Neurobiology of Posttraumatic Stress Disorder

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ABSTRACT

Exposure to a traumatic event is required for the diagnosis of posttraumatic stress disorder (PTSD). The symptoms of PTSD are believed to reflect stress-induced changes in neurobiological systems and/or an inadequate adaptation of neurobiological systems to exposure to severe stressors. More recently, there have been attempts to link the identified neurobiological changes to the specific features that constitute PTSD, such as altered mechanisms of learning and extinction, sensitization to stress, and arousal. Furthermore, there have been efforts to understand whether certain neurobiological changes in PTSD reflect preexisting vulnerability factors rather than consequences of trauma exposure or correlates of PTSD. Genetic variability, sex differences, and developmental exposures to stress influence neurobiological systems and moderate PTSD risk. On the basis of these findings, important hypotheses for developing novel strategies to identify subjects at risk, promote resilience, and devise targets for the prevention or treatment of PTSD can be derived.

Needs Assessment

This article provides an update on the state of the research regarding the neurobiology of posttraumatic stress disorder (PTSD). There have been several important recent developments in the field, including linking neurobiological changes to specific features of PTSD, identifying neurobiological markers of PTSD risk, deriving new intervention strategies based on neurobiological findings, and providing insight into gene-environment interactions in determining PTSD risk versus resilience. Current needs and open issues are discussed based on the literature overview.

Learning Objectives

At the end of this activity, the participant should be able to:
- Summarize current neurobiological findings in PTSD
- Link neurobiological findings to specific features of PTSD
- Explain the potential mechanism of a neurobiological marker of PTSD risk
- Give an example of a novel treatment strategy derived from neurobiological findings in PTSD

Target Audience: Psychiatrists

INTRODUCTION

In addition to the large numbers of soldiers deployed to combat around the world, civilians in modern societies face surprisingly high rates of exposure to traumatic stressors, including war, terrorism,
childhood abuse, rape, assault, accidents, and a wide variety of other severe psychological traumas. Experience of any such trauma may be associated with potentially lasting effects on the individual. A traumatic event is defined as an experience that is threatening to oneself or a close person, accompanied by intense fear, horror, or helplessness. Exposure to a traumatic event, defined as this, is required for the diagnosis of posttraumatic stress disorder (PTSD), making PTSD a psychiatric disorder that by definition is related to and occurs as a consequence of a stressful or traumatic event. Although initial theorists proposed that PTSD represents a normative response to exposure to extreme stressors, it soon became evident that only a minority of individuals who experience a traumatic event will develop the disorder. Thus, while most individuals are able to cope with the stressor and maintain or regain homeostasis, a small but significant minority of persons fails to recover and exhibits prolonged and abnormal behavioral and physiological responses to the traumatic experience, as manifested in the symptoms of PTSD.

The symptoms of PTSD are believed to reflect stress-induced changes in neurobiological systems and/or an inadequate adaptation of neurobiological systems to exposure to severe stressors. Consequently, much research has been focused on elucidating alterations in stress-regulating neurobiological systems in patients with PTSD. Neurobiological systems that have been implicated in the pathophysiology of PTSD include the hypothalamic-pituitary-adrenal (HPA) axis, as well as various neurotransmitters and neuropeptides that comprise a network of brain regions that regulate fear and stress responses, including the prefrontal cortex, hippocampus, amygdala, and brainstem nuclei. More recently, there have been attempts to link the identified neurobiological changes to the specific features that constitute PTSD, such as altered mechanisms of learning and extinction, sensitization to stress, and arousal. Furthermore, there have been efforts to understand whether certain neurobiological changes in PTSD reflect preexisting vulnerability factors rather than consequences of trauma exposure or correlates of PTSD. Accordingly, there is increasing consideration of factors that affect outcome after trauma. Genetic variability, sex differences, and developmental exposures to stress influence neurobiological systems and moderate responses to trauma likely contributing to individual vulnerability versus resilience against developing PTSD. On the basis of such neurobiological findings, important hypotheses for developing novel strategies to identify subjects at risk, promote resilience, and devise targets for the prevention or treatment of PTSD can be derived. In the following, we summarize core neurobiological findings in PTSD, describe current developments, discuss unresolved issues in the field, and suggest strategies for future research.

