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PROGRESS

The psychobiological basis of posttraumatic stress disorder

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Posttraumatic stress disorder is a disorder with an identifiable etiological factor (exposure to a traumatic event) and with a complex symptomatology (ie intrusive memories, avoidance, hyperarousal) that suggests dysfunction in multiple psychobiological systems. This review considers studies of the neurobiological consequences of acute and chronic stress showing that traumatic experiences can produce long-lasting alterations in multiple neurochemical systems. The role of the locus coeruleus noradrenergic system, prefrontal cortex dopaminergic system, endogenous opiates, hypothalamic-pituitary-adrenal axis, and cortico-releasing factors are reviewed. Several models of PTSD are highlighted, including fear conditioning, kindling, and sensitization. In particular, fear conditioning to explicit and contextual cues is proposed as a model for intrusive memories reactivated by trauma-related stimuli and hyperarousal, respectively. It is argued that the amygdala plays a crucial role in the encoding and retrieval of fear memories activated by specific stimuli that have been associated with aversive events. Association involving more complex environmental stimuli and aversive events may require the involvement of the hippocampus and the bed nucleus of the stria terminalis. Repeated activation of conditioned fear memories may produce a kindling-like process which results in spontaneous intrusive memories.

Keywords: posttraumatic stress disorder; anxiety; trauma; neurobiology; human

Introduction

Posttraumatic stress disorder (PTSD) as defined by DSM-IV[1] is an anxiety disorder characterized by somatic and psychological symptoms that develop following exposure to catastrophic stressors, including war, torture, rape, being held hostage, genocide, concentration camps, assault, natural or industrial disasters, and vehicular accidents. Nearly one-third of Vietnam veterans have developed PTSD at some time following exposure to war-zone stressors.[2] The prevalence rate of PTSD is alarmingly high. Surveys of general adult populations have estimated a prevalence of PTSD ranging from 1%[3] to 12.3%.[4]

One important criterion for the diagnosis of PTSD is the presence of an identifiable etiologic factor, that is, exposure to an extreme traumatic event. The core symptoms of PTSD are intrusive, involuntary re-experiencing of the traumatic event (eg nightmares, flashbacks, intrusive memories); persistent avoidance of stimuli reminiscent of the trauma, emotional unresponsiveness and numbing; and persistent hyperarousal (eg hypervigilance, insomnia, startle). These symptoms can develop immediately after the trauma or may be delayed for several months or years.[1,5]

This review will first consider the neurobiological consequences of acute and chronic stress. Preclinical and clinical studies showing that traumatic experiences can produce long-lasting alterations in multiple brain systems will be reviewed. We will then attempt to integrate preclinical and clinical findings in order to propose neurobiological mechanisms that may help to elucidate the pathophysiology of PTSD. Because PTSD is considered a multi-system disorder, several animal models that can explain specific biological processes relevant to PTSD will be presented. It will be argued that, in particular, cross-species (ie in animals and humans) studies of fear conditioning to explicit and contextual cues offer a framework to further our understanding of PTSD symptoms. Other processes include sensitization and kindling. Finally, we will discuss implications for future preclinical and clinical studies.

The present review will attempt to integrate findings from various research areas that use different methodologies. Results from studies using the fear-potentiated startle paradigm will be emphasized to delineate certain neural mechanisms activated during or following stress. The startle reflex, a cross-species response to intense stimuli with abrupt onset, is specifically sensitive to fear and negative affect (as opposed to arousal).[6,7] In humans, it is an ideal probe to assess emotional reactions to aversive events that might not

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readily be indexed by other more traditional psychophysiological measures such as the skin conductance response. In addition, 'exaggerated startle' is a pathognomic symptom of PTSD,[1,8,9] suggesting that startle studies might tap into symptom predisposition. Moreover, the neurobiological and pharmacological substrates of stress-altered startle reflex in animals provide a rich and invaluable source of information for further understanding central nervous system dysregulation following aversive events or trauma.[6]

Neurobiological response to stress

Fear and stress affect multiple neurobiologic systems that are crucial for survival. The behavioral effects of these systems are not completely understood. However, a large body of evidence suggests that these systems are involved in identification of stimuli associated with threat or aversive events, immediate activation of behaviors related to confrontation (eg fight) or escape (eg flight), adaptive homeostatic responses, coping, and encoding of memories. More specifically, the immediate response to an aversive event is characterized by sympathetic activation which subserves the flight-or-fight response. Release of norepinephrine (NE) has been implicated in orienting, selective attention, hypervigilance, autonomic arousal, and fear. The hypothalamo-pituitary-adrenal (HPA) response is also involved during this 'alarm reaction'. Several hormones are released during the stress response. Their action and interrelationship is complex and not fully understood. The autonomic nervous system appears to initiate short-term corrective responses. Hormonal mechanisms provide a more long-term defense against aversive events. For example, secretion of cortisol stimulates the activation of corrective metabolic processes necessary for sustained physical demands and tissue repair. However, the view that stress results in a general adaptation syndrome[10] has been replaced by the hypothesis that the response to stress involves a constellation of adaptive alterations that are idiosyncratic to each individual and are influenced by innate characteristics as well as past experiences. In this context, the psychological concept of 'coping' has been introduced. One important coping strategy involves the ability to predict and control stressors.[11] Substantial evidence suggests that the HPA response to stress serves as an important coping mechanism.[12,13] More recent studies also suggest the involvement of dopamine (DA) in the prefrontal cortex in the acquisition of stress-related coping strategies.[14] Similarly, stress-activated endogenous opioids appear to produce substantial analgesia.[15,16] In addition to these short-term effects, these stress-related neurochemical systems have long-term, and sometimes time-dependent, effects. They contribute to sensitization processes and to the encoding of memories for events, especially emotional memories.[17,18]

Several brain structures are also involved in the fear reaction to an aversive event. Accumulating evidence points to the amygdala as a mediator of unconditioned and conditioned fear. The amygdala assigns emotional significance to otherwise innocuous stimuli and may play a crucial role in the recollection of emotional events. Other structures that are activated by severe stress include the hippocampus, the locus coeruleus, and the prefrontal cortex. The hippocampus is not necessary for basic learning, but it does play an important role in more complex learning such as spatial and contextual learning[19,20] and assigning emotional meaning to places and complex stimuli.

Synaptic plasticity is believed to play a central role in learning and memory. One model of such synaptic plasticity is long-term potentiation (LTP), which is the long-lasting enhancement of synaptic transmission following brief trains of high-frequency stimulation.[21] LTP has been proposed as a physiological mechanism in learning and memory because of the rapidity with which it can be established and because of its longevity.[22] Such a mechanism is likely to be central to the enduring changes in synaptic transmission that result from fear and terror. LTP has been demonstrated in several structures activated by fear, including the amygdala and the hippocampus, further suggesting the involvement of these structures in encoding fear memories.

The neurobiological responses to severe stress are clearly adaptive and protective, and have survival value, but they also can have maladaptive consequences when they become chronically activated. Chronic adrenergic activation can lead to noradrenergic receptor downregulation, as well as depletion of norepinephrine, perhaps leaving the organism more vulnerable to subsequent stress. Similarly, glucocorticoids can have neurotoxic effects in the hippocampus[23] that appear to affect learning and memory.[24,25] Although PTSD can result from exposure to a single catastrophic event, the intrusive symptoms themselves can serve as chronic or intermittent stressors. Hence, when considering animal models of PTSD, one must take into account neurobiological changes resulting from exposure to the single overwhelming trauma itself as well as to potential changes that accompany the stressful reliving of the trauma.

