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# Clinical correlates of neurological change in posttraumatic stress disorder: an overview of critical systems

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Today's research investigating the neurological basis of post-traumatic stress disorder (PTSD) is occurring within a climate of significant social, financial, and political consequence. The social consequences result, in part, from the sheer magnitude of the problem. Evidence from epidemiological studies indicates that more than half of all adults have experienced at least one traumatic event in their lifetime, making it clear that psychological trauma is part of the human experience [1]. Such percentages place a large number of individuals at risk for the development of trauma-related disorders like PTSD. Present estimates of PTSD in the United States suggest that anywhere from 3% to 10% of the population suffers from the disorder [1,2]. Even the most conservative of estimates would propose that 300 million individuals worldwide meet criteria for a diagnosis of PTSD.

Increasing the concern is the fact that PTSD is a psychiatric disorder that leads to substantial functional impairment at tremendous cost to the individual and society. Individuals with PTSD are less satisfied with life, suffer from poorer health, have higher unemployment rates, and struggle with frequent family and interpersonal difficulties [3,4]. More chronic forms of the disorder have impairments on par with individuals who carry diagnoses of other serious mental illnesses [5,6].

Given the number of individuals affected, it is ironic that PTSD is a disorder that struggles for legitimacy in the eyes of the public. In part, this

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is because of the numerous controversies that surround the field. As recently as March 2003, the *Sunday London Times*, a paper with a readership of 2.6 million individuals, published an article titled "Stiff Upper Lip Beats Stress Counseling" based on a serious misrepresentation of the stress debriefing literature. The article, making no effort to distinguish between psychological debriefing and other forms of treatment, concluded that "counseling was at best useless and at worst made people more likely to suffer [from] PTSD" [7]. This article stands on the shoulders of the false memory debate, which long has given the impression that PTSD might be nothing more than a clinician's creation or a figment of one's imagination, an impression that occasionally has been supported by significant court rulings [8,9]. The use of the word trauma to cover phenomena as wide-ranging as divorce, lay-offs, and harassment, has led to the public perception that both trauma and PTSD are overused and overdiagnosed. False disability claims by military personnel, injured workers, and motor vehicle accident survivors have undermined the validity of the diagnosis further, as no gold standard has been developed to reliably separate the false claims from the true [10]. The unfortunate effect of these multiple controversies is to erode public confidence, both in the validity of PTSD and in the clinicians who treat it. Tragically, such doubts discourage potentially needy patients from accessing the care they need.

It is for this reason that establishing the neurological underpinnings of the disorder is so critical. In the current context, it is simply not sufficient to catalog patient reports of symptoms resulting from trauma, as those very reports are the ones in question. Likewise, it may not be enough to report positive treatment outcomes based on patient reports alone, as such outcomes are vulnerable to internal and external threats to validity. Quite simply, business as usual may not be enough to convince the public, the policy makers, and the media that PTSD is a serious, albeit treatable, disorder. The readership of a single newspaper article discouraging individuals from seeking treatment after a traumatic event will reach an incalculably larger number of individuals than the average scholarly research article. To combat such negative press and controversy, it is not sufficient to state that trauma results in certain sets of defined symptoms; it is critical to specify just how and why this happens.

Research into the neurobiological consequences of trauma is in the perfect position to provide such answers. Although many neurobiological hypotheses are in various stages of refinement, they at least provide a substantive and tangible explanation for certain elements of the disorder. Fortunately, there are a growing number of empirical studies on the neurobiology of PTSD. Although sorting through this literature presents a challenge, the larger context in which this research is occurring provides an inherent structure to a discussion on the topic. It is most valuable to identify the neurological systems responsible for prominent clinical patterns in PTSD. This principle will guide this article, in which four structures and

their related networks are discussed: the locus coeruleus, the hippocampus, the amygdala, and the thalamus. The symptoms resulting from alterations in these systems are defined and characterized. Further, the authors will speculate on the relationships between neurological alternations and the clinical presentation of PTSD with an emphasis on some recent work that adds to existing neurobiological models.