**NEUROBIOLOGY OF PTSD: STATE OF SCIENCE**

**Hypothalamic-Pituitary-Adrenal Axis**

The HPA axis, an organism’s major neuroendocrine stress response system, has been closely scrutinized in patients with PTSD. Upon exposure to stress, neurons in the hypothalamic paraventricular nucleus (PVN) secrete corticotropin-releasing factor (CRF) from the median eminence into the hypothalamo-hypophyseal portal circulation, in which the peptide is transported to the anterior pituitary where it stimulates the production and release of adrenocorticotropic hormone (ACTH). ACTH, in turn, stimulates the release of glucocorticoids from the adrenal cortex. Glucocorticoids exert effects on metabolism, immune function, and the brain, adjusting physiological functions and behavior to the stressor. Several brain pathways modulate HPA axis activity. The hippocampus and prefrontal cortex (PFC) inhibit the HPA axis, whereas the amygdala and monoaminergic input from the brainstem stimulate the activity of PVN CRF neurons. Glucocorticoids exert negative feedback control of the HPA axis by regulating hippocampal and hypothalamic PVN neurons, as well as ACTH secretion, through binding to glucocorticoid receptors (GR) and mineralocorticoid receptors. Sustained glucocorticoid exposure has adverse effects on hippocampal neurons, including reduction in dendritic branching, loss of dendritic spines, and impairment of neurogenesis, though the latter is controversial.

Although acute stressors activate the HPA axis, initial studies in combat veterans with PTSD revealed paradoxical decreases in cortisol concentrations, measured in urine or blood, compared to healthy controls and other diagnostic groups. This counterintuitive finding has been replicated in Holocaust survivors, refugees, and abused persons with PTSD, although findings are not uniformly consistent across studies. Differences in type and timing of the psychological trauma, symptom patterns, comorbidity, personality, and genetic dispositions, among other factors, may contribute to this inconsistency. Studies using low-dose dexamethasone...
suppression and metyrapone testing, two pharmacologic agents that alter the availability of stress hormones exerting feedback on the HPA axis, revealed that hypocortisolism in PTSD occurs in the context of increased sensitivity of the HPA axis to negative glucocorticoid feedback.6 Findings of increased GR binding and function support the assumption of increased negative feedback sensitivity of the HPA axis in PTSD.6 At the central nervous system (CNS) level, marked and sustained increases of CRF concentrations have been measured in the cerebrospinal fluid (CSF) of patients with PTSD.8,9 Evidence of blunted ACTH responses to CRF stimulation in PTSD supports the hypothesis that PTSD involves elevated levels of hypothalamic CRF activity and corresponding down-regulating of pituitary CRF receptors.6 In addition, reduced volume of the hippocampus, the major brain region inhibiting the HPA axis, is a cardinal feature of PTSD.10 Taken together, the specific constellation of neuroendocrine findings in PTSD reflects sensitization of the HPA axis to exposure to stressors.6 This neuroendocrine pattern distinguishes PTSD from major depression, a frequently comorbid but distinct disorder.6

Interestingly, prospective studies have shown that low cortisol levels at the time of exposure to psychological trauma predict the development of PTSD,11,12 suggesting that hypocortisolism might be a preexisting risk factor that is associated with maladaptive stress responses such as PTSD. Consequently, administration of hydrocortisone directly after exposure to psychological trauma has been shown to effectively prevent PTSD in humans in several studies.13,14 In addition, it was recently demonstrated that hydrocortisone treatment, simulating normal circadian cortisol rhythm, is effective in the treatment of PTSD.15 Indeed, decreased availability of cortisol, and hence lack of regulatory effects in the CNS, may have permissive effects towards the sustained activation of neural systems involved in stress reactivity and fear processing, including the CRF and noradrenergic (NE) systems.6,16 Glucocorticoids further interfere with the retrieval of traumatic memories and thereby may prevent or reduce symptoms of PTSD.14,17

NEUROTRANSMITTERS AND NEUROPEPTIDES

Corticotropin-Releasing Factor

As noted above, increased CSF concentrations of CRF have been measured in patients with PTSD, both in single lumbar puncture and serial sampling studies.8,9 Sustained elevations in CRF concentrations were observed despite comparably low cortisol concentrations, and the latter were negatively correlated with PTSD symptoms.8 Although the precise neuroanatomical source of CRF in CSF remains obscure, CSF CRF concentrations are believed to reflect CRF activity at extra-hypothalamic sites. In view of the CNS effects of CRF, as described in various animal models, increased CNS CRF activity may promote certain of the cardinal features of PTSD, i.e., conditioned fear responses, increased startle reactivity, sensitization to exposure to stressors, and hyperarousal. These results suggest that CRF1 receptor antagonists may well represent a novel therapeutic approach for the treatment of PTSD.