Locus coeruleus-norepinephrine system

The locus coeruleus (LC) is the major noradrenergic (NA) system in the brain. It has widespread efferent projections throughout the neuroaxis that suggest a more general role in aspects of central processing, rather than a specific role in sensory or motor processing. There is substantial evidence indicating that various stressors increase both the firing of LC neurons and the turnover of noradrenaline in terminals. However, there is no consensus regarding the functional role of the noradrenergic system in the brain.[26,27] It has been suggested that the LC plays an important role in orienting behavior, vigilance, selective attention, and in learning the significance of sensory events as well as encoding these events.[26] Because the LC is particularly sensitive to stress, threat, and noxious stimuli, it has been described as a central component of the organ-

isms's alarm system.[27] Thus, innocuous tones, lights, or tactile stimuli produce a modest increase in LC neuron activity which habituates rapidly. Aversive or stressful stimuli are more potent in this regard and result in major increases in firing in the LC as well as autonomic activity.[28] In addition, uncontrollable stress, which has been proposed as a model of PTSD, produces increased norepinephrine in several brain structures associated with the regulation of emotions including the locus coeruleus, amygdala, hippocampus, and neocortex.[29] Increased turnover of central norepinephrine is associated with enhanced activity of the sympathetic nervous system.[30] Recently, it has been proposed that the nucleus of the paragigantocellularis (Pgi) in the ventrolateral rostral medulla is a key brain area which controls both the central and peripheral reactions to stress via the LC and the sympathetic nervous system, respectively.[31] This structure may be an important contributor to peripheral sympathetic hyperactivity (eg sweating, increased heart rate) and to PTSD symptoms that may be mediated by central noradrenergic disturbances (eg hypervigilance).[31]

The activation of norepinephrine following acute stress is adaptive for the survival of the species. In the case of uncontrollable stress, the concurrent alterations in catecholamine systems may become maladaptive.[32] Exposing rats to uncontrollable stress produces fear and anxiety and can lead to a chronic enhancement of responsivity of LC neurons to excitatory stimulation due to decreased stimulation or 'functional blockade' of alpha 2 receptors following norepinephrine depletion.[32] Blockade of alpha 2 receptors, but not blockade of other inhibitory LC receptors (eg opiate receptors, $GABA_A$ receptors, serotonin), can increase the responsiveness of LC neurons to stimulation, suggesting a unique role of alpha 2 receptors in modulating the response of LC neurons to excitatory stimulation.

Clinically, individuals with PTSD exhibit several signs of central noradrenergic dysfunction and peripheral sympathetic hyperactivity. Tonic, as well as, phasic autonomic system dysregulations have been identified following traumatic war experiences. Sleep disturbance, anger, irritability, exaggerated startle, and various signs of physiological arousal have been described since the early reports of combat stress reactions in soldiers who were diagnosed with 'irritable heart' or 'shell-shock'. These conditions are now referred to as PTSD.[5,6,33]

In 1919, Wearn and Sturgis reported that injection of epinephrine produced a rise in systolic blood pressure and heart rate, with accompanying signs of nervousness, palpitation, tremor, flushing and sweating in traumatized soldiers with irritable heart.[33] Soldiers who were not characterized with irritable heart did not show this pattern of response, suggesting that irritable heart was associated with an unstable and over-reactive autonomic nervous system. Over the last two decades, this psychophysiological instability of autonomic nervous system activity has been repeatedly documented, mostly in Vietnam veterans with PTSD. Heightened psychophysiological arousal in PTSD has been consistently found in responses to stimuli that are reminiscent of the trauma. Combat-related stressful stimuli, including sounds of combat, audiovisual movie clips, and personal imagery scripts elicit greater autonomic activation in veterans with PTSD, compared to those without PTSD.[34–38] This hyper-reactivity is not found in response to stressful but non trauma-related events, suggesting that abnormal conditioning could be an etiological factor for PTSD. Less clear is whether or not baseline autonomic arousal is elevated in PTSD. In a comprehensive review of psychophysiological dysfunction in PTSD, Prins *et al*[39] reported that eight of 13 studies found normal baseline heart rate among subjects with PTSD. They suggested that individuals with PTSD did not suffer from a chronic elevation of autonomic arousal and attributed basal differences in heart rate (in five of 13 studies) to anticipatory anxiety associated with the experimental context. In sum, psychophysiological studies suggest enhanced sympathetic reactivity in PTSD. Although conditioned trauma-related stimuli are powerful mediators of noradrenergic hyper-reactivity, stressful experimental settings can also affect sympathetic activity. Hence, in addition to a conditioned activation of the sympathetic nervous system, a sensitization process might underlie the autonomic hyper-responsiveness to trauma-unrelated contextual stimuli.

Consistent with the hypothesis of a conditioned activation of the sympathetic nervous system in PTSD, there have been reports of increased plasma epinephrine[38] and plasma norepinephrine[40] that paralleled the increased psychophysiological arousal recorded during the viewing of films that were reminiscent of the trauma. These parallel increases were not found during the viewing of trauma-unrelated films. Further, the most dramatic increase in plasma epinephrine was noted during the recovery period and was accompanied by intrusive war-related memories. These results suggest a close association between the presence of distressing memories (ie flashback) and sympathetic activation. In addition, the failure of plasma epinephrine to rapidly return to baseline may indicate dysfunction in mechanisms responsible for terminating sympathetic activation.[38]

Clinically, neuroendocrine studies also have reported evidence of chronic dysregulation in noradrenergic systems in PTSD. Kosten *et al*[41] found elevated 24-hour urine norepinephrine excretion in veterans with PTSD, compared to healthy subjects or patients with other psychiatric disorders. These results were confirmed and extended by Yehuda *et al*[42] who reported that norepinephrine levels were correlated with the severity of intrusive symptoms. Similarly, De Bellis *et al*,[43] found increased epinephrine and norepinephrine activity in 8- to 15-year-old sexually abused girls, suggesting that dysregulation in noradrenergic activity is not restricted to traumatized adults. Consistent with these results, a 40% reduction in the number of high-affinity platelet alpha-2 adrenergic receptors has been found in patients with PTSD.[44] This downreg-

ulation may be secondary to chronic elevation of circulating catecholamines. There is also evidence to suggest that in patients with PTSD, platelet alpha-2 adrenergic receptors are more sensitive to downregulation by agonist, compared to controls.[45] Finally, Lerer reported lower cAMP[46] and basal adenylate cyclase[47] levels in patients with PTSD, compared to controls.

Other evidence of noradrenergic dysregulation is provided by sleep studies. Preclinical studies suggest that arousal levels during sleep are regulated by noradrenergic activity.[48] A dysregulation in sleep/awake noradrenergic activity in stressed individuals is suggested by a study from the Three Mile Island nuclear plant where it was found that norepinephrine during sleep was increased relative to daytime values in subjects with PTSD, but decreased in controls.[49] A similar finding was reported in Vietnam veterans with PTSD.[50] Nocturnal urine norepinephrine and MHPG levels exceeded the daytime values in individuals with PTSD, but not in controls.[50] These results suggest that the normal reduction in norepinephrine activity that occurs at night is not found in traumatized individuals with PTSD. These results raise the possibility of an association between noradrenergic dysregulation and nightmares among subjects with PTSD.[51] In fact, nightmares in PTSD are frequently precipitated by sympathetic arousal during stage II sleep.[52] These nightmares, unlike usual nightmares, are more characteristic of real-life events.

In addition to peripheral catecholaminergic studies, a more direct probe of central noradrenergic activity has been assessed using yohimbine.[53] Although yohimbine affects several neurotransmitters, its primary action is to increase noradrenergic activity by acting as an alpha-2 adrenergic receptor antagonist. Southwick *et al* reported that yohimbine produced behavioral and physiological signs of fear in Vietnam veterans with PTSD. More specifically, 70% of PTSD patients experienced yohimbine-induced panic attacks. Yohimbine also caused a significant greater increase in blood pressure, heart rate, and plasma MHPG in the subgroup of patients with panic attacks, compared to controls, suggesting that this sub-group of PTSD patients had an abnormal sensitivity of presynaptic noradrenergic activity. Of particular relevance was the impact of yohimbine on the core symptoms of PTSD including increases in hypervigilance, intrusive memories, and flashbacks.

