HOMEOSTASIS, STRESS, TRAUMA, AND ADAPTATION

A Neurodevelopmental View of Childhood Trauma

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Life is dynamic. From birth, even prior to birth, we are bathed in a continuous stream of experience. Through this flow of time, our complex physiology maintains a balancing act, ever changing to maintain some stability, equilibrium, and homeostasis. To survive and flourish, we must sense, process, store, and respond to elements of our dynamic environment. The brain is the primary organ responsible for these tasks. By internalizing and storing elements of the unique sequence and collection of our individual experiences, the brain forces us to become reflections of our personal histories. These histories may be filled with consistent, predictable, nurturing, and enriching experiences or marred by chaotic, threatening, and traumatic experiences. The nature, pattern, and timing of these experiences influence our subsequent functioning. It is from this catalog of life events that our brain shapes our perceptions and reactions as we move, feel, and think; laugh, love and cry; and remember, create, or hate.

This article discusses the impact of traumatic experiences on child development and function as viewed through the lens of developmental neurobiology. This focus may provide some insight for those seeking to understand the neuropsychiatric problems resulting from childhood trauma. The recurring theme in a neurodevelopmental view is the remarkable malleability of the developing brain. The brain's exquisite sensitivity to experience in early child-

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hood allows traumatic experiences during infancy and childhood to impact all future emotional, behavioral, cognitive, social, and physiologic functioning.

BACKGROUND: TRAUMA AND CHILDREN

It is the rare child who escapes childhood without some cruelty, threat, pain, or loss. Far too many children experience severe chronic or traumatic stress. Millions of children each year experience traumatic events: natural disasters,[64] physical abuse,[70, 73] sexual assault,[17, 55] and a host of other terrorizing experiences.[6, 29] Millions of other children live in the traumatizing maelstrom of domestic or community violence.[47, 93, 94, 100] These experiences wound and scar the vulnerable, developing child, often resulting in impairments severe and chronic enough to be labeled neuropsychiatric disorders (e.g., reactive attachment disorder, posttraumatic stress disorder [PTSD], dissociative disorder). Conservative estimates suggest that more than 8 million children, at any given time, are suffering from a trauma-related neuropsychiatric disorder, and that millions more suffer subclinical but serious problems.[74] The cost to individuals and society by any measure, economic or human, is high.

NEUROPSYCHIATRIC DISORDERS AND CHILDHOOD TRAUMA

The best-characterized neuropsychiatric problems following childhood trauma are posttraumatic stress disorders.[77, 87] Terr's landmark studies[103] started the modern era of interest in the psychologic sequelae of childhood trauma. Over the last 20 years, lagging behind a similar rediscovery of adult PTSD, various important aspects of the phenomenology of childhood PTSD have been studied.[30, 76, 83, 88, 92, 102] Terr has described two broad categories of PTSD in children: the effects of discrete, encapsulated traumatic events (Type I) versus chronic, pervasive trauma (Type II).[102] This distinction is a good start, but better phenomenology is required to understand the various neuropsychiatric syndromes related to childhood trauma.[29, 30, 40, 76, 83, 92]

Children respond to and are affected by traumatic experiences in a host of different ways and in ways different from adults. Independent of the direct effects of the trauma, the capacity of traumatic experiences to disrupt and interfere with emotional, behavioral, cognitive, social, and physical development leads to important secondary and tertiary effects on the child. The current *Diagnostic Statistical Manual* (DSM-IV)[7a] diagnostic labels do not capture the diversity of adaptive and maladaptive syndromes that appear to be related to early life traumatic experiences. Among the comorbid neuropsychiatric diagnoses associated with childhood trauma are major depression, attention deficit hyperactivity disorder (ADHD), dissociative disorder, and, following severe early life neglect and trauma, various developmental disorders. Although PTSD is not the only nor an inevitable outcome of trauma during childhood, posttraumatic hyperarousal or dissociative-like symptoms often coexist with these other disorders.[7, 64, 87, 95] Furthermore, severe early trauma appears to be an expresser of underlying constitutional or genetic vulnerability and may be a primary causal factor in the development of a broad range of disorders later in life.[15, 71, 76]