Catecholamines: Norepinephrine and Dopamine

The catecholamines comprise a family of neurotransmitters derived from the amino acid tyrosine. The rate-limiting factor in the synthesis of catecholamines is tyrosine hydroxylase, an enzyme that converts tyrosine into DOPA, which subsequently is converted into dopamine (DA) by the action of DOPA decarboxylase. In noradrenergic neurons, dopamine β hydroxylase converts DA into NE. NE is one of the principal mediators of the CNS and autonomic stress responses. The majority of CNS NE is derived from neurons of the LC that project to various brain regions involved in the stress response, including the PFC, amygdala, hippocampus, hypothalamus, periaqueductal grey, and thalamus. There is evidence for a feedforward circuit connecting the amygdala and the hypothalamus with the LC, in which CRF and NE interact to increase fear conditioning and encoding of emotional memories, enhance arousal and vigilance, and integrate endocrine and autonomic responses to stress. Glucocorticoids inhibit this cascade.19 In the periphery, sympathoadrenal activation during exposure to stressors results in the release of NE and epinephrine from the adrenal medulla, increased release of NE from sympathetic nerve endings, and changes in blood flow to a variety of organs, reflecting an alarm reaction that mobilizes the body to allow for optimal coping. The effects of NE are mediated via postsynaptic α1, β1 and β2 receptors, whereas another NE-activated receptor, the α2 receptor, serves as a presynaptic autoreceptor inhibiting NE release. Because of its multiple roles in regulating arousal and autonomic stress responses, as well as promoting the encoding of emotional memories, NE has been a central candi-
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open label trials, though this did not prevent the development of PTSD, it
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tion, and other psychophysiological measures. Accordingly, increased urinary excretion of NE and epinephrine, and their metabolites, has been documented in combat veterans, abused women, and children with PTSD. In addition, patients with PTSD exhibit increased heart rate, blood pressure, and NE responses to challenge, such as traumatic reminders. Decreased platelet \( \alpha_2 \) receptor binding further suggests NE hyperactivity in PTSD.\(^{20,21}\) There is also evidence for a role of altered CNS NE function in PTSD. Administration of the \( \alpha_2 \) receptor antagonist yohimbine, which increases NE release, induces symptoms of flashbacks and increased autonomic responses in patients with PTSD.\(^{21}\) Serial sampling revealed sustained increases in CSF NE concentrations and increased CSF NE responses to psychologi-

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sure to psychological trauma has been reported to reduce PTSD symptom severity and reactivity to reminders of the traumatic event.\(^{26}\) Although this did not prevent the development of PTSD, it may have blocked traumatic memory consolidation,\(^{27}\) and therefore may reduce the severity or chronicity of PTSD. Various anti-adrenergic agents have been tested for their therapeutic efficiency in the treatment of PTSD in open label trials, though there is a paucity of controlled trials.\(^{21}\)

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ating risk for PTSD.

**Serotonin**

Serotonin, also known as 5-hydroxytryptamine (5-HT), is a monoamine neurotransmitter synthe-
sized from the amino acid tryptophan. Serotonergic neurons originate in the dorsal and medial nuclei raphé in the brainstem and project to multiple fore-

increased startle, and encoded fear memories.\(^{21}\)

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**GABA/Benzodiazepine Receptor System**

Gamma-aminobutyric acid (GABA) is the princi-
pal inhibitory neurotransmitter in the CNS. GABA
exerts anxiolytic effects and dampens behavioral and physiological responses to stressors, in part by
Glutamate/NMDA Receptor System

Glutamate is the primary excitatory neurotransmitter in the CNS. Exposure to stressors and the release or administration of glucocorticoids increase glutamate release in the brain. Glutamate binds to several so-called excitatory aminoacid receptors, one of which is the \( \text{N}-\text{methyl} \ \text{\( \alpha \)-aspartate (NMDA)} \) receptor. The glutamate/NMDA receptor system has been implicated in synaptic plasticity, learning, and memory, including the well studied phenomenon of longterm potentiation (LTP), the extended excitation of neural circuits, leading to long-lasting enhancement in communication between neurons. This process is believed in part to underlie the process of conditioning and memory consolidation. LTP plausibly contributes to consolidation of trauma memories in PTSD. Of note, the partial NMDA-receptor antagonist D-cycloserine (DCS) has been shown to improve the extinction of fear in rodents and in phobic patients undergoing exposure therapy. Whether or not DCS is effective in enhancing the outcome of exposure therapy in PTSD remains to be studied.\(^\text{34}\) In addition to its role in learning and memory, overexposure to glutamate is associated with excitotoxicity, and plausibly could contribute to a loss of neurons in the hippocampus and PFC in PTSD. Of note, elevated glucocorticoids increase the expression and/or sensitivity of NMDA receptors, which may sensitize the brain to excitotoxic insults.