## Signs and symptoms of post-traumatic stress disorder

The signs and symptoms of PTSD are categorized into three clusters: the re-experiencing cluster (criterion B), the avoidance/numbing cluster (criterion C), and the hyperarousal cluster (criterion D) (see Box 1 for summary of current Diagnostic and Statistical Manual, 4th edition [DSM-IV] diagnostic criteria). After exposure to a traumatic event, an individual must have at least one symptom from the re-experiencing cluster, three from the avoidance/numbing cluster, and two from the hyperarousal cluster. Signs and symptoms in the re-experiencing cluster all represent a manner in which an individual with PTSD relives the initial traumatic experience. As specified in the DSM-IV criteria, re-experiencing the trauma can occur in memories, dreams, emotions, or physiological processes. Signs and symptoms of the avoidance/numbing cluster represent behavioral and cognitive strategies that minimize present or future contact with reminders of the traumatic event to the point of interference with daily activities. These strategies can be employed with purpose (as in behavioral avoidance of reminders) or without conscious awareness (as in amnesia or emotional detachment). The hyperarousal cluster of PTSD captures symptoms common in anxiety disorders such as sleep disruption, hypervigilance, exaggerated startle, and irritability/anger. For a diagnosis of PTSD to be made, these symptoms must cause significant emotional distress or functional impairment (criterion E).

## The locus coeruleus and its relevance to hyperarousal and memory consolidation

### *Anatomy*

Most noradrenergic (norepinephrine or NE) neurons in the central nervous system (CNS) are located in the locus coeruleus (LC). The LC falls within the boundaries of the pons, close to the midbrain, and is considered part of the pontine reticular activating system (RAS). LC neurons project to locations throughout the brain, including the thalamus, hypothalamus, hippocampus, amygdala, and cortex. The LC is known to receive afferents from two structures in the medulla, the paragigantocellularis lateralis and prepositus hypoglossi, although there is some evidence indicating that afferents may be more widespread than this [11,12].

**Box 1. Diagnostic and Statistical Manual, 4th edition criteria for diagnosis of post-traumatic stress disorder**

Criterion A. Exposure to a traumatic event, in which both of the following have been present:

1. The person has experienced, witnessed, or been confronted with an event or events that involve actual or threatened death or serious injury, or a threat to the physical integrity of oneself or others.
2. The person's response involved intense fear, helplessness, or horror. Note, in children, it may be expressed instead by disorganized or agitated behavior.

Criterion B. Re-experiencing of the traumatic event, in at least one of the following ways:

1. Recurrent and intrusive distressing recollections of the event, including images, thoughts, or perceptions. Note, in young children, repetitive play may occur in which themes or aspects of the trauma are expressed.
2. Recurrent distressing dreams of the event. Note, in children, there may be frightening dreams without recognizable content.
3. Acting or feeling as if the traumatic event were recurring (includes a sense of reliving the experience, illusions, hallucinations, and dissociative flashback episodes, including those that occur upon awakening or when intoxicated). Note, in children, trauma-specific re-enactment may occur.
4. Intense psychological distress at exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event.
5. Physiologic reactivity upon exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event.

Criterion C. Avoidance/numbing as indicated by at least three of the following:

1. Efforts to avoid thoughts, feelings, or conversations associated with the trauma
2. Efforts to avoid activities, places, or people that arouse recollections of the trauma
3. Inability to recall an important aspect of the trauma
4. Markedly diminished interest or participation in significant activities

5. Feeling of detachment or estrangement from others
6. Restricted range of affect (eg, unable to have loving feelings)
7. Sense of foreshortened future (eg, does not expect to have a career, marriage, children, or a normal life span)

Criterion D. Hyperarousal, indicated by at least two of the following:

1. Difficulty falling or staying asleep
2. Irritability or outbursts of anger
3. Difficulty concentrating
4. Hypervigilance
5. Exaggerated startle response

Criterion E. Duration of criteria B–D is greater than 1 month.
Criterion F. There is clinically significant distress or impairment in social, occupational, or other important areas of functioning.

The multiple widespread efferent connections of the LC are critical to the neuromodulatory role it plays throughout the CNS. The LC sets the tone for baseline levels of cortical arousal throughout numerous areas in the brain [13]. This notion is supported by studies showing that increases in LC firing are associated with increased alertness, physiological arousal, acute stress, and the presences of fearful stimuli [14,15].