With regard to specificity, yohimbine has relatively little effect in normal controls or in patients with schizophrenia, major depression, obsessive-compulsive disorder, and generalized anxiety disorder.[54] Panic disorder patients, however, have a similar rate of yohimbine-induced panic attack, suggesting that PTSD and panic disorder share common neurologic abnormalities related to altered sensitivity of the noradrenergic system.

Adding to the array of behavioral, biochemical, and cardiovascular effects of yohimbine in PTSD, a recent study reported a differential effect of yohimbine on startle in Vietnam veterans with and without PTSD.[55] Yohimbine was found to produce a substantial facilitation of startle amplitude only in the veterans with PTSD. These results again point to the involvement of the noradrenergic system in mediating a major symptom of PTSD (ie exaggerated startle).

Finally, in a recent study, a single bolus of (F-1802)-Fluoro-2-deoxyglucose (FDG) was administered to 10 Vietnam veterans with PTSD and 10 healthy controls immediately before either yohimbine or placebo infusion.[56] The metabolic response to yohimbine differed significantly in neocortical brain regions (prefrontal, temporal, parietal, orbitofrontal cortices) between patients and controls. Controls showed a tendency toward increased metabolism where PTSD patients showed a tendency toward decreased metabolism. Animal studies have shown that high levels of NE can lead to decreased brain metabolism.[57,58] The authors hypothesized that PTSD patients, being unusually sensitive to yohimbine, release more NE than controls with a resultant decrease in brain metabolism and a positive increase in signal-to-noise ratio of neuronal activity, leading to enhanced selective attention, and hypervigilance.

Hypothalamic-pituitary-adrenal axis

The hypothalamic-pituitary-adrenal (HPA) axis plays a crucial role in the adaptive response to stress via homeostatic mechanisms. Perception of the stressors leads to the release of corticotropin-releasing-hormone (CRH), arginin vasopressin (AVP) and other secretagogues of adrenocorticotropin (ACTH).[59] ACTH, in turn, promotes the release of glucocorticoids from the adrenal gland which has as a primary target the glucocorticoid receptor in the hippocampus. Glucocorticoids have metabolic, immune, and neural preservative functions, but excessive elevations of glucocorticoids can have neurotoxic effects on the hippocampus[23] and an adverse impact on cognitive functions.[24,25] Hence, several of the learning deficits associated with uncontrollable stress could be due to neurotoxic glucocorticoid levels in the hippocampus. Under normal circumstances these neurotoxic effects are avoided because glucocorticoids exert a negative feedback on the HPA axis which maintains hormonal levels within nontoxic ranges.

Prior experiences with stress alter subsequent HPA responses to a stressor. Whether the HPA response shows habituation or sensitization is dependent upon several factors. These include the nature and severity of the stressor, the time between stressors, and the nature of the new stressor (same or different from the original stressor). Animals that are exposed to the same stressor on a daily basis adapt through a progressive attenuation of the adrenocortical response to stress.[60–62] Unusually severe or uncontrollable stressors can interfere with this adaptation in rodents.[63–65] Similarly, an attenuated adrenocortical response to chronic stress can be disrupted following the introduction of a novel stressor.[66,67]

In humans, psychologically distressing stimuli are particularly potent in eliciting an HPA response. In

fact, without significant psychological arousal, the pituitary adrenal system shows little if any activation.[68] In the context of PTSD, intrusive memories can be thought of as psychological stressors that repeatedly activate the HPA axis with its potentially damaging consequences. Given their neurotoxic effects, high levels of glucocorticoids in the hippocampus could account for some of the cognitive deficits associated with chronic stress. In fact, individuals with PTSD are characterized by substantial dysfunction in learning and memory,[69] including deficits in short-term memory[70] which have been found in individuals with hippocampal damage.[71,72] The possibility of neurotoxic effects of glucocorticoids in PTSD has recently received some support. A magnetic resonance imaging study found a reduced right hippocampal volume in Vietnam veterans with PTSD.[73] This reduction could not be accounted for by alcohol or drug abuse and was correlated with verbal memory deficits.

Evidence for HPA axis dysregulation in humans following exposure to a stressor has included measures of basal HPA functioning and neuroendocrine challenges (reviewed in Ref. 74). Compared to individuals without PTSD, those with PTSD have been found to have: (1) lower 24-hour urinary cortisol excretion and lower plasma cortisol levels.[75–77] These alterations may persist for several decades since low cortisol levels have been reported in holocaust survivors with PTSD.[74] One study, however has reported an increase in urinary cortisol levels in women with childhood sexual abuse-related PTSD.[78] Further, women with no prior assault exhibit increased cortisol levels following a high-severity rape while women with a previous history of assault have lower cortisol levels after rape.[79] It is possible that HPA axis dysfunction is influenced by gender, nature of the trauma, age at which the trauma occurred (eg childhood *vs* adulthood), time since trauma, and number of traumas; (2) increased lymphocyte glucocorticoid receptor numbers;[77,80,81] (3) increased responsivity to low doses of dexamethasone.[76,80] This 'hypersuppression' was even found in PTSD patients who met co-morbid criteria for major depressive disorder;[76] (4) a blunted ACTH response but normal cortisol response to a CRH challenge;[82] and (5) increased CSF levels of CRH.[83] In sum, these results have been interpreted as indicating an enhanced negative feedback inhibition of the HPA axis in PTSD.[84] According to this model, CRH would be hyper-secreted in patients with PTSD, resulting in abnormal responsivity of the pituitary. Enhanced negative feedback inhibition secondary to altered glucocorticoid receptor responsivity is consistent with low cortisol levels, attenuated baseline ACTH, and enhanced suppression to dexamethasone.[74]

Corticotropin-releasing-hormone

Although CRH is an important component of HPA activation, many of its effects are mediated outside the hypothalamic-pituitary axis.[85,86] For example, CRH acts through extensive extra-hypothalamic connections with several brain structures implicated in stress such as the central nucleus of the amygdala, the bed nucleus of the stria terminalis, the hippocampus, and the locus coeruleus.[87,88] Substantial evidence indicates that CRH is centrally involved in the response to stress. Central administration of CRH produced 'anxiety-like' behavioral and autonomic effects that are not suppressed by hypophysectomy.[87,88] For example, intracerebroventricular (icv) injection of CRH produces a marked, long-lasting, and dose-dependent elevation of startle amplitude[89,90] which is reduced by the anxiolytic compound chlordiazepoxide.[91] The anxiogenic effects of CRH can be attenuated by alpha-helical CRH, a CRH receptor antagonist.[92–94]

The precise brain sites where CRH exerts its anxiogenic effects are not known. Mounting experimental evidence suggests that the LC noradrenergic neurons play a pivotal role in CRH effects. The firing rate of LC neurons is increased in a dose-dependent manner by CRH;[95] stressful conditions profoundly affect CRH concentration in the LC;[96] CRH injected into the LC intensifies anxiety-related responses[97,98] and produces a profound increase in NE metabolites in the amygdala and hypothalamus.[98] These results suggest a close synergy between LC and CRH during stress, whereby stressful conditions increase CRH release into the LC, which in turn enhances NE synthesis and release.