Neuropeptide Y

Neuropeptide Y (NPY) is a neuropeptide with anxiolytic and stress-buffering properties. NPY has been shown to inhibit CRF/NE circuits involved in stress and fear responses and reduces the release of NE from sympathetic nerve cells. A relative lack of NPY may promote maladaptive stress responses and contribute to the development of PTSD. Indeed, patients with PTSD have been reported to exhibit decreased plasma NPY concentrations and blunted NPY responses to yohimbine challenge compared to controls, suggesting that decreased NPY activity may contribute to noradrenergic hyperactivity in PTSD.\(^\text{35}\) However, it has been suggested that NPY may be involved in promoting recovery from or resilience to PTSD because combat veterans without PTSD have been demonstrated to exhibit elevated plasma NPY levels compared to veterans with PTSD.\(^\text{36}\)

Endogenous Opioids

Endogenous opioids, such as the endorphins or enkephalins, are endogenous neuropeptides that act upon opiate receptors also activated by synthetic or naturally occurring opiates (such as morphine or heroin). Alterations in endogenous opioids have been postulated to be involved in symptoms of numbing, stress-induced analgesia, and dissociation in PTSD. Endogenous opioids further exert inhibitory influences on the HPA axis. Naloxone, a \( \mu \) opiate receptor antagonist, increases HPA axis activity by blocking an inhibitory opioidergic influence on hypothalamic CRF secretion, and patients with PTSD have been reported to exhibit an exaggerated HPA axis response to naloxone. Interestingly, naloxone also has been shown to reverse the analgesia of PTSD patients after exposure to traumatic reminders. Finally, PTSD patients exhibit increased CSF \( \beta \)-endorphin levels, suggesting increased activation of the endogenous opioid system. Interestingly, the opiate receptor antagonist, naltrexone, has been reported to be effective in treating symptoms of dissociation and flashbacks in traumatized patients.\(^\text{21,37}\) Administration of morphine has been shown to prevent the development of PTSD.\(^\text{38}\)

STRUCTURAL AND FUNCTIONAL NEUROANATOMY

The neurotransmitters discussed above serve as the chemical messengers of a connected network of brain regions that have been implicated in the development of PTSD. Changes in brain structure and function have been identified in patients with PTSD.
using brain imaging methods. Brain regions that are altered in patients with PTSD include the hippocampus, amygdala, and prefrontal cortical regions, including anterior cingulate and orbitofrontal cortex. These brain regions interact and form a connected neurocircuit that mediates adaptation to stress and fear conditioning, and changes in this circuit are proposed to be directly linked to the development of PTSD.

**Hippocampus**

The most reproducible finding in structural imaging studies of PTSD is reduced volume of the hippocampus. The hippocampus is implicated in the control of stress responses, declarative memory and contextual aspects of fear conditioning, and is known as one of the most plastic regions in the brain. As noted above, prolonged exposure to stress and high glucocorticoid levels damages the hippocampus, leading to reduction in dendritic branching, loss of dendritic spines, and impairment of neurogenesis. Initial magnetic resonance imaging studies demonstrated smaller hippocampal volumes in Vietnam veterans with PTSD and patients with abuse-related PTSD compared to controls. Small hippocampal volumes were associated with the severity of trauma and memory impairments in these studies. These findings were generally replicated in subsequent studies. Studies using proton magnetic resonance spectroscopy (MRS) observed reduced levels of N-acetyl aspartate (NAA), a marker of neuronal integrity, in the hippocampus of adult patients with PTSD. Of note, NAA reductions were correlated with serum cortisol concentrations. Interestingly, reduced hippocampal volume was not observed in children with PTSD. Hippocampal volume reduction in PTSD may reflect toxic effects over time of repeatedly increased glucocorticoid exposure or increased glucocorticoid sensitivity, though recent evidence also suggests that a small hippocampus might represent a pre-existing vulnerability factor for developing PTSD. Moreover, our group reported that in patients with major depression, early life trauma in the form of childhood abuse is associated with reduced hippocampal volume. Indeed, hippocampal deficits may promote activation of and failure to shut down stress responses, and may contribute to impaired extinction of conditioned fear as well as deficits in discriminating between safe and unsafe contexts. Studies using functional neuroimaging have further revealed that PTSD patients exhibit deficits in hippocampal activation during a verbal declarative memory task. Both hippocampal atrophy and functional deficits reverse after successful treatment with SSRIs, which have been demonstrated to increase neurotrophic factors and neurogenesis in preclinical studies.

