showing decreased hippocampal volume in adults with PTSD was conducted by Bremner and associates (1995), who found that among 26 combat veterans with PTSD, right mean hippocampal volumes were 8% smaller than in healthy combat veterans without PTSD. Those veterans with PTSD and reduced right hippocampal volume also had short-term verbal memory deficits that correlated with hippocampal volume (Bremner *et al.*, 1995). However, in a study of 21 women with histories of severe childhood sexual abuse, 15 of whom had PTSD, significant reductions in left hippocampal volumes were observed in those with abuse histories, but not in controls without abuse histories (Stein *et al.*, 1997). Generalized white matter atrophy as well as bilateral reductions in hippocampal volume were found in another study, with depression and PTSD symptom scores negatively correlated with left hippocampal volume (Villarreal *et al.*, 2002).

Whether the apparent unilaterality of the structural differences reported in these studies is a measurement artifact due to insufficient sample size is not known. The fact that these changes in hippocampal volume may not occur in the first 6 months after a traumatic experience, and that they have not been found in children may indicate that decreased hippocampal volume may take time to develop and/or that it is associated with comorbid mental disorders, or alcohol/substance use. Further, a recent neuroimaging study conducted among identical twins raises the possibility that small hippocampal volume may be a risk factor for developing PTSD. Identical twins of veterans with reduced hippocampal volume and PTSD themselves had reduced hippocampal volume, despite having had no exposure to combat and no history of PTSD. In some individuals, smaller hippocampal volumes may

pre-date their trauma exposure and PTSD, and may represent a risk factor for PTSD, rather than a consequence of PTSD (Gilbertson *et al.*, 2002).

PTSD: findings from functional neuroimaging studies

Functional imaging studies using cognitive activation models, script-driven imagery, or other methods of provoking the experience of symptoms have generally found exaggerated activation of the amygdala and/or reduced activation of the prefrontal cortex, to revealing that an overactive amygdala may be receiving insufficient negative feedback from the anterior cingulate gyrus and the medial prefrontal cortex.

To date, most functional imaging studies have examined responses to threat or trauma-relevant stimuli. However, the nature and anatomical bases of attentional and working memory deficits in PTSD are also becoming the focus of intense study in functional neuroimaging. Using positron emission tomography (PET), working memory deficits in PTSD have been found to be associated with reduced left dorsolateral prefrontal cortical (DLPFC) activity (Clark *et al.*, 2003). However, it is also important to sort out how neural networks function in PTSD in the absence of threat-related stimuli. A recent study explored PTSD responses to a selective attention task that engages anterior cingulate cortex networks, but in response to a non-threatening stimulus. Bryant and colleagues (2005) investigated whether anterior cingulate-amygdala dysregulation in PTSD was specific to processing threat-related stimuli, or generalized to more generic, nonthreatening stimuli. They believe that their findings of enhanced anterior cingulate responses, as well as activation in the left amygdala and posterior parietal networks, in response to nonthreatening stimuli, may reflect generalized hypervigilance.

In the first ligand binding neuroimaging study in PTSD, Bremner and colleagues (2000) used ^{123}I iomazenil and single positron emission computer tomography (SPECT) to measure changes in benzodiazepine neuroreceptor binding in combat veterans and matched healthy controls. In the prefrontal cortex, benzodiazepine receptor binding was 41% lower in PTSD (Bremner *et al.*, 2000). It may be that this decrease in receptor binding is associated with chronic PTSD, as Fujita and colleagues (2004) did not replicate this finding in more recently traumatized Desert Storm veterans.

In summary, in PTSD, numerous but not all structural MRI studies have found that decreased hippocampal volume is associated with PTSD in adults. In general, functional neuroimaging studies in trauma survivors with PTSD have reported exaggerated rCBF in the amygdala and other paralimbic regions, as well as relative decreases in prefrontal cortical rCBF. Increased stress-induced activation of the amygdala in combination with reduced inhibition by the prefrontal cortex might leave the trauma survivor with an exaggerated and relatively unchecked amygdala-driven "fight or flight" response.

Genetic risk of stress-related psychopathology

There is mounting evidence that genetic factors influence vulnerability to stress-related psychopathology such as PTSD. In an investigation of twin pairs from the Viet Nam twin Registry, True and colleagues (1993) found that genetic factors accounted for approximately one-third of the variance with regard to PTSD symptoms and exceeded the contributions made by trauma severity. With regard to specific genes, recent studies have failed to confirm an association between a dopamine receptor polymorphism and PTSD (Gelernter *et al.*, 1999).