*The locus coeruleus and hyperarousal symptoms in post-traumatic stress disorder*

In addition to the increase in general arousal associated with LC activation, the LC plays a specific role in the poor sleep, hypervigilance, and irritability/anger that make up part of the hyperarousal cluster (criterion D) of the PTSD diagnosis [16]. It generally is accepted that LC activity is elevated in PTSD subjects, leading to increased norepinephrine release at numerous terminals throughout the brain. The hypothesis that increased LC activity leads quite directly to hyperarousal symptoms in PTSD is supported by a series of preclinical studies that have shown that LC activity increases under stress and results in fear-like behavior in animals [17]. Whether the stimulation is electrical or chemically induced through norepinephrine agonists such as yohimbine or piperoxonen, increased LC firing leads to increased sensitivity to novelty, vigilant behavior, aggression, sleep disruption, and peripheral physiological activity [18,19]. LC activity and its related behaviors seem to increase rather than decrease over time as the norepinephrine systems become sensitized to stress and repeated activation.

Animals that are exposed repeatedly to stress become vigilant to novel stimuli. These behaviors are thought to be caused by increases in

norepinephrine activity that result in changes to attentional processes. Phasic activity of the LC is thought to increase selective attentional processes, while its tonic activity may increase scanning behaviors [20]. In concert with the prefrontal areas, the LC forms a network that allows for proper selection of environmental stimuli and the screening out of irrelevant input. In individuals with PTSD, low tonic activity and over-reactive phasic activity may play respective roles in the concentration difficulties and hypervigilance that characterize the disorder [21].

### *The locus coeruleus and memory consolidation*

In PTSD, abnormalities in the central norepinephrine system and the catecholamines in general have been linked closely with symptoms such as intrusive memories and flashbacks in light of considerable evidence that epinephrine and norepinephrine release is associated with memory consolidation [18]. Norepinephrine release associated with the stress response affects learning and memory through its influence on norepinephrine levels in structures such as the amygdala and the hippocampus. In the laboratory, norepinephrine or epinephrine administration at the time of memory testing has been shown to increase recall of emotional material [23]. Naturally occurring epinephrine and norepinephrine release to stressful stimuli theoretically would improve memory in a similar fashion.

Individuals who go on to develop PTSD may have an increased release of epinephrine and norepinephrine when initially exposed to a traumatic event relative to those who do not develop PTSD. This release may lead to vivid recollections of the initial trauma that results in PTSD-related intrusive memories and flashbacks. To compound matters, individuals with PTSD are known to be physiologically over-reactive to reminders of their trauma. Activation of memory through traumatic cues or general arousal states may lead to further release, which likely leads to a further consolidation of the memory trace [22]. The critical role of catecholamine release in memory consolidation in people has been supported further by preliminary work indicating that beta-adrenergic blockers such as propranolol that block norepinephrine and epinephrine activity after a trauma minimize the likelihood of developing PTSD at 1 month and negate physiological reactivity to trauma reminders at 3 months [24].

## The hippocampus and its relevance to declarative and fragmented memory

### *Anatomy*

The hippocampus is a structure in the midbrain located in the medial temporal lobe extending over the floor of the descending horn of each lateral ventricle. The hippocampus is considered an integral part of the limbic system and a main component of the neuroregulatory limb of the hypo-

thalamic pituitary axis (HPA). The HPA system plays a primary role in the human stress response. The HPA cascade starts when stress causes the hypothalamus to release corticotrophin releasing factor (CRF) that regulates the release of adrenocorticotropine releasing factor (ACTH) from the pituitary gland. ACTH enters the blood stream and results in the release of cortisol from the adrenal cortex. Cortisol affects the hippocampus as it binds with the numerous cortisol receptors in that structure.

The hippocampus aids in converting short-term memories to long-term memories and in integrating multiple sensory inputs into one coherent memory. Damage to the hippocampus by surgery, stroke, or injury can result in significant anterograde amnesia and a specific inability to lay down new declarative memories. Cushing's syndrome, with its associated hypersecretion of cortisol, results in hippocampal volume reduction and memory impairments [25].

### *The hippocampus and post-traumatic stress disorder*

There is compelling evidence that increased cortisol release caused by stress damages the hippocampus in animals. From this, one might predict that the increased stress associated with a traumatic experience and the subsequent development of PTSD might lead to chronic cortisol secretion and ultimately hippocampal damage. There is not reliable evidence in traumatized individuals with PTSD for either hypersecretion of cortisol or decreased hippocampal volume, however [26,27]. Cortisol secretion has been found to be quite complicated in individuals with PTSD with low baseline levels of cortisol, increased HPA reactivity to stress, and quick termination of the stress cycle because of enhanced negative feedback inhibition [26]. These complexities point toward a dynamic and ever-changing system that is not consistent with the notion that any PTSD-related hippocampal reductions are related to a steady-state cortisol hypersecretion.