**Amygdala**

In addition to the hippocampus, other brain structures implicated in a neural circuitry of stress include the amygdala and the prefrontal cortex. The amygdala is a critical limbic structure involved in emotional processing and in the acquisition of fear responses. The amygdala is connected to both cortical and subcortical regions. The basolateral complex is innervated by neocortical and subcortical sensory regions and sends information to the central nucleus of the amygdala. The central nucleus projects to the midbrain and brainstem nuclei to coordinate rapid autonomic, endocrine, and behavioral responses to danger. The central nucleus also receives visceral information from brainstem regions. Connections between the amygdala and the hippocampus are implicated in context conditioning. Connections between the PFC and the amygdala modulate stress responsiveness and mediate extinction of fear memory, inasmuch as the PFC exerts inhibitory control over the amygdala. The functional role of the amygdala in mediating both stress responses and emotional learning suggests that changes in this region and its connected circuitry may be implicated in the pathophysiology of PTSD. Although there is no clear evidence for structural alterations of the amygdala in PTSD, functional imaging studies have revealed hyperresponsivity of the amygdala in PTSD during the presentation of traumatic scripts, cues, and other reminders. PTSD patients further show increased amygdala responses to general emotional stimuli that are not associated with the trauma, such as emotional faces. Of note, the amygdala also seems to be sensitized to subliminally presented threatening cues in PTSD. Increased amygdala activation has also been reported for PTSD patients during fear acquisition in a conditioning experiment. Given that increased amygdala reactivity has been linked to genetic traits, which moderate risk for PTSD, increased amygdala reactivity may represent a biological risk factor for the development of PTSD.

**Prefrontal Cortex**

The medial prefrontal cortex (mPFC) comprises the anterior cingulate cortex (ACC), subcallosal
cortex, and the medial frontal gyrus. The mPFC is connected with the amygdala, where it exerts inhibitory control over stress responses and emotional reactivity. The mPFC further mediates extinction of conditioned fear through active inhibition of acquired fear responses. Patients with PTSD exhibit decreased volumes of the frontal cortex, including reduced volumes of the ACC. The reduction in ACC volume was correlated with PTSD symptom severity in some of these studies. Altered shape of the ACC and decreased NAA concentrations in the ACC have also been reported in PTSD patients. A recent twin study suggests that volume loss in the ACC is an acquired correlate of having PTSD, rather than a preexisting risk factor. Functional imaging studies have found decreased activation of the mPFC in PTSD patients in response to stimuli, such as traumatic scripts, combat pictures and sounds, trauma unrelated negative narratives, fearful faces, emotional Stroop, and others, though there are also discordant findings. Reduced activation of the mPFC was associated with PTSD symptom severity in several of these studies and successful SSRI treatment restored mPFC activation patterns. Of note, in the above cited conditioning experiment, extinction of conditioned fear was associated with decreased activation of the ACC, providing a biological basis for imprinted traumatic memories in PTSD. Given the connectivity between the amygdala and mPFC, interactions in activation patterns between these regions have been reported in PTSD, though the direction of the relationship is inconsistent across studies.

SUMMARY OF NEUROBIOLOGICAL FINDINGS AND CURRENT DEVELOPMENTS

In summary, core features of PTSD include low basal cortisol secretion and enhanced negative feedback control of the HPA axis that occurs in the context of increased autonomic responsiveness as well as increased CNS CRF and noradrenergic activity. Additional neurochemical changes include alterations in serotonergic, GABA-ergic, glutamatergic, NPY, and opioid systems. These neurotransmitter systems comprise a connected network of brain regions that is involved in the regulation and integration of stress and fear responses. A hallmark feature of PTSD is reduced volume of the hippocampus. Other brain changes involved in PTSD include exaggerated amygdala responsiveness and impaired mPFC function.