A recent epidemiologic investigation found that adults possessing a common functional allele (the "s" allele) of a variant of the serotonin transporter gene (5-HTTLPR), which is associated with reduced transcription and functional capacity of the serotonin transporter, were at increased risk for developing depression if they had a history of childhood maltreatment or recent stressful events. Having the "s" allele was not associated with depression in adults who did not have a history of

childhood maltreatment or recent stressful events. In contrast, having two "l" alleles appeared to confer relative protection from stress-induced depression (Caspi *et al.*, 2003).

Multidisciplinary studies that use neurochemical, neuroimaging, genetic, and psychosocial approaches may in the future clarify the complex relationships between genotype, phenotype, and psychobiological responses to stress. For example, recent studies have begun to assess gene and environment interactions in the response to extreme stress. In a recent study examining social-support-maltreated children, Kaufman *et al.* (2004) found a moderating effect of social support on the risk of trauma-related depression even in children with the "s" allele of the 5-HTTLPR.

Neurobiology of resilience

While postdisaster psychopathology is relatively common, it is important to note that it is the exception rather than the rule. Even after significant exposures to trauma, most survivors do not develop lasting psychopathology. Increasing interest in stress resilience has led to research on the neurobiological basis of protective factors as well as risk factors for post-traumatic psychopathology. We will briefly review preliminary results of studies characterizing neurochemical, neuroanatomic and genetic factors which may contribute to resilience in the face of stress (see Table 5.3).

Neurochemistry of resilience

In recent years several neurochemicals have been associated with resilience. Undoubtedly the neurochemistry of stress resilience is extremely complex and the following discussion only touches briefly on a few potential neurochemical candidates.

Table 5.3 Neurobiology of resilience

- Neuropeptide Y
- Galanin
- Neurosteroids
- Neurobiology of social support and attachment
- Neurobiology of trust

Neuropeptide Y

Neuropeptide Y (NPY) is a highly conserved 36-amino-acid peptide, and is one of the most abundant peptides found in the mammalian brain. It is also found in the autonomic nervous system, and is colocalized and released with neurons containing NE. In addition to its actions in the modulation of appetite and vascular tone, NPY has anxiolytic properties and has been implicated in the regulation of energy balance, memory, and learning. Neuropeptide Y is released along with NE when the SNS is strongly activated (Southwick *et al.*, 1999). One of its actions is to inhibit the continued release of NE, maintaining SNS activity within an optimum window of activity.

In rats exposed to anxiety-inducing laboratory tests, NPY agonists act as an anxiolytic: microinjection of NPY into the central nucleus of the amygdala reduces anxious behaviors; NPY mRNA becomes upregulated after chronic stress, suggesting that NPY may be involved in adaptation to stress exposure (Thorsell *et al.*, 1999); and NPY opposes the actions of CRH (which is known to increase anxiety-related behaviors).

Preliminary studies in highly resilient special operations soldiers (Special Forces) have shown that during extreme training, robust NPY responses are associated with better performance (Morgan *et al.*, 2000a, 2000b). These robust increases in NPY may constrain the parallel stress-related increases in NE. In contrast, resting and yohimbine-induced levels of NPY have been found to be low in combat veterans with PTSD when compared with controls (Rasmusson *et al.*, 2000). The exaggerated yohimbine-induced increases in heart rate, blood pressure, respiratory rate, anxiety, panic, vigilance, and intrusive combat-related memories observed in combat veterans with PTSD may have resulted from excess release of NE and/or insufficient release of NPY to appropriately contain the robust noradrenergic response (Southwick *et al.*, 1999).

Taken together, these results suggest that the ability to mount a vigorous NPY response in the face of extreme stress may serve as a neurochemical resilience factor.

Galanin

Approximately 80% of noradrenergic cells in the LC co-express the neuropeptide galanin. A dense galanin fiber system originating in the LC innervates the hippocampus, amygdala, and prefrontal cortex, as well as other structures (Gentleman *et al.*, 1989; Perez *et al.*, 2001). Galanin is involved in diverse physiological and behavioral functions, including learning, memory, pain control, and cardiovascular regulation. It is preferentially released under conditions of high NE activity, and, like NPY, reduces the firing rate of neurons in the LC. In animal studies involving rodents, galanin inhibits the firing of rodent NE, serotonin and dopaminergic neurons and reduces their release in forebrain target regions, possibly through a galanin 1 receptor, which acts as an autoreceptor (Sevcik *et al.*, 1993; Xu *et al.*, 2001). Intracerebral administration of galanin reduces fear- and anxiety-related behaviours. Thus, like NPY, galanin appears to modulate the behavioral effects of NE hyperactivity.