Initial progress in the area of childhood PTSD was made by comparison with findings or conceptual views derived from adult populations, especially male combat veterans.[72, 84] These comparisons, once useful, are now very limiting. They leave key questions unasked. What explains the different responses to, and effects of, the same traumatic event on children of different ages? By what mechanisms do traumatic events influence development? What makes an experience traumatic? Why do children of the same age react differently to the same traumatic event? Where do resilience or vulnerability come from? Are the effects of trauma in childhood reversible? Advances in understanding childhood trauma require conceptual approaches and research that recognize the unique and distinctive properties of childhood. One such approach uses the core principles of neurodevelopment to frame these issues.

A NEURODEVELOPMENTAL VIEW OF CHILDHOOD TRAUMA

The functional capabilities of the mature brain develop throughout life, but the vast majority of critical structural and functional organization takes place in childhood. Indeed, by 3 years of age the brain has reached 90% of adult size, whereas the body is still only about 18% of adult size.[96] Childhood experiences define the adult by shaping the developing brain. This definition occurs because neurodevelopment is characterized by sequential development and sensitivity (from the brainstem to the cortex) and use-dependent organization.[79, 81] The mature organization and functional capabilities of brain reflect aspects of the quantity, quality, and pattern of the somatosensory experiences of the first years of life.[12, 16, 37, 59, 74, 79, 83, 97] The sequential and use-dependent properties of brain development result in an amazing adaptive malleability, ensuring that, within its specific genetic potential, an individual's brain develops capabilities suited for the environment in which he or she is raised.[83] Simply stated, children reflect the world in which they are raised.

Equilibrium, Stress, and Trauma

All living organisms have mechanisms to sense and respond to changes in their environments. These environments—external as sensed by our five senses and internal as sensed by a set of specialized neurons throughout the body (e.g., glucose- or sodium-sensitive neurons)—are always changing. Our physiology and neurophysiology are characterized by a continuous, dynamic process of modulation, regulation, compensation, and activation designed to keep our body's systems in some state of equilibrium or homeostasis. Each of our many complex physiologic systems has a rhythm of activity that regulates key functions. For example, when blood sugar falls below a certain level, a set of compensatory physiologic actions are activated. When tissue oxygen is low from exertion, or when an individual is dehydrated, sleepy, or threatened by a predator, still other regulatory activities respond to the specific need. For each of these systems there are basal or homeostatic patterns of activity within which the majority of environmental challenges can be sustained.

When there are dramatic, rapid, unpredictable, novel, or threatening changes in the environment, however, special stress-response mechanisms are activated. These brain-mediated responses recruit a set of central and peripheral nervous system, neuroendocrine, and immune responses that promote adaptive survival functions and, later, return to equilibrium or homeostasis. Events that disrupt homeostasis are, by definition, stressful. If this stress is severe, unpredictable, prolonged, or chronic, the compensatory mechanisms can become overactivated or fatigued and incapable of restoring homeostasis, and so the physiologic

system reorganizes its basal patterns. An event is traumatic if it overwhelms the organism dramatically and negatively disrupts homeostasis. In a very real sense, trauma throws the organism off balance and creates a persisting set of compensatory responses that, in turn, create a new but less flexible state of equilibrium. Trauma-induced homeostasis consumes more energy and is maladaptive compared with "normal" homeostasis. By inducing this expensive homeostasis and compromising full functional capacity, trauma robs the organism. It has survived the traumatic experience, but at a cost.