Linking Neurobiological Findings with Features of PTSD

Neurotransmitter changes observed in PTSD patients likely reflect sensitization of stress-mediating systems and/or decreased ability to restrain stress responses in order to regain homeostasis. A relative lack of cortisol at the time of the trauma may facilitate the activation of the central CRF-NE cascade, potentially resulting in enhanced and prolonged stress responses. Lack of regulatory effects of GABA, serotonin, and NPY may further accentuate stress responsiveness. In addition to mediating stress responses, several of the altered neurochemical systems are critically involved in processes of learning and extinction, thereby impacting conditioned fear responses and the consolidation or retrieval of traumatic memories. Norepinephrine enhances the encoding of fear memories. Glucocorticoids block the retrieval of emotional memories. Thus, the constellation of elevated noradrenergic activity and relative hypocortisolism may lead to enhanced encoding of traumatic memories and lack of inhibition of memory retrieval, which could plausibly underlie intrusive memories in PTSD. The glutamate/NMDA receptor system mediates LTP and may further promote conditioning and consolidation of traumatic memories.

These neurotransmitter systems represent a network of brain regions, including the hippocampus, amygdala, and mPFC that regulate and integrate stress and fear responses. An impaired hippocampus in PTSD patients may contribute to increased neuroendocrine stress reactivity. In turn, increased cortisol responses to stress, together with increased glucocorticoid receptor sensitivity, may further promote hippocampal damage. Moreover, hippocampal damage may underlie some of the cognitive symptoms of PTSD, such as declarative memory deficits. Finally, because the hippocampus is critical for context conditioning, a damaged hippocampus may facilitate generalization of learned fear to other contexts and may impair the ability to discriminate between safe and unsafe contexts, thereby promoting the development of PTSD. Exaggerated amygdala responses, as seen in patients with PTSD, promote the activation of stress responses and acquisition of fear associations. Impaired prefrontal cortical function may underlie deficits in suppressing stress responses and fear associations and interferes with extinction. These hypotheses...
have yet to be fully tested and integrated in a neurocircuitry model of PTSD.

**Are Neurobiological Changes Preexisting Risk Factors of PTSD?**

A number of studies have raised the important question of whether the identified neurobiological changes in PTSD patients might, in fact, represent markers of neural risk to develop PTSD upon exposure to extreme stress, rather than markers of PTSD itself. For example, low cortisol levels and elevated heart rates at the time of a trauma predict subsequent development of PTSD. Therefore, hypocortisolism might represent a preexisting risk factor that promotes the manifestation of PTSD. As noted above, low cortisol concentrations may disinhibit CRF/NE neurocircuits and thereby promote autonomic stress responses, as well as fear conditioning and traumatic memory consolidation. Similarly, the reduced size of the hippocampus in PTSD has been a “chicken-or-egg” question for many years. There was considerable debate on whether this brain region shrinks as a result of the trauma exposure or due to the presence of PTSD itself, or whether a small hippocampus is a risk factor for the development of PTSD. Studies in twins discordant for trauma exposure provide an excellent opportunity to discern the contributions of predisposition, trauma exposure, and PTSD to neurobiological findings in PTSD. Gilbertson and colleagues studied 40 pairs of monozygotic twins, including Vietnam veterans who were exposed to combat trauma and their co-twins who did not go to Vietnam, and measured the size of the hippocampus in all the twins. As expected, among Vietnam veterans, the hippocampus was smaller in those who had PTSD as compared to those who did not develop the disorder. However, this brain region was also smaller in the co-twins of the men with PTSD. This suggests that a smaller hippocampus is a preexisting, potentially genetic, vulnerability factor that predisposes a person to PTSD, as well as other trauma spectrum disorders, after the experience of stress or trauma. In contrast, more recent results from the same group suggest that grey matter loss in the ACC is an acquired feature that occurs as a result of PTSD.

**Deriving New Strategies for the Prevention and Treatment of PTSD Based on Neurobiological Findings**

New strategies for the prevention and treatment of PTSD are currently being tested that directly target the above-described neurobiological mechanisms that appear to be implicated in the development of PTSD. Administration of hydrocortisone shortly after a traumatic experience has been reported to be effective in preventing the development of PTSD. In addition, hydrocortisone treatment simulating a normal circadian cortisol rhythm appears to be beneficial in the treatment of PTSD. Glucocorticoid substitution is hypothesized to exert inhibitory effects on sustained stress responses and blocks traumatic memory retrieval. Similarly, because NE promotes encoding of traumatic memories, administration of the centrally acting β adrenergic antagonist propranolol after exposure to psychological trauma has been tested for its potential to prevent the development of PTSD. Although propranolol did not prevent the development of PTSD, this intervention reduced symptom severity and reactivity to reminders of the traumatic event, potentially reflecting blockade of traumatic memories, administration of the centrally acting β adrenergic antagonist propranolol after exposure to psychological trauma has been tested for its potential to prevent the development of PTSD. Not all individuals who undergo a trauma develop PTSD. Why some individuals develop PTSD following trauma while others do not is an important unexplored area. Moreover, it is equally unclear why some patients develop PTSD after trauma exposure, whereas others develop depression or another Axis I disorder. In most cases, the manifestation of a trauma spectrum disorder will be influenced by a complex interplay of preexisting vulnerabilities, including genetic disposition, personality styles, and prior experiences, as well as psychological and situational factors at the time of and in the aftermath of the trauma. Because the majority of trauma survivors will not develop a disorder, it is crucial to identify vulnerability and resilience factors. We discuss below the role of genetic factors, sex differences, and early developmental stress experiences in moderating risk for developing PTSD in response to trauma.
GENETIC RISK FACTORS OF PTSD