Neurosteroids

Dehydroepiandrosterone (DHEA) is a steroid hormone that is synthesized de novo from cholesterol in the central nervous system (Pisu & Serra, 2004). Neurosteroids have heterogeneous effects on fear and anxiety. Some are associated with increases in anxiety and anxiety disorders, while others are associated with anxiolysis. In humans, data support DHEA as a potential neurobiological resilience and stress protective factor. In response to the administration of ACTH, Rasmusson and colleagues (2000) found a negative correlation between DHEA reactivity and severity of PTSD symptoms. Additionally, a positive correlation between the DHEA/cortisol ratio and performance has been observed in Special Forces soldiers undergoing intense survival school training (Morgan *et al.*, 2004).

Neuroanatomic basis of resilience

Neural pathways involved in fear conditioning, consolidation of memory, reconsolidation of memory, and extinction are potentially involved in resilience. These neural circuits have all been implicated in the pathophysiology of PTSD (Bremner *et al.*, 1999). It has been hypothesized that when compared to people who are vulnerable to stress, stress-resilient individuals are less likely to over-consolidate emotional memories, and may have an enhanced ability to reorganize existing emotional memories and extinguish traumatic memories (Charney, 2004b). Such individuals may also be less likely to overgeneralize specific conditioned stimuli to a larger context.

In recent years, significant advances have also been made in delineating brain neurocircuitry involved in the regulation of reward and motivation. The mesolimbic dopamine system plays a central role in motivation and reward. In nonhuman primates, the firing patterns of dopamine neurons in the ventral tegmental area are sensitive indices of reward expectations. These neurons increase their firing relative to the predictability of reward, and decrease activity when rewards are omitted or less than expected. They do not change their rate of firing if rewards are consistent with expectations (Yun *et al.*, 2004).

The neural mechanisms that mediate these functions may be relevant to understanding the role that reward plays in some individuals during and in response to a disaster. During acute stress, reward neurocircuitry is activated (Piazza *et al.*, 1996) and it may be that some individuals have exceptionally active reward and motivation neural circuits, enabling them to experience rewards even under extreme uncontrollable stress. It is possible that the capacity for acts of heroism, altruism, and teamwork often reported after a disaster result from enhanced activity in the neural circuitry of motivation and reward. Similarly, optimal functioning in

these neural pathways may enhance other resilience-enhancing characteristics, such as the ability to maintain hopefulness, optimism, and a positive outlook when exposed to chronic stress, abuse, and an unrewarding environment (Charney, 2004a). The ability to maintain a positive self concept and hopefulness could lead to an enhanced ability to seek out support and perhaps to bond with other supportive individuals.

Neurobiology of social support and attachment

Among psychological sources of resilience, high levels of perceived psychosocial support have repeatedly been identified as protective. In a study of 2490 Viet Nam veterans, Boscarino and colleagues found that after controlling for level of combat exposure, veterans with low social support had approximately 180% greater risk for PTSD than those with higher levels of social support (Boscarino, 1995). Strong social support has also been associated with better psychological outcomes after a trauma in survivors of a cruise ship disaster (Joseph *et al.*, 1992).

A number of animal studies have implicated the opiate system, oxytocin, and vasopressin in the central mediation of numerous complex social behaviors related to support, including affiliation and parental care. In nonhuman primates, the role of the neuropeptide oxytocin is well established in social interactions, as well as in the initiation of maternal behavior and pair bonding. Recent data from Insel and Winslow demonstrate that a genetically engineered mouse lacking oxytocin emitted few isolation calls and was socially withdrawn (Winslow *et al.*, 2000).

Research on a monogamous rodent, the prairie vole (*Microtus ochrogaster*), and a closely related species, the montane vole (*Microtus montanus*), suggests that oxytocin and vasopressin are also involved in the control of behaviors associated with monogamy, including pair bonding, paternal care, and mate guarding. Prairie and montane voles are similar genetically but vary greatly in their social behavior. The prairie vole is highly social and forms long-lasting attachments (Carter & Getz, 1993; Shapiro & Dewsbury, 1990). Comparative studies in voles have identified species-specific patterns of oxytocin- and vasopressin-receptor expression in the brain that appear to be associated with a monogamous versus nonmonogamous social structure (Young *et al.*, 1998). Molecular studies suggest that differences in the regulation of oxytocin- and vasopressin-receptor gene expression underlie these species differences in receptor distribution. In particular, the more social prairie voles have high levels of oxytocin receptors in the nucleus accumbens and basolateral amygdala relative to the less social montane voles. Similarly, prairie voles have higher densities of the vasopressin 1A receptor on the ventral pallidum and medial amygdala than montane voles (Young *et al.*, 1997). Infusion of vasopressin produced dramatically different effects in the two voles. Prairie voles increased social interaction, whereas montane voles increased nonsocial behaviors such as grooming themselves. The neural mechanisms responsible for the effects of oxytocin and vasopressin on social behavior are thought to involve some of the same circuitry (the nucleus accumbens and ventral pallidum) involved in reward-related behavior.