The amygdala is thought to be another important site of CRH effects. CRH injection into the amygdala reduces exploratory behaviors[99] and attenuates stress-induced gastric ulcer.[100] Stress increases the release of CRH into the amygdala.[101] Recent findings, however, suggest that the amygdala might not be the primary site of CRH effects. As indicated earlier, startle is facilitated by CRH. Lesions of the central nucleus of the amygdala attenuate CRH facilitation of startle[89] but local injection of CRH into the amygdala does not significantly elevate startle. This suggests that the amygdala is only part of the neural circuit necessary for CRH to elevate startle. Recent studies have shown that lesions of either the hippocampus or the bed nucleus of the stria terminalis (BNST) completely block the CRH-enhanced startle. Relatively little is known about the functional role of the BNST, compared to other structures such as the amygdala or the hippocampus. However, the BNST is involved in the response to various stressors.[102–105] It has extensive efferent projections into the paraventricular nucleus[106,107] and presents many anatomical similarities with the central and the medial nuclei of the amygdala.[108] The BNST has brain projections into hypothalamic and brainstem sites that are essentially the same as the central nucleus of the amygdala,[109] and it receives direct projection from the amygdala[110] and the hippocampus,[111] suggesting that the BNST may play a crucial role in behavioral and hormonal responses to stress. Lee and Davis[112] have recently suggested that the BNST might be a primary cite of CRH effects. They have shown that chemical lesions of either the ventral hippocampus or the BNST, but not chemical lesions of the amygdala, blocked CRH-enhanced startle. CRH infusion into the ventral hippocampus did not affect startle, whereas CRH infusion into the BNST produced a dose-dependent facilitation

of startle. Finally, CRH-enhanced startle was blocked by alpha-helical CRH.

Dopamine

Dopamine (DA) in the prefrontal cortex has long been shown to be associated with stress.[14,113] The prefrontal cortex has one of the highest concentrations of benzodiazepine receptors in the brain[114] and diazepam blocks stress-induced prefrontal DA turnover.[15] Stress-related DA activation is rather selective since mild shock activates DA in the prefrontal cortex, but not in mesolimbic and negrostriatal areas.[115–117] Higher shock levels are necessary to increase DA utilization in the nucleus accumbens.[118] Several distinct afferent systems to the prefrontal cortex participate in this stress-induced DA activation, including NMDA, substance P, and opiates.[115] The excitatory effect of stress on prefrontal cortex DA is mediated by the amygdala. Lesions of the central nucleus of the amygdala attenuate stress-induced increases in DA turnover in the prefrontal cortex.[119] There is a great heterogeneity in the efferent projections from the prefrontal cortex as well as a large difference in stress-induced DA utilization between regions within the prefrontal cortex.[14] These characteristics suggest that the prefrontal cortex subserves different stress-related functions.[14]

One of the major functions associated with prefrontal DA is cognition,[120] and more specifically coping. A substantial number of studies suggest that DA in the prefrontal cortex is associated with the acquisition of coping mechanisms.[118,121,122] According to this model, activation of prefrontal cortical DA during exposure to a stressor does not reflect stress *per se*, but an attentional or cognitive response that has been elaborated in order to deal with the threat.

The mesoaccumbens DA system seems to be involved in different aspects of coping. This system is involved in mechanisms that increase the probability and the strength of behavioral responses.[120] Acute exposure to a non-escapable stressor induces a time-dependent biphasic alteration of DA in the nucleus accumbens whereby an initial increase in DA release is followed by an inhibition.[123] It is possible that DA release accompanies the organism's initial behavioral reaction to cope with the situation. When no escape or control is possible, a different emotional response takes place with a reduction in DA functioning. The implication of stress-induced DA release in coping responses seems to run counterintuitive to the finding that release of cortical DA can be increased by prior exposures to stressors and by the hypothesis that cortical DA is involved in sensitization processes[124] (see below). However, these studies have mostly involved cross-sensitization between drugs and stress challenges. In addition, sensitization studies have typically used a novel stressor for the final challenge day which is likely to activate coping mechanisms.

Clinically, there is evidence of elevated urinary[42,78] and plasma[125] DA in PTSD. The central or peripheral origins of DA concentration are unknown. DA hyperactivity could be associated with specific symptoms. Startle is increased by increases in DA activity;[126] there is a correlation between DA metabolite and the severity of anxiety in panic disorder;[123] cocaine and amphetamine increase vigilance, suggesting a relation between hypervigilance in PTSD and DA function; and the symptoms of paranoia and hallucinations that are described in subgroups of PTSD individuals[120,127] could be related to DA hyperactivity. This is suggested by the observation that increased DA function is associated with psychosis in schizophrenia. Finally, DA function could determine the choice of drugs used and abused by individuals with PTSD. Indeed, stress and psychostimulants cross-sensitize, an effect in which the mesocorticolimbic DA system plays a pivotal role.[124]

Opioids

Some of the behavioral responses following exposure to a stressor, including analgesia (ie stress-induced analgesia), catalepsy and changes in motor activity, are similar to those induced by endogenous opioid peptides.[128–130] In fact, substantial evidence indicates that endogenous opiates are involved in stress-induced analgesia[15] (ie stress-induced analgesia) as well as some of the behavioral deficits associated with stress.[131] Stress-induced analgesia is found following uncontrollable but not controllable stress.[16] It is also observed under various stressful circumstances which include electric shocks,[15] aggressive conspecifics,[132] predators,[133] or initially innocuous stimuli that have been paired with aversive stimuli.[133] This later effect is dependent upon the integrity of a neural circuit that includes the amygdala. Lesions of this structure block the expression of conditioned stress-induced analgesia.[134] Pain modulation is accomplished via action of multiple systems in the periaqueductal grey, nucleus raphe magnus, and the spinal cord.[134b] Activation of these multiple systems is influenced by the nature, intensity, and duration of the stressor. Three pharmacologically and neuroanatomically distinct analgesia systems that are sequentially activated by increasing numbers of tail-shock have been identified.[135,136] The *k*-opioid receptors within the spinal cord are involved in both early (following two shocks) and late (80–100 shocks) analgesia. The late analgesia is also mediated by supraspinal delta-opioid receptors. Analgesia at intermediate stages (5–40 shocks) is not affected by naltrexone.[135] The *k*-opioid receptors are also involved in psychological stress.[137] Further, conditioned analgesia is mediated by the activation of mu- and delta-opioid receptors and analgesia produced by mu- and delta-opioid receptor agonists is blocked by safety signals.[138]

The nature of the endogenous opioid response to chronic stress is unclear as both tolerance and sensitization have been reported.[16,139,140] Similarly, there is evidence that, depending on the circumstances, opioid activity is either increased or reduced in individuals with chronic PTSD. Vietnam veterans with PTSD exhibit a naloxone-reversible reduced pain sensitivity upon exposure to trauma-related stimuli.[141] However, the

finding that patients with chronic PTSD have a lower pain threshold,[142] lower plasma beta endorphin levels,[143] and reduced release of methionin-enkephalin[144] suggests chronic opioid depletion.

It has been hypothesized that dysregulation of endogenous opioids is associated with the core PTSD symptoms of numbing and emotional withdrawal.[145] This hypothesis is consistent with theories linking brain opioids to social emotions.[146] In fact, naloxone can reduce gregariousness.[147] However, the direction of causation between dysregulation in endogenous opioids and numbing and emotional withdrawal is not known. Numbing could be caused by conditioned activation of endogenous opioids following exposure to traumatic stressors.[145] Alternatively, numbing and withdrawal could lead to reduced endogenous opioids. In the rat, social isolation for a few days produces consistent hyper-algesia and reduced morphine sensitivity.[148] Opiate consumption is also increased by social isolation.[149]

In addition to stress-induced analgesia, stress produces other endogenous opioid-mediated behavioral changes such as immobility and catalepsy.[131,139,140] This motor suppression may be a model for some of the symptoms of behavioral depression (eg masked faces, reduced eyeblink, rigidity)[8] found in humans following exposure to a traumatic experience. There is evidence that stress-induced motor suppression and stress-induced analgesia are associated with different opioid systems.[131] Similarly, independent opioid systems may be involved in kindling-induced analgesia and behavioral depression.[150] Mu- and/or delta-opioid receptors mediate footshock-induced analgesia, but *k*-opioid receptors may underlie footshock-induced motor suppression.[151]