Studies on the genetics of PTSD, like those of other complex disorders that are characterized by both genetic and environmental risk factors, have been hampered by a variety of factors, including genetic heterogeneity (e.g., a similar phenotype likely develops from different risk genotypes) and incomplete penetrance of the phenotype (e.g., a person with a genetic risk for PTSD, who is not exposed to trauma, will not develop PTSD). Despite these difficulties, there is increasing evidence that risk for PTSD is influenced by genetic factors. Evidence from family and twin studies has long suggested a heritable contribution in the development of PTSD. In addition, there is evidence for heritable contributions to some of the neurobiological endophenotypes of PTSD, such as decreased hippocampal volume\(^71\) or exaggerated amygdala reactivity.\(^57\) Although it is beyond the scope of this chapter to comprehensively discuss the genetics of PTSD, it should be noted that there is an exciting literature emerging on genetic variations in neurobiological systems that determine responses to trauma and, consequently, risk versus resilience to develop PTSD.\(^72\) For example, one study has linked a polymorphism in the DA transporter gene to PTSD risk. An excess of the SLC6A3 9 repeat allele was present in those with PTSD. This finding suggests that genetically determined changes in DA reactivity may contribute to PTSD among trauma survivors.\(^73\) Several studies have investigated polymorphisms in the D2 receptor to PTSD risk, though results have been inconsistent.\(^72\) Finally, there is considerable evidence linking a low expression variant of the serotonin transporter, the so-called “s” allele of the serotonin-transporter-linked polymorphic region (5-HTTLPR), to stress responsiveness and risk for developing depression in relation to life stress. The same variant has now been associated with risk for developing PTSD, particularly in the presence of low social support.\(^58\) This finding is intriguing because the same polymorphism is

FIGURE.
FKBP5 Polymorphisms Moderate PTSD Risk After Child Abuse (Panels A and B) as well as Association between PTSD and Dexamethasone Suppression (Panels C and D)\(^75\)

![Graph A](image1)

![Graph B](image2)

![Graph C](image3)

![Graph D](image4)

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associated with increased amygdala reactivity as well as the trait of neuroticism, the latter another risk factor for PTSD.

Particularly exciting are recent results that genetic variation of the glucocorticoid receptor co-chaperone, FKB5, moderates risk to develop PTSD in relation to childhood abuse. The study tested interactions of child abuse, adulthood trauma, and genetic polymorphisms in the FKB5 gene in 900 non-psychiatric clinic patients. Childhood abuse and adulthood trauma each predicted PTSD symptoms. FKB5 polymorphisms significantly interacted with child abuse to predict adult PTSD symptoms. FKB5 genotype was further linked to enhanced glucocorticoid receptor sensitivity, as reflected by dexamethasone hypersuppression, a hallmark feature of PTSD (Figure). Identifying interactions between genetic disposition and trauma exposure in determining PTSD risk and the underlying neurobiological phenotypes, as well as illness course and treatment response, is a vast area of future research. A multitude of candidate genes as well as genome-wide associations have yet to be tested.

**SEX DIFFERENCES AND RISK FOR PTSD**

Women more frequently suffer from PTSD than men, perhaps in part due to sex differences in the exposure to different types of trauma. In addition, there might be sex differences in the neurobiological response to trauma. Rodent studies suggest that females generally exhibit a greater magnitude and duration of HPA axis responses to stress than males, though findings in humans are not entirely consistent. Sex differences in neuroendocrine stress responses have been attributed to direct effects of circulating estrogen on CRF neurons. Sex steroids also interact with other neurotransmitter systems involved in the stress response, ie, the serotonin system. Progesterone has also been implicated in modulating these systems. However, sex differences in HPA axis responses to stress have also been observed independent of acute gonadal steroid effects. Other factors that might determine sex differences in the stress response include genomic differences, organizational differences in brain structures, or developmentally programmed effects of gonadal steroids. Of note, sex steroids play a role in lifelong structural plasticity of several brain regions, including areas involved in stress responsiveness, ie, the hippocampus and amygdala. Functional imaging studies identified sex differences in the brain’s response to fear stimuli. Such processes may eventually converge into the basis of sex differences in the consequences of trauma that translate into differential risk for PTSD.