The complexity of the findings regarding cortisol and PTSD are mimicked by considerable variability regarding hippocampal volume reductions in the disorder. Although several early studies demonstrated either unilateral or bilateral volume reductions associated with PTSD, numerous other studies have not been able to replicate this finding [28]. Both alcohol abuse and depression, each associated with hippocampal reductions themselves, are regular confounders in this work, and the nature and severity of the trauma varies across the studies. Gilbertson et al recently reported hippocampal volume reductions in noncombat twins of combat veterans with PTSD (who themselves had hippocampal volume reductions). These findings indicate that hippocampal volume reductions, when they exist, may represent a vulnerability factor for PTSD rather than the result of stress-related or PTSD-related cortisol irregularities [29]. Bonne et al investigated whether the development of PTSD was associated with hippocampal volume reductions over time [30].

Subjects were assessed directly after a traumatic experience and then 6 months later. Subjects showed no differences in hippocampal volume between individuals who developed PTSD and those who did not, indicating that the sequelae of PTSD do not result in hippocampal volume reductions in the early stages of the disorder.

*The hippocampus and declarative memory impairment in post-traumatic stress disorder*

Impairments in hippocampal-related cognitive functioning do not require measurable volume reductions in the hippocampus to occur. In fact, most studies that have predicted a negative relationship between hippocampal volume and memory in subjects with PTSD have found no significant association between the two [28]. Although reduced hippocampal volume is not correlated negatively with memory deficits in people exposed to trauma as one might predict, it is certainly possible that far more subtle alterations in hippocampal functioning could explain certain aspects of memory impairment in PTSD.

In fact, deficits in declarative memory related to PTSD are more consistent with irregularities in hippocampal function than with significant cell death in the structure. In a review of 19 studies investigating attention and memory impairment in PTSD, Horner and Hamner described the memory impairment in PTSD as mild [27]. In addition, there have been several large-scale studies of neuropsychological functioning in subjects with PTSD that have found no evidence of obvious declarative memory impairment. Performance on tests of verbal learning and verbal subtests of the Wechsler Adult Intelligence Scale-Revised (WAIS-R) were not significantly different between PTSD and non-PTSD groups [31,32]. Even those studies that have reported deficits have not regularly demonstrated that that the memory deficits are not attributable to comorbid psychiatric conditions or more fundamental, better documented attentional disturbances [33]. Therefore, mild memory impairments are more common than are severe deficits, and these may be associated with changes in hippocampal structure that cannot be measured reliably as this time.

*The hippocampus and traumatic amnesia in post-traumatic stress disorder*

Traumatic amnesia refers to an individual's inability to recall significant aspects of their traumatic experience. In the DSM-IV, this symptom is operationalized as amnesia for the event, but the nature and extent of the amnesia is not described in detail [16]. The amnesia is not considered traumatic amnesia, however, if it is caused by head injury, substance use, or general childhood amnesia. Given that the symptom falls within the avoidance/numbing cluster (criterion C), it is presupposed that the amnesia is a conscious or unconscious strategy to avoid memories too disturbing to recall. Although there have been many explanations for traumatic amnesia

throughout the years, only recently has there been an appreciation for the potential neurobiological factors that may shape the symptom.

Initial reports of reduced hippocampal volumes have resulted in conjecture that hippocampal damage may play a role in amnesia for the trauma. Such a mechanistic explanation seemed unlikely, however. How could a relatively slow-changing injury like cortisol-related hippocampal atrophy lead to memory traces in which relatively discrete elements of the memory do not exist, while coinciding elements to the memory (time just prior or after) remain intact? Clearly a more dynamic and functional explanation was necessary.

The fact the traumatic memories long have been reported to be fragmented, compartmentalized, and disintegrated suggests that the hippocampus still may have a role to play in the phenomena of traumatic amnesia. The groundbreaking work of Zola-Morgan and Squires in the late 1980s highlights the role of the hippocampus in integrating memories across sensory modalities [34]. The implications of their work are that dysregulation in the hippocampal system has the potential to generate narratives of traumatic events that are spotty and unreliable.