Neural mechanisms related to PTSD symptoms

Because PTSD develops following exposure to one or more severe traumatic life stressors, animal models of PTSD involve severe stress or trauma. Intriguing connections have been made between two animal models and the symptoms of PTSD: *conditioned fear to explicit cues* and *inescapable stress*. The conditioned fear model is based on the observation that discrete stimuli that are reminiscent of the trauma can promote the retrieval of fear memories and induce a conditioned emotional response.[5,152] Investigators have hypothesized that PTSD is fundamentally a psychophysiological disorder involving conditioned activation of the sympathetic nervous system.[152] Additional support for the conditioning model comes from animal studies where dogs trained to avoid an extremely aversive shock that has been paired with a warning signal, will continue to exhibit the avoidance response even when exposed only to the warning signal.[153] This instrumental response, as well as its autonomic concomitants is particularly resistant to extinction. It has been argued, that this avoidance behavioral response upon presentation of stimuli previously associated with the shock is analogous to the avoidance symptoms of PTSD.[154]

The inescapable stress model derived from studies of experimental neurosis (see Krystal *et al*[155]) in which animals exposed to severe inescapable physical stress present neurobiological deficits and behavioral symptoms similar to those of individuals with PTSD. Exposure to inescapable stress produces an immediate alarm response accompanied by an increase in norepinephrine turnover, increased levels of plasma catecholamines, depletion of central noradrenergic neurons, and increased levels of noradrenergic metabolites.[156,157] The immediate fear reaction is followed by more long-lasting impairments such as sleep disturbances, chronic distress, deficits in learning new escape strategies, and behavioral depression. These impairments can be attributed, in part, to lasting neurobiological alterations which sensitize the organism to subsequent stressors. In fact, sensitization phenomena have been proposed as models for some of the PTSD symptoms.[158–160]

There is an additional model derived from conditioning studies that provides further insight into possible brain dysfunction in PTSD. Animals placed back in the experimental context where they have previously received shocks exhibit symptoms of heightened generalized fear that are similar to the PTSD symptoms of distress, persistent anxiety, and arousal.[161] Contextual fear is a process predicted by classical conditioning theory. It refers to fear conditioning that develops to environmental or contextual stimuli (eg the cage) that are present during conditioning procedures. Hence, procedures involving an aversive event (eg a shock) produces contextual fear conditioning, especially when the aversive event is administered in an unpredictable manner (see below). Classical conditioning models, therefore, are of heuristic value, not only to examine brain mechanisms involved in the encoding and remembering of traumatic memories, but also to explain many of the cardinal symptoms of PTSD, such as heightened vigilance and generalized fear.

Fear conditioning: an overview

In a typical aversive conditioning experiment, animals are placed in an experimental chamber where they are exposed to a brief neutral stimulus (eg a light) that is repeatedly paired with an aversive unconditioned stimulus (US) (eg a shock). Subsequent presentations of the neutral stimulus elicit a constellation of behavioral and physiological responses (conditioned responses, CR), such as freezing and increased heart rate, that have been used to index a central state of fear. The neutral stimulus is referred to as a *discrete* or *explicit* conditional stimulus (CS) because it is presented for a short period and its physical characteristics are specifically defined. Conditioned associations are also formed with the contextual stimuli that were present at the time of conditioning. Thus, in addition to fear of the explicit CS, the animal rapidly learns to fear the experimental context where shocks were administered, ie the cage.[162,163] The environmental

context consists of the various static contextual cues that were available to the animal at the time of the initial conditioning. These cues are referred to as *contextual* CS. Contextual fear is increased as shocks become more unpredictable. The contextual fear model, therefore, is paradigmatically equivalent to models of experimental neuroses where shocks are unpredictable and uncontrollable. Both models result in generalized fear.

The CR is not a simple reflexive response, but is influenced by non-associative processes taking place following conditioning. These non-associative processes, which can modulate the strength of the CR, play a critical role in the maintenance of fear responses. For example, the pairing of a mild US with a CS, followed by the presentation of a similar US of greater intensity that is presented in a non-associative manner, result in a greater CR.[164] Such a result is consistent with the view that the CS activates a mental representation of the US. In humans, reevaluation of this mental representation can be obtained through a new experience with the US or through verbal information about the US.[165,166] The malleability of this mental representation can contribute to the maintenance or enhancement of conditioned fear responses.

Although contemporary models adopt a 'cognitive' interpretation of conditioning, the role of automatic processes is still recognized, indicating that the meaning associated with stimuli is not always available to awareness.[167] Using a backward masking technique which prevents conscious awareness of a stimulus, Ohman[167] has reported that conditioned fear to 'fear-relevant' stimuli (eg snakes, spiders) can be elicited automatically. These automatic processes might also be crucial to the maintenance of conditioned fear and may be associated with specific subcortical pathways that have recently been identified[168–170] (see below).

Aversive conditioning to discrete cues and the symptoms of re-experiencing: the amygdala and traumatic memories

The study of neural systems involved in conditioned fear to explicit cues permits the examination of brain mechanisms associated with encoding of traumatic memories and their retrieval following presentation of innocuous conditioned stimuli. However, some of the re-experiencing symptoms such as flashback, nightmares, and intrusive recollections are not preceded by identifiable triggering stimuli. It has been argued that conditioned fear can also model some aspects of the re-experiencing symptoms that appear 'spontaneously' because the critical factor in re-experiencing is the activation of fear memory.[161]

A basic principle of the stress response according to Selye[171] is that all stimuli which are considered stressors must elicit a stereotyped physiological and behavioral response. This requires that information concerning all possible environmental stressors is conveyed to a structure that can assign emotional significance to stimuli and can relay stress-related information to brainstem structures that mediate the behavioral and physiological responses to stress. The amygdala is one site where such processes could potentially take place. The amygdala received afferents from the external word and the internal milieu, and sends efferents to structures involved in the generation of emotional behaviors. Sensory information enters the amygdala through its lateral and basolateral nuclei.[172–174] These nuclei, in turn, project to the central nucleus of the amygdala[172,175] which has direct connections to hypothalamic and brainstem regions involved in symptoms of fear and anxiety.

There is substantial evidence that the amygdala is crucial for conditioned and unconditioned fear. Unconditioned fear can be triggered in laboratory rats when they are confronted with a natural predator (eg a cat) for the first time. This response disappears after lesions of the amygdala.[162] The possible role of the amygdala in eliciting unconditioned fear memories is also suggested by the fact that electrical stimulation of this structure in humans can result in mental (eg feeling, dreamlike, mental images) and physiological (eg arousal, hormonal secretion, visceral sensations) signs that normally accompany emotional states (see review in Ref. 176). Interestingly, the content of the mental images can be related to the subjects' ongoing concerns.[177–179] These results do not imply that memories for traumatic events are stored in the amygdala. It is more likely that memory is stored in a neural network and that stimulation of the amygdala results in retrieval of selective fear memories by facilitating the access to specific trauma-related associative networks.

Although the amygdala has been shown to be central in mediating fear produced by many conditioned and unconditioned stimuli, there are fear responses in which the amygdala do not seem to play a crucial role.[180–182] Davis[183] has reviewed evidence suggesting that the amygdala seems to be critical for fearful behaviors elicited by a readily identifiable source such as those produced by aversive shocks.