**EARLY DEVELOPMENTAL FACTORS AND PTSD**

Previous experience clearly moderates risk for developing PTSD in response to trauma. Thus, childhood adversity is associated with increased risk to develop PTSD in response to combat exposure in Vietnam veterans. There is a burgeoning literature documenting that early adverse experience, including prenatal stress and stress throughout childhood, has profound and long-lasting effects on the development of neurobiological systems, thereby “programming” subsequent stress reactivity and vulnerability to develop PTSD. For example, non-human primates exposed to a variable foraging demand condition, which causes unpredictable maternal care infants, produce an adult phenotype with sensitization to fear cues, CRF neuronal hyperactivity, and hypocortisolism similar to features of PTSD. In another non-human primate study, maternal separation interacted with female gender and the 5-HTTLPR polymorphism of the serotonin transporter gene in determining adult sensitization to acute stress. Adult women with childhood trauma histories exhibit sensitization of neuroendocrine and autonomic stress responses. Studies are needed to identify sensitive periods for the effects of early stress and their reversal, and to scrutinize interactions between dispositional (genes, sex) and developmental factors in determining neurobiological vulnerability to PTSD.

**FUTURE RESEARCH NEEDS**

We have provided an overview of the state of science and current developments concerning the neurobiology of PTSD. In the following section, selected unmet needs are described together with future research recommendations:

1. It must be stressed that neurobiological findings in PTSD are not unequivocal (the finding of hypocortisolism has not been replicated in all studies and some studies even report hypercortisolism in PTSD). The field must address and explain such inconsistencies by considering potential effects of disease stages, symptom constellations, different types or timing of the trauma, time elapsed since the trauma, and dispositional factors among others. Meta-analyses of existing studies might be a fruitful approach to reconcile inconsistent results.
2. Related to the above topic, trajectories of neurobiological changes (pre-trauma, immediately following trauma, longer-term changes related to illness manifestation/chronicity versus changes related to compensatory regulation associated with resilience/remission) must be identified in longitudinal studies, assessing populations before exposure to trauma (e.g., deployed soldiers).

3. Further research is needed to fully understand the mechanisms of PTSD. For example, molecular mechanisms contributing to the neurobiological phenotypes and pathophysiology of PTSD have not been sufficiently studied. It will be critical to consider neurotrophic factors and neural plasticity/remodeling, gene expression changes, proteomics, and effects of trauma on DNA methylation. A specific animal model of PTSD as well as human postmortem brain studies will be helpful to address some of these research needs.

4. Brain imaging research must further scrutinize the neural circuitry of PTSD. Studies in depression might be used as a framework to conceptualize a neural network model of failed adaptation to stress/trauma in PTSD. Such a model could be useful in identifying neural markers of PTSD risk, disease state, compensatory regulation, and treatment response.

5. One major unmet need is integrating findings from different neurobiological domains in PTSD. For example, effects of neuroendocrine dysregulation on brain function and fear responses can be experimentally tested by combining neuroendocrine challenges with functional imaging paradigms. Contributions of genetic and developmental factors to neuroendocrine-neural interactions must be elucidated.

6. Insights from the above studies will serve to identify subjects at risk based on genetic, developmental, and neurobiological features. Prospective follow-up studies are needed that characterize subjects pre-trauma and identify pre-trauma predictors of pathological response versus resilience.

7. Based on insights into resilience markers, new strategies to promote resilience could be derived. Future studies should consider the role stress-protective neurobiological systems, such as the oxytocin and NPY systems, as potential targets for prevention. Prospective studies could implement and test the efficacy of such pharmacological or cognitive-behavioral interventions before trauma (i.e., stress inoculation, stress management techniques, relaxation methods, and CRF antagonists) to enhance resilience.

8. Novel treatments should further be developed based on new insights into the neurobiology of PTSD. Insights from depression research may be translated to PTSD (i.e., in depression research, there are efforts to predict differential responsiveness to different types of treatment based on neural patterns and developmental/genetic factors). Similarly, individual features of PTSD patients may be used in the future to select the optimal treatment approach for a given patient. **CNS**

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