Neurobiology of trust

In addition to preclinical evidence of oxytocin's involvement in the regulation of social attachment-related behaviors, recent clinical studies in humans suggest a role for oxytocin in promoting trust-associated behaviors. If given intranasally, oxytocin crosses the blood–brain barrier and enters the central nervous system. In a placebo-controlled double-blind study, 37 healthy men were exposed to experimentally produced social stress and randomized to receive intranasal oxytocin or placebo as well as either psychosocial support from a friend during the preparation period or no support. The results showed that oxytocin enhanced the buffering effects of social support on stress responsiveness (Heinrichs *et al.*, 2003), as salivary cortisol responses to stress were reduced.

In another recent study, subjects participated in a game involving the actual exchange of money, and assessed whether the administration of oxytocin to the central nervous system before the game would affect the amount of trusting behavior displayed in the game. Before playing, each individual in the experiment was randomized to receive either an intranasal dose of oxytocin, or an intranasal dose of placebo, and then assigned the role of investor or trustee. In the game, the risk is taken by the investor, and it is based on the uncertainty about how the trustee will behave, i.e., the risk is embedded in a social interaction. Of the 29 subjects, 13 (45%) in the oxytocin group displayed increased trust behavior, compared to only 6 of the 29 (21%) in the placebo group ($p < 0.05$) (Kosfeld *et al.*, 2005).

Concluding remarks

It is anticipated that within disaster mental health, increasing focus on neurobiological as well as psychosocial studies of risk and resilience in the face of uncontrollable stress will lead to the development of new approaches to the prevention and treatment of disaster-related mental distress and mental disorders such as PTSD. Interventions designed to bolster resilience and prevent the development of disaster-related psychopathology will most likely focus on a number of neurobiological processes including stress sensitization, memory consolidation, memory retrieval, fear conditioning, fear extinction, modulation of excessive arousal and limbic reactivity, cortical and executive function, attachment, and relevant gene–environment interactions. Efforts to enhance prevention will require a better understanding of genetic, developmental, and environmental factors that either increase or reduce the risk for developing postdisaster psychopathology. The importance of these factors will differ from one person to the next and require a sophisticated understanding of gene–environment interactions as they relate to trauma exposure and its aftermath. The effect of social support, training and preparedness and stress inoculation on psychosocial and neurobiological resilience is an emerging and important area of study. In addition to research on prevention, scientists have begun to study the efficacy of early interventions for disaster survivors who become symptomatic. These efforts are challenging since a high percentage of disaster survivors experience some stress-related symptoms immediately after the disaster but only a minority of survivors go on to develop long-standing psychopathology. Accurately predicting which disaster survivors are most likely to develop long-standing psychopathology is of critical importance, since it is well known that repeated bouts of excessive arousal may increase the likelihood that stress-related neurobiological systems (e.g., noradrenergic system and HPA axis) become sensitized and that once these systems are sensitized, treatment is more difficult and probably less successful (Morgan *et al.*, 2003). Currently, psychological and pharmacological interventions are being targeted at survivors who experience excessive peritraumatic arousal (Brewin *et al.*, 1999), dissociation (Bremner *et al.*, 1992; Koopman *et al.*, 1994), and depression (Shalev *et al.*, 1998) because these responses are known to predict later PTSD.

Pharmacological intervention aimed at treating early severe symptoms which are known to be predictive of later PTSD, such as excessive arousal, is one possible avenue of study. One rational pharmacologic approach to treating excess arousal involves the short-term use of hypnotics and benzodiazepine anxiolytics to treat pronounced insomnia and anxiety. Other potential avenues for decreasing arousal in highly symptomatic individuals might include short-term use of anti-adrenergic agents such as propranolol, which may prevent the overconsolidation of fear-related memories and thus prevent PTSD (Morgan *et al.*, 2003; Pitman *et al.*, 2002). As with benzodiazepines, the use of beta-blockers for the treatment of trauma survivors remains controversial, since in addition to potential effects on overconsolidation of emotional memory, beta-blockers have been shown to interfere with extinction of fear-related memories. Another approach might target trauma-induced depressive symptoms. Freedman *et al.* (1999) found

that high levels of depressive symptoms 1 and 5 weeks after a trauma predict the development of PTSD. Already shown to be effective in the treatment of PTSD, selective serotonin reuptake inhibitors (SSRIs) might also be shown in future studies to be effective in the immediate postdisaster period in the prevention of PTSD among at-risk trauma survivors. Other pharmacologic approaches to prevention of PTSD might include the administration of NPY, particularly in people who do not naturally release sufficient amounts. The development of new CRH antagonists such as antalarmin show potential promise in the treatment and prevention of PTSD as well. Randomized trials of pharmacological agents such as these, as well as other interventions aimed at prevention of PTSD in the acute aftermath of trauma are clearly indicated.

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