Mechanisms of conditioned fear to an explicit cue

There is now considerable evidence indicating that neural plasticity within the amygdala is crucial for the acquisition of aversive conditioning to discrete cues. Cellular activity in the amygdala parallels the development of aversive behavioral responses.[184] Disruption of conditioned fear results from post-training subseizure electrical stimulation of the amygdala and from pharmacological manipulations that disrupt the activity in this structure.[185,186]

While the amygdala is believed to be a crucial component of the fear circuit, it appears to have a broader role as a central element of a neural network involved in emotional processing. This is suggested by studies that have indicated that conditioned fear increases *c-fos* expression, a marker of physiological activity, in several subcortical and cortical regions, including allocortical regions, various amygdaloid nuclei, locus coeruleus, periaqueductal grey,

dorsomedial striatum, lateral septum, and hypothalamus.[187–190]

The fear-potentiated startle paradigm is a particularly relevant model to examine the neurobiological mechanisms of conditioned fear in PTSD because the symptom of exaggerated startle has been viewed as a part of the conditioned emotional response to stimuli reminiscent of the trauma.[152] Fear-potentiated startle refers to the increased startle that is found following the delivery of a startling stimulus in the presence of an aversively conditioned stimulus (eg a light that has been previously associated with an electric shock). In humans, startle can also be potentiated when emotionally significant stimuli are viewed or imagined.[7] Thus, exaggerated startle might result from presentation of a startle-eliciting stimulus (eg a slamming door or a ringing phone) during recollection of prior trauma.

Recent findings suggest that the encoding of traumatic memories might be dependent upon a LTP process at the level of the amygdala. Infusion of N-methyl-D-aspartate (NMDA) antagonist into the basolateral nucleus of the amygdala completely blocks the acquisition of fear-potentiated startle using either a visual or an auditory CS.[191,192] Other measures of fear conditioning, such as freezing or inhibitory avoidance are also blocked by injection of NMDA antagonists into the amygdala.[193–195] However, non-NMDA receptors seem to be implicated in the expression or retrieval of a previously learned fear response as suggested by the fact that injection of 6-cyano-7-nitroqinoxaline-2,3-dione (CNXQ), a non-NMDA ionotropic antagonist, disrupts the expression of fear-potentiated startle.[6] Expressions of these conditioned responses might involve activation of G-proteins.[196]

A crucial question regarding aversive conditioning processes concerns the nature of the sensory interface with the amygdala and the extent of the processing that sensory stimuli undergo before entering the amygdala. The central nucleus of the amygdala receives input from late-stage modality specific processing from polymodal association cortex via the lateral and basal nuclei and from higher-order modality independent inputs from the hippocampus via the entorhinal cortex and subiculum.[172,174] These anatomical connections suggest that sensory information relayed to the amygdala receives substantial higher-level processing. For example, the amygdala receives elaborated visual information from the inferotemporal cortex, a structure involved in object perception and recognition. More complex information is also relayed to the amygdala via the hippocampus. Considering the role of the hippocampus in the processing of spatial and complex cues, the hippocampus-amygdala connection appears to be a critical step in assigning significance to complex contextual stimuli. The fact that a cortical pathway underlies fear conditioning is theoretically important because several theories of emotions posit that cognition, which presumably is a cortical function, is a critical determinant of emotions.[197] It is also clinically relevant because it offers the possibility that putative emotional stimuli are under control of cognitive processes, and thus could be amenable to reappraisal through psychotherapy.

However, in addition to the thalamo-cortico-amygdala pathway, a subcortical thalamo-amygdala pathway has also been reported to be functional after cortical lesions.[168–170] Unlike the thalamo-cortico-amygdala pathway, the thalamo-amygdala pathway provides only a crude and superficial analysis of stimuli, suggesting that fear-conditioned responses can be elicited without awareness of the cause of the emotional response. Based on the finding that lesions of the thalamo-amygdala connection, but not lesions of the thalamo-cortico-amygdala connection, prevent aversive conditioning and that cortical lesions prevent extinction of aversive conditioning, Ledoux[198] has proposed that the subcortical trace of emotional memories might be indelible. These observations have led to the suggestion that the traumatic memories experienced by individuals with PTSD[199] are examples of this indelible encoding.

The finding that there is a subcortical pathway for conditioned fear which bypasses the cortex also suggests that traumatic memories might be elicited automatically (ie without conscious awareness) by sensory events. This view is consistent with human data showing that conditioned fear can be mediated unconsciously[167] (see above). Of particular interest in the context of the present review is that the subcortical mediated conditioned responses in rats, the conditioned fear responses to fear-relevant stimuli in humans, and the conditioned emotional responses to stimuli reminiscent of the trauma in PTSD fail to extinguish. Further, like the conditioned emotional responses in PTSD, conditioned fear to fear-relevant stimuli is resistant to verbally mediated instructions. The verbal instruction that the aversive US will no longer be presented results in slower extinction of conditioned fear to fear-irrelevant, compared to fear-relevant stimuli. A pertinent conclusion drawn from these studies is that an unconscious (thalamo-amygdala) mediated process might underlie the reemergence of conditioned traumatic memories in PTSD. The validity of such an hypothesis could be tested by examining the physiological responses of individuals with PTSD during the presentation of stimuli that are reminiscent of the trauma using backward masking techniques that prevent awareness of conditioned stimuli.

Neural mechanism of extinction

A possible failure of extinction has been proposed to account for the persistence of intrusive traumatic memories in response to stimuli reminiscent of the trauma in individuals with PTSD.[158] Theoretically, when a conditioned fear stimulus is no longer associated with a painful or otherwise aversive outcome, the conditioned fear response that was elicited by the stimulus gradually disappears or extinguishes. Although extinction suppresses the signs of fear, it does not necessarily erase the original learning (eg the traumatic memories). In fact, extinction is thought to be an active process

involving the formation of new memories.[200,201] This new memory, therefore, masks or competes with the memory of conditioned fear.[202] The brain mechanisms underlying extinction have not been as extensively investigated as the brain mechanisms of fear acquisition. Nevertheless, important clues have been discovered. In particular, recent findings suggest that a similar plasticity in the amygdala that underlies conditioned fear also underlies extinction. Infusion of NMDA antagonist AP5 into the amygdala prevents extinction of fear-potentiated startle,[203] suggesting that a NMDA-dependent type of plasticity might be involved. Extinction could result from increases in synaptic efficacy of inhibitory neurons within the amygdala. For example, GABAergic neurons within the amygdala could be activated by excitatory amino acids.[204] Alternatively, because lesions of auditory,[205] visual,[198] and prefrontal cortex[206] interfere with extinction, it is possible that extinction involves the suppression of subcortical emotional memories by cortical inputs.

Failure to extinguish is not the only possible explanation for the maintenance of conditioned traumatic memories. Because extinction does not destroy the memory of the original association, the memory of conditioning offers the potential for re-emergence of conditioned responses. Bouton *et al* have provided examples of situations that lead to the reappearance of conditioned responses,[202] some of which (eg *reinstatement* and *renewal*) are relevant to PTSD. For example, reinstatement refers to the recovery of an extinguished response following the presentation of the unconditioned aversive event.[207] Reinstatement may explain the reactivation of combat-related PTSD in Israeli veterans following the 1982 war in Lebanon after having apparently fully recovered from the combat stress reaction of the 1967 Yom Kippur War.[208] Renewal is another important phenomenon which refers to the reappearance of an extinguished conditioned response in a context that is different from the extinction. Renewal emphasizes the role of contextual information in extinction. It suggests that conditioned stimuli have ambiguous meaning because they are signs of fear in some 'threatening' contexts, but not in other 'safe' contexts. It has been argued that conditioned fear inhibition mechanisms (eg extinction) are more fragile than fear conditioning mechanisms because they do not generalize across contexts and they tend to be forgotten with the passage of time.[209] This fragility might be found in PTSD. Following this argument, one can posit that individuals with PTSD do not adequately handle contextual stimuli and that the neural mechanisms of contextual fear might provide clues as to the nature of brain dysfunction in PTSD.