Neuromodulators, such as NE, have the potential to affect hippocampal functioning in a more dynamic fashion. The LC, for example, projects directly to the hippocampus and modulates its functioning through NE release. The effects of such a network are unclear, although the implications are that stress-related memory alterations might occur on a split-second basis, and deficient or extreme LC input may disrupt normal hippocampal processing severely. Given that the hippocampus plays a role in integrating input from diverse sources when encoding memory, disruptions in its functioning may lead to memories that seem fragmented and nonlinear. Over time, fragments of the memory may become consolidated, vivid, and easily recalled, while other fragments rarely are accessed.

## The amygdala and its relevance to conditioned fear, startle, and physiological reactivity

### *Anatomy*

The amygdala are nuclei located in the medial temporal lobe anterior to the hippocampus. Along with the hippocampus, cingulate cortex, fornix, septum, and mammillary bodies, it makes up the limbic system, a circuit of interconnected nuclei that play a critical role in elements of emotional behavior. The amygdala also is richly connected with the prefrontal cortex (PFC), which is thought to have an inhibitory effect on amygdala responding. The amygdala is the central structure associated with the learning of fear, fearful responding, and associated autonomic and behavior responses. Amygdaloidal lesions result in hampered fear conditioning, while amygdaloidal stimulation results in classic fear responses such as defensive and aggressive behavior and autonomic reactivity [35].

Researchers have speculated that a process similar to kindling in the amygdala is responsible for aspects of the post-traumatic response. Kindling is a term originally used to describe how subthreshold seizure activity becomes increasingly active and severe with successive seizures. It is increasingly clear that partial kindling also can occur in the amygdala, and it appears related to increased defensive responses and anxiety-like behavior in animals [36]. In people, it has been proposed that the amygdala is involved in integrating emotional and contextual information that are parts of the human stress response [37]. In PTSD, it is thought that the amygdala-related pairings of emotional and contextual information develop quickly and in a manner that results in more lasting change. Although partial kindling can explain enhanced responding by animals in the laboratory, a more endogenous and enhanced long-term potentiation process may be responsible for increased conditionability in the amygdala and its efferents in PTSD [36]. Fear responses acquired by individuals who develop PTSD may differ in their strength of acquisition, their generalizability, and their resistance to extinction.

### *The startle response*

One of the more overt behavioral signs of the psychological stress response is the increased startle response, a symptom delineated even in the earliest characterizations of trauma victims [38,39]. The DSM-IV counts exaggerated startle as one of the symptoms in the hyperarousal cluster. The most dramatic expression of the startle response includes defensive muscle flexion in response to startling auditory or visual stimuli. Studied more often in people, however, is the more subtle blink reflex to acoustic startle stimuli. This typically is measured by placing electrodes around the eyes to measure the magnitude of the blink response to startling acoustic bursts.

It has been demonstrated that the amygdala plays a role in conditioned fear responding in general and the startle response in particular. Fear conditioning is a process by which a previously neutral stimulus acquires the same level of responding as an original unconditioned stimulus such as a footshock or a startle probe. In the laboratory, individuals with PTSD have been shown to acquire fear responses more readily and extinguish them more slowly [40,41].

The conditioned fear response has been studied widely using the acoustic startle as a probe to produce a blink reflex. In PTSD, findings have been variable with respect to PTSD-related differences in the startle blink response. It is proposed, however, that the startle response is potentiated and more reliable in PTSD under generally threatening conditions [42]. This is consistent with the notion that individuals with PTSD have higher levels of arousal in trauma-specific and threatening conditions and easily generalize from conditioned stimulus to conditioned stimulus to produce a wide array of circumstances in which they become physiologically over-reactive. Thus, in individuals with PTSD, an exaggerated startle response can occur in a seemingly harmless context.

With respect to the conditioned fear response, it is clear that the amygdala works in tandem with the PFC with which it is richly connected. Among its many functions, the PFC inhibits amygdala responding. For example, lesions to the PFC result in prolonged startle responding even after numerous extinction trials [43]. Of relevance is the fact the PFC is thought to be hypoactivated in PTSD, particularly during trauma memory activation [41,44]. It is possible that such PFC hypoactivation may be related to startle responses that are larger in PTSD when exposed to contexts in which they know they will be shocked or know they will be exposed to reminders of their trauma.