Homeostasis and Memory

In this regard, the human organism is no different from others. Although exquisitely complex, the core framework of the human brain is designed to sense and respond to the changing environment to promote survival. At the heart of our survival neurobiology is the capacity to make and store internal representations of the external world—memory.[75] The brain creates memories owing to the capacity of neurons and neural systems to change from one homeostatic state to another. In response to a set of stimuli-induced alterations in activity (e.g., sensations), neurons undergo molecular changes that reflect this activity.[35, 52, 53] In a very real sense, unless the homeostatic dynamic of a neural system is altered by use, it will not change and will not make internal representations of the experience—it will not make memories. Neurons and neural systems change in a use-dependent fashion.[25] Therefore, when neural systems are influenced by new or extreme patterns corresponding to new or extreme environmental situations, they will change their molecular neurophysiology, creating memories.[79]

This process has important implications for understanding how we create memories of traumatic experiences. For adults, most experiences have only a small component that is new or unique. Typically, the majority of places, faces, words, sounds, smells, and tastes in any given moment are familiar; the brain has sensed, processed, and stored these patterns before. In these situations only some portions of the brain are activated and process outside of their homeostatic range. In the classroom, for example, a lecture may result in cortical activation but will cause little new emotional, motor, or arousal activity. The result, hopefully, is new cognitive memories that store the information from the lecture. Similarly, practicing piano may result in new cerebellar-basal ganglia-motor cortex activity and create motor memories, but it will have little effect on emotional or state-regulation areas of the brain.

Trauma, however, induces a total brain response. All parts of the brain will be involved in trying to survive the threat. A traumatic event, by altering activity (and altering the homeostasis) in all parts of the brain—the cortex, limbic, midbrain, and brainstem portions—can create different types of memory. Altering cortical homeostasis creates cognitive or narrative memory; the limbic emotional memory; the midbrain motor memory; and the brainstem, physiologic state memories.[23, 62, 78, 86] These memories, reflections of the altered equilibrium resulting from a traumatic event, are the heart of trauma-related neuropsychiatric signs and symptoms.

Children are more vulnerable to trauma than adults. Traumatic events modify an adult's original state of organization or homeostasis but may be the original organizing experience for the child, thereby determining the foundational organization and homeostasis of key neural systems. Experience in adults alters the organized brain, but in infants and children it organizes the developing brain.[76] This difference has profound implications for understanding the differences between trauma in children and adults.

The Dynamic Environments of Development

The neurobiologic capabilities to sense, store, and respond to our environments evolved over millions of years as our pre-hominid and hominid ancestors adapted to the changing demands of their environments. These environments had many components: climate, weather, habitat, predators and prey, and, crucial to understanding humans, social structures. Humankind lived for thousands of years in small hunter-forager bands. Our complex social and communication capabilities allowed small, naked, slow, and weak individual humans to survive by creating larger, stronger, and more flexible biologic systems to compete in the harsh natural world inhabited by larger, stronger, faster, and naturally armed animals.[60]

Central elements of our human development—then and now—are the dramatic changes in the major environmental challenges associated with the life cycle. The world to which the brain must adapt is dynamic, with dramatic shifts in the major sensory stimuli occurring at key transitional life stages. Our stream of experience is comprised of shifting environments: new demands, expectations, tasks, and capabilities.

It is important to emphasize environments. During the life cycle, the primary internal and external environments are changing. In utero, the sensory cues from the environment include darkness, a constant temperature, a liquid embracing space, and the constant vibratory and auditory rhythm from the mother's heart rate. The homeostatic states developing in the environment of the third trimester fetus are challenged and shifted by birth. The major sensory cues (i.e., environment) of the newborn come from the primary caregiver; the mother's embrace, rhythmic rocking, and soft humming are familiar and soothing to the newborn. But most sensations and perceptions are new and challenge the rudimentary homeostatic patterns created during intrauterine life. Over time, the newborn's environment expands, enriches, and becomes more complex. More sights, sounds, tastes, and touch push the developing neural systems of the infant, child, and adolescent out from a previous set of homeostatic states to find newer and more functionally flexible organizational equilibria. This development can proceed in an optimal fashion when the presentation of new stimuli is safe, nurturing, predictable, repetitive, gradual, and attuned to the infant's or child's developmental stage. When new experience is chaotic, extreme, or mismatched to developmental stage, development is disrupted.