Contextual fear conditioning and the symptoms of increased arousal and generalized anxiety: role of the bed nucleus of the stria terminalis

Beside the phasic behavioral and physiological changes associated with intrusive symptoms, there are the more tonic symptoms of persistent increased sympathetic arousal such as sleep impairments, irritability, reduced concentration, hyper-vigilance and exaggerated startle responses (DSM-IV). This tonic dysregulation of arousal and vigilance has characteristics of generalized anxiety displayed in unsafe environments and may reflect a chronic perception of threat. As indicated above, several characteristics of behavioral indices of animals placed in an environment where they have previously been stressed (eg crouching, increased heart rate, enhanced startle) suggest that contextual fear conditioning may model some of the symptoms of increased arousal and generalized anxiety.[161] Thus, both individuals with PTSD and animals placed in a cage where they have previously received shocks experience their environment as unsafe and threatening.

Our understanding of the neurobiology of contextual fear has substantially increased in recent years. A great deal of evidence now suggests that separate mechanisms mediate conditioned fear to explicit cues and contextual fear conditioning.[210,211] In addition to being involved in conditioned fear to explicit stimuli, the amygdala is also involved in contextual fear conditioning. Lesions of the amygdala block the normal freezing behavior exhibited by rats that have been reintroduced into an experimental cage where fear conditioning took place.[162,211] However, lesions of the hippocampus also block contextual fear, but do not affect conditioned fear to an explicit cue.[210,211] The association between the hippocampus and contextual fear is consistent with the literature on the role of this structure in processing spatial and contextual cues. The neural plasticity underlying the acquisition, but not the expression, of contextual fear conditioning is dependent upon an endogenously-generated NMDA-dependent LTP.[212,213]

There is also evidence for a differential role of various neurotransmitters in conditioning to explicit and contextual cues. Consistent with the role of noradrenergic activity in selective attention, 6-hydroxydopamine lesions of the dorsal noradrenergic bundles which cause depletion of forebrain noradrenaline, impairs conditioned fear to explicit stimuli while enhancing contextual fear conditioning.[214] Loss of hippocampal acetylcholine following excitotoxic lesions of the medial septum also impairs fear conditioning to explicit cues, while enhancing contextual fear conditioning.[215] By contrast, forebrain depletion of 5HT produced by intracerebroventricular 5,7-dihydroxytryptamine impairs conditioning to contextual cues, but not to explicit cues.[216]

Recently, the BNST has been found to play a critical role in contextual fear conditioning. Despite some similarities between the amygdala and the BNST, these two structures appear to play different roles in conditioning processes. Placing rats in an environment where they have previously received shock increases baseline startle.[190,217] Lesions of the BNST block this effect, but do not block fear-potentiated startle to an explicit cue.[217] These results suggest that the BNST is

involved in conditioned fear to contextual cues, but not to explicit cues.

The BNST might also be implicated in another type of aversive learning, inhibitory avoidance. In this test, animals who enter one of two boxes are given strong shocks. When subsequently tested, they avoid entering the box where shocks were previously given. Many of the treatments of the amygdala which alter inhibitory avoidance are blocked by lesions of the stria terminalis,[218–221] which connects the amygdala to the BNST. The BNST may be important for inhibitory avoidance because this test has important contextual conditioning components. Further, treatments which facilitate NA transmission enhance the consolidation of inhibitory avoidance via activation of beta-adrenergic receptors in the amygdala.[222] However, such treatments do not affect the acquisition of fear-potentiated startle to an explicit cue.[223] These results suggest that although inhibitory avoidance appears to be modulated by the amygdala, the encoding of this type of aversive learning is ultimately stored outside the amygdala, perhaps in the BNST. Hence, facilitation of NA transmission in the amygdala via beta-adrenergic receptors might be especially important in contextual fear conditioning as opposed to explicit cue conditioning.

There is some evidence that individuals with PTSD exhibit abnormal contextual fear. Although an exaggerated startle response is one of the core symptoms of PTSD, there has been conflicting empirical evidence of elevated startle in PTSD.[224–228] We have repeatedly found normal baseline startle in Vietnam veterans in the absence of experimental stress,[229] but increased startle throughout experiments that involve stressful procedures.[55,230]

Recently, we have investigated startle in Vietnam veterans with PTSD in the absence of stress and one week later during a threat of shock experiment.[231,232] During the threat of shock experiment, startle was elicited in alternating threat and safe periods. Subjects were told that they could receive shocks only during the threat, but not during the safe periods. Startle was normal in the PTSD patients during the initial non-stressful testing procedure. However, startle was consistently and significantly larger in the PTSD, compared to the controls, throughout the threat of shock procedure, even though subjects were clearly told that shock could be delivered only when the threat signal was presented. By contrast, the magnitude of fear-potentiated startle to the explicit cue (ie the threat period) did not significantly differ between the controls and the PTSD patients. It is possible that the increase in baseline startle in the veterans with PTSD during the threat of shock experiment was analogous to contextual fear conditioning in rats. In humans, the conditioned aspects of this measure of anxiety are based not on actual conditioning experiments in the laboratory, but rather on general knowledge (gained through lifetime experience or vicarious conditioning) that an electric shock is painful. Because contextual fear is modulated by NA, the increased contextual fear in veterans with PTSD might be a reflection of the dysregulation of the NA system that characterizes these individuals. These results begin to explain how dysregulation of the NA system can lead to a chronic state of generalized anxiety. Of note, the BNST has some of the densest noradrenergic innervations of any area in the brain.[233]

Persistence of intrusive fear memories: the noradrenergic system, kindling, and spontaneous emotional memories

Intrusive traumatic memories that are initially activated by identifiable external stimuli can become 'spontaneous' with the passage of time. Several mechanisms could explain this effect. Arguably, such memories could be accounted for by reinstatement, whereby endogenous release of stress hormones during non-specific stress recreates the internal state experienced during the original trauma. This hypothesis is consistent with the finding that activation of noradrenergic neurons by infusion of the alpha-2 adrenergic antagonist yohimbine induces vivid traumatic memories.[53] Many studies in animals have indicated that alterations in the activity of the noradrenergic system can affect the consolidation and retrieval of emotional memories.[234–236] Memory retrieval correlates with epinephrine blood levels following training.[237] Injection of low doses of epinephrine immediately after training enhances retention,[238] an effect that is long-lasting.[235] The effects of epinephrine on emotional memory seem to be mediated by activation of beta-adrenergic receptors both centrally and peripherally.[17] The possible involvement of the noradrenergic system in the storage of traumatic memories in PTSD is further suggested by the recent finding in humans that propanolol, a beta-adrenergic receptor antagonist, impairs memory for an emotional story, but not for a neutral story.[239] This suggests that the neurobiological consequences of severe trauma (ie release of high levels of endogenous adrenaline) produce an overconsolidation of traumatic memories.[240] Such a process might explain the persistence of traumatic memories. Although this interpretation appears inconsistent with evidence indicating that administration of high doses of adrenaline can impair memory storage,[241] it should be noted that it is unknown whether high levels of endogenous adrenaline can impair memory consolidation.[239] In addition, if excessively high levels of endogenous adrenaline interfere with memory storage, such an effect could account for the amnesia and fragmented memory seen in some individuals with PTSD.[240]

Although an hyperactive noradrenergic system can explain the selective consolidation of traumatic memories and their subsequent retrieval in stressful contexts, it cannot in itself explain the presence of spontaneous intrusive traumatic recollections. Several characteristics of *kindling* suggest that such a process could help to understand the principles behind the neural mechanisms of spontaneous intrusive memories in PTSD.[160]

Originally described by Goddard *et al*,[242] kindling is

an intermittent stimulation of specific brain areas which produces no initial observable effects. With repeated stimulation, there is a progressive lowering of the threshold for afterdischarges in the amygdala with progressive spreading of these discharges to other brain areas. This results in marked electrophysiological and behavioral effects including the emergence of full-blown seizures. With sufficient repeated stimulation, seizures can occur in the absence of exogenous stimulation. Several pharmacological substances that are involved in the organism's response to stress can trigger kindled seizure, including GABA antagonists, endogenous opiates, and CRH.[243] One of the drawbacks of the kindling model is that the effects of kindling (ie the seizures) do not actually mimic PTSD symptoms. However, it might be conceptually useful to consider that just as seizures are the consequences of paroxysmal discharges of motor circuits, flashbacks are paroxysmal discharges of memory circuits.[160] Repeated conditioned activation of traumatic memories may produce a kindling-like process which eventually leads to intrusive recollections in the absence of environmental triggers. Such a process could constitute a positive loop, whereby conditioned memories lead to kindling, which increases the likelihood of spontaneous recollections, which enhances memory traces, which further strengthen conditioning.