*Relevance to physiological reactivity*

Enhanced startle response is just one of a number of indicators of increased physiological reactivity in post-traumatic stress disorder. One of the most consistent findings in the empirical literature is increased autonomic reactivity in PTSD subjects when reminded of their trauma, providing direct and unequivocal support to the inclusion of physiological reactivity to the DSM-IV criteria for PTSD [45]. The DSM-III-R originally placed these symptoms in the hyperarousal cluster (criterion D), but they were moved into the re-experiencing cluster (criterion B) as it became evident that enhanced physiological reactivity occurred most frequently when exposed to internal (visualized) or external (experimenter presented) reminders of the trauma [46]. Individuals with PTSD were found to be reactive not only to the details and memories of their own specific trauma but were also physiologically reactive to nonspecific reminders or cues that were relevant to their trauma (combat veteran presented with generic pictures of combat) [45].

Although the entire HPA axis is primarily responsible for the physiological reactivity associated with the acute and chronic stress response, the amygdala in combination with the hippocampus is critical in pairing the fear response to specific cues and stimuli. This is particularly relevant for PTSD when physiological reactivity is found most reliably in response to traumatic cues. Recent positron emission tomography (PET) studies have found that the amygdala is clearly active when individuals are thinking about their trauma. Such data suggest that activation of trauma memories involves the amygdala and can explain the anxiety and physiological reactivity PTSD sufferers often report when exposed to trauma cues [47].

## The thalamus and its relevance to dissociation, attentional bias, and traumatic amnesia

*Anatomy*

The thalamus is a two-lobed medial structure that that sits just above the brain stem and is bounded on its dorsal surfaces by the lateral ventricles.

The two lobes of the thalamus are in communication through the massa intermedia, which is situated in the middle of the third ventricle. The thalamus consists of multiple nuclei whose primary role is to send incoming signals from sensory receptors for further processing in the cerebral cortex. With the exception of olfaction, all sensory input goes through thalamic nuclei before being sent onto the cortex. The thalamus, however, functions in a far more complex manner than the relay nuclei would indicate. The thalamus receives afferents from multiple systems and sends efferents to more than just cortical sensory areas. For example, the thalamus receives input from the LC, sends information to the hippocampus and amygdala, and has rich bidirectional connections with the PFC. This places the thalamus in a position to greatly affect the quantity and quality of sensory processing.

*The thalamus and dissociation in post-traumatic stress disorder*

Dissociative symptoms are common among survivors of trauma, and maladaptive levels of dissociation can develop alongside other pathological responses to trauma. In the DSM-IV, dissociation is defined as a disruption in the usually integrated functions of consciousness, memory, identity, or perception of the environment, and the term dissociative symptoms in the literature have been used to capture a range of symptoms that can include changes in time perception, altered sensory perception, flashbacks, psychogenic amnesia, reduction in awareness, affective blunting, feelings of detachment, depersonalization, multiple identities, and derealization [16].

Krystal et al have produced some of the first elaborated neurobiological models of dissociation in traumatized individuals [48,49]. Central to their models is the thalamus, which receives input from sensory receptors and brainstem arousal systems and then relays this information to the frontal cortex, the cingulate gyrus, the amygdala, and the hippocampus. The fact that basic sensory information and arousal signals converge in the thalamus explains why even basic sensory signals can be distorted under conditions of high arousal. Although moderate arousal may facilitate transmission, conditions of high stress likely will distort or hinder transmissions to target structures throughout the brain.

High arousal states during acute trauma and in individuals who have a chronic form of the disorder may explain some of the dissociative symptoms that occur with PTSD. In particular, reductions in awareness, derealization, amnesia, distorted sensory input, and alternations in time perception can be understood through arousal-modulated thalamic disruption. Situations of high stress have resulted in reported symptoms such as feeling as if everything is moving in slow motion, visual distortions of objects including body parts, feeling as if everything around is changed or unreal, and narrowing of attentional focus to the point that awareness of the surroundings is reduced. All of these symptoms can be understood by

thalamic processes, as the thalamus may change the rate at which it receives or passes along information, influence the thresholds for when information is passed, or selectively attend to particular information in the internal or external environment. In patients with chronic PTSD, laboratory studies have shown that chemically induced high arousal states result in flashbacks, a dissociative symptom that integrates all of these symptoms with specific memory elements [49].