Sensitization as a model for the delayed hyper-responsivity to non-specific stressors

The behavioral hyper-responsivity of individuals with PTSD is not restricted to trauma-related stimuli. PTSD patients exhibit exaggerated startle, bursts of anger, and are sensitive to various psychosocial stressors.[208,244] In addition, PTSD can have a delayed onset with symptoms increasing over time. Neurological sensitization has been proposed as a model for such characteristics.[156–160,245] Some of the features that make sensitization a valuable model for PTSD are: (1) single or repeated exposure to physical stimuli or pharmacological agents sensitize the organism to subsequent stressors. Similarly PTSD can result from different types of catastrophic events and prior trauma enhances the likelihood of developing PTSD;[246,247] (2) the response of the sensitized organism can be behavioral, neurophysiologic, or pharmacologic and can occur to stressors that are of the same or different nature (cross-sensitization) relative to the original stressor. Some reports suggest that in PTSD the response to subsequent non-specific stressors is increased and can affect multiple neurobiological systems; (3) sensitization can be dose-related. The relationship between the severity of the trauma and the risk of developing PTSD has been well documented;[2,248] (4) sensitization has delayed effects which grow stronger with the passage of time. Likewise, PTSD symptoms can be delayed for months or even years and become more pronounced with the passage of time.[159] Behavioral sensitization can be examined using the startle reflex. In the rat, a single shock can elevate startle for a relatively long period of time.[249] The facilitation is not immediate but appears with a delay that increases with an increase in the intensity, number of shocks, and number of shock sessions administered.[249,250] The shock sensitization of startle might be time-limited. Servatius *et al*[250] reported that startle was facilitated 7 days, but not 10 days after a one-session shock exposure. These results suggest that the PTSD symptom of exaggerated startle might reflect a sensitization process during the initial period following the trauma. Morgan *et al*[251] reported increases in baseline startle among Desert Storm veterans with PTSD approximately 3 years after the initial trauma. However, Grillon *et al*[229] did not find exaggerated baseline startle in Vietnam veterans with PTSD. It is possible that startle is no longer sensitized by the initial trauma after 30 years; (5) like PTSD symptoms, sensitization can be context-dependent or context-independent. Sensitization is context-dependent following exposure to a single stressor, but context-independent with repeated stressors;[160] (6) finally, sensitization is subject to genetic factors, developmental phase, and gender,[160] each of which seems to play a role in PTSD.[252]

Sensitization involves multiple neurobiological systems, especially the mesocorticolimbic dopamine system. The noradrenergic and serotonic systems, as well as CRH and corticosterone are also involved, but their specific role is unclear. Context-dependent and context-independent sensitization are mediated by different neural systems. In particular the amygdala is required for context-dependent, but not for context-independent sensitization.[160] In addition, sensitization can be separated into two separate processes that have different neural substrates, that is, initiation and expression. Initiation following exposure to stress leads to a permanent alteration in dopamine responsiveness. Initiation appears to take place in the ventral tegmental area (VTA). Microinjections of amphetamine in the VTA, but not in the nucleus accumbens (NAC), produce sensitization.[253,254] Prevention of somatodentritic dopamine release in the VTA by GABA agonist or NMDA antagonist blocks behavioral sensitization.[255] Perhaps explaining the delay in onset of certain core symptoms following a traumatic experience in PTSD, the expression of sensitization requires time before permanent neural changes permit enhanced DA responses. Initiation has been mostly examined in the mesoaccumbens dopamine projections where sensitization has been shown to be associated with enhanced striatal and NAC dopamine release.[256] This increase in function is due to alterations in the effectiveness of dopamine cells firing in the VTA or to an increased ratio of release to reuptake of dopamine in the NAC.[124] It has been suggested that sensitization results in permanent changes in terminal fields.[257,258]

Conclusion: PTSD as a multiple neurobiological systems disease

Animal studies indicate that several brain structures, and multiple neurotransmitter and hormonal systems are involved in the reaction to acute trauma. During

exposure to trauma, the reaction of the organism is initially adaptive and protective. Activation of the LC-NA and DA systems increase autonomic arousal and enhance vigilance. Cortisol hyper-secretion facilitates tissue repair and metabolic activation necessary for sustained physical demands. Release of endogenous opioids contributes to the reduced sensitivity to pain that, for example, soldiers might experience on the battlefield, enhancing their chance of survival in the face of danger. The organism is also involved in cognitive activity to deal with the impending danger and to prepare for future encounters with stressors. Thus, release of prefrontal DA is associated with attempts to cope with the present situation, whereas activation of norepinephrine facilitates the encoding of emotional memories that might subserve adaptive responses to future stressors. Such responses are also largely influenced by the amygdala. The amygdala is critically involved in forming associations between specific stimuli and aversive events. Retrieval of these associations is also dependent upon the integrity of the amygdala. Associations between more complex environmental stimuli and aversive events might require the involvement of additional structures such as the hippocampus and the BNST.

Although these multiple neurobiological responses to stress are usually beneficial, they can cause maladaptive neural changes such as those that seem to underlie some of the symptoms of PTSD. Several neurobiological (catecholamine, CRH) and behavioral systems (startle) may become sensitized after exposure to trauma. Sensitization processes may be responsible for increased sensitivity to subsequent stress in individuals with PTSD.[208,244,246,247] The more tonic symptoms of hypervigilance and increased arousal in PTSD are similar to the behavioral symptoms of contextual fear in animals[161] and may reflect dysregulation of NA systems acting via the BNST. Traumatic memories may be relatively indelible in individuals with PTSD. These memories can be reactivated by innocuous stimuli that are reminders of the trauma. However, they can also appear spontaneously taking the form of flashbacks or nightmares. The maintenance of these fear memories seems to be promoted by interactions between several processes including over-consolidation of fear memories at the time of the trauma (possibly mediated by activation of beta-adrenergic receptors), conditioning and kindling. The persistence of the conditioned emotional response to trauma-related stimuli suggests a failure of extinction in PTSD[158] which could be indicative of damages to the medial prefrontal cortex.[206] Alternatively, the finding that a subcortical thalamo-amygdala pathway can mediate conditioned fear[168,170] raises the possibility that trauma-related stimuli produce an automatic retrieval of conditioned emotional memories in PTSD. The repeated conditioned activation of traumatic memories may produce a kindling-like process which ultimately results in spontaneous intrusive memories. In turn, these memories can strengthen the representation in memory of the conditioned traumatic memories, preventing extinction.

Several of the hypotheses advanced in this review could help guide future clinical and preclinical research. Clinical studies should examine the nature of conditioning deficits in individuals with PTSD. It is possible to use the backward masking technique developed by Ohman[167] to examine whether conditioned emotional responses to trauma-related stimuli are automatically mediated. Other conditioning procedures can be utilized to assess whether patients with PTSD are unable to adequately extinguish conditioned responses or unable to acquire conditioned inhibitors. Finally, clinical studies should attempt to better understand the impact of the experimental context on patients with PTSD. Conditioned response and sensitization processes might be affected by contextual cues. Preclinical studies should attempt to elucidate the psychopharmacology and neurobiology of extinction, conditioning inhibition, reinstatement, and renewal. They should also examine the impact of exposure to traumatic events on these processes. This might lead to a more targeted approach to the psychotherapy and pharmacotherapy of PTSD.

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