*The thalamus and attentional bias*

Although severe disturbances in sensory processing may occur under conditions of extreme stress, more subtle changes may occur even at baseline. The thalamus has rich bidirectional connections with the cingulate gyrus and the frontal cortex, two of the structures responsible for the prioritization and shifting of attention. Despite its reputation as a relay station, there is substantial evidence indicating that the thalamus has substantially more afferents from cortical structures than it has efferents to those areas, suggesting significant top-down control of thalamic functioning [50]. In combination with input from the LC and cortical areas, the thalamus is thought to mediate interactions between arousal and attention, and it has been proposed that noradrenergically mediated changes in attentional performance may be attributed primarily to thalamic mechanisms [51,52]. Although the LC may create a general state, it is the thalamus in combination with top-down cingulate gyrus and PFC input that is involved in selecting stimuli that are relevant, salient, and novel. During conditions of moderate stress and arousal, the thalamus likely will play a key role in facilitating increased attention to trauma-relevant or threatening stimuli in PTSD, or conversely in generating intense attentional focus on nontraumatic, safe stimuli as a cognitive avoidance strategy.

*The thalamus and traumatic amnesia*

During the extreme stress of an actual trauma, it is likely that the thalamus impairs rather than facilitates the processing of environmental stimuli. In this sense, the thalamus has a role to play in amnesia for traumatic events. For example, disruption in the relay of contextual and traumatic information could contribute to the fragmentation and inaccuracies associated with traumatic memory. Unlike the role the hippocampus might play in fragmenting sensory elements of the memory, however, thalamic interference would result in an initial interference with basic stimulus encoding. Thus thalamic-mediated amnesia would result in distorted or nonexistent information reaching downstream structures. Intense attentional focus during a trauma on internal thoughts or external nonthreatening stimuli may result in minimal encoding of the traumatic experience. Under such circumstances, there would be minimal sensory information reaching downstream memory structures like the hippocampus

and the cortex, and therefore minimal memory to recall. This may account for cases of complete amnesia for traumatic events.

## Summary

Knowledge about the biological basis of psychological trauma is changing at an exponential rate. A PsychINFO search on the search terms locus coeruleus and PTSD revealed one peer-reviewed journal article between 1982 and 1992 and 51 in the subsequent decade. A similar search revealed zero articles on hippocampus and PTSD between 1982 and 1992 and 170 in the past decade. As clinicians, it is important to become increasingly familiar with this growing literature to use that knowledge to treat and educate patients. Imagine the relief that can be provided to survivors of trauma if clinicians can tell them that they have a good idea about what causes their symptoms and even clearer ideas about how to treat them.

One ancillary but invaluable outcome to this work is the fact that understanding the neurological underpinnings of PTSD will go a long way to establishing a necessary equilibrium in nature and nurture's role in the etiology and maintenance of the disorder. In its early conceptualization, PTSD was thought by many to be an ordinary reaction to an extraordinary event, thus placing responsibility for the disorder firmly in the hands of environmental factors. A subsequent emphasis on vulnerability and resiliency factors in the disorder, however, gave the impression that genetic and potentially hard-wired neurological factors were dominant in the expression of the disorder. Appreciating the balance between nature and nurture in the development of stress disorders like PTSD will allow clinicians and patients alike to appreciate the role of personal responsibility in the process of recovery. A parallel, albeit more mature process, has occurred in the area of schizophrenia in the past four decades. Early conceptualizations of schizophrenia placed a heavy burden on parenting and behavioral factors, leaving the patients angry at their parents and parents with unnecessary guilt. The later dominance of genetic and biological theories in the disorder allayed parents of their guilt, but left both parents and patients wondering what might be done in the face of such an affliction. Modern theories of schizophrenia seem to have achieved an appropriate balance that recognizes biological vulnerabilities, but also emphasizes familial and patient responsibilities in recovery and care.

In PTSD, a similar equilibrium needs to be found, and understanding the neurobiology of the disorder will go far in achieving that goal. When it is understood how trauma affects the brain and how treatment produces neurobiological changes that may remediate trauma-related effects, the patient will be in a better position to make choices about what can and cannot be done in the process of recovery. Giving patients this critical

internal locus of control will provide therapeutic benefits such as confidence, self-esteem, and hope that are likely to enhance changes that occur with intervention.

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