What may be a dramatic, rapid, or unpredictable shift in environment for the newborn (e.g., a diaper change, which does induce a stress response) may be a familiar, comforting pattern for the 1-year-old and a distressing, humiliating experience for the incontinent 6-year-old or 60-year-old. It is not surprising, then, that the neurobiologic systems and solutions for responding to stress change with the unfolding demands and tasks of various stages during the life cycle.[37, 38] Infants, for example, cannot fight or flee. In turn, adults could not survive minor life stresses with the labile stress-response systems of the newborn. The pattern of stress response preferred at any age is generally matched to the demands and tasks of that developmental stage; what may be extremely stressful (or traumatic) at one age may not be at another. A newborn infant that is not touched for 2 weeks will be severely traumatized, whereas this experience will have little effect on an adolescent. As with many other brain-mediated

functions, stress response neurobiology and functioning are experience- or use-dependent. The individual stress-response style and capacities of any child, then, are related to the process of cataloging experience during development.

Cataloging Experience

Throughout life, the brain is sensing, processing, and storing patterns of neuronal activation (i.e., making memories) that correspond to various sights, sounds, smells, tastes, and movements. Using various modes of memory (e.g., cognitive, emotional, motor) the brain stores these patterns, making associations among multiple sensory stimuli and creating templates of experience against which all future experience is matched.[78]

In this regard, the brain is a conservative organ. It does not like to be surprised. All unknown or unfamiliar environmental cues are judged to be threatening until proven otherwise. Novel stimuli focus attention, increase arousal, and induce an alarm response until they can be proven neutral or safe. New patterns and cues that do not match the stored memories of previous experience prime the stress-response systems in the brain.[5, 26, 57, 61, 63] Once categorized as neutral, safe, or threatening, these stored memories are added to the catalog of patterns, cues, and associations against which subsequent environmental cues are matched.

What is safe and comfortable becomes so through experience. In contrast, when the environment, internal or external, matches stored neuronal patterns associated with a previous threatening experience, the brain's stress-response systems are activated. Key signs and symptoms of trauma-related neuropsychiatric disorders result from these memories of fear. Later events can recall stored elements of the traumatic experience by triggering complex, multisystem responses (i.e., cognitive, emotional, motor, state) that were associated with original trauma, but now have generalized to similar cues. Memories of fear are created at multiple levels in the brain's hierarchical systems.

Processing Environmental Cues of Threat

Sensory information from the external environment (visual, auditory, tactile, olfactory, gustatory) and the internal environment (e.g., blood glucose, arterial pressure, CO_2 levels) enters the central nervous system at the level of the brain stem and midbrain.[36] As this primary sensory input comes into the brain stem and midbrain, it is matched against previously stored patterns of activation; if the input is unknown, or if it is associated with previous threat, an initial alarm response begins.[8, 9] The alarm response initiates a wave of neuronal activation in key brainstem and midbrain nuclei, which contain neurons utilizing a variety of neurotransmitters (e.g., norepinephrine, dopamine, serotonin), neuromodulators and neuropeptides such as adrenocorticotropin (ACTH), corticotropin releasing factor, and vasopressin.[11, 18] Activation of these key systems results in patterns of neuronal activity that spread from the brainstem through the midbrain, to thalamic, limbic, and cortical areas. At the level of the brainstem and midbrain, there is little subjective perception. It is at the level of the thalamus and limbic areas that specific patterns of neuronal activity result in emotional sensations associated with threat—fear, anxiety, and anger.[26, 86] At the subcortical and cortical level, more complex cognitive associations are made, allowing interpretation of the experience. The event can be categorized, contexualized, and understood within a larger perceptual or cognitive framework.[97]

Sensing and perceiving threat must be paired with response to threat if the organism is to survive. At each level of the central nervous system, just as the afferent input is interpreted and matched against previous similar patterns of activation an efferent arm is initiated. Each level and area of the brain has some role in the efferent response to the threat. The brainstem regulates the autonomic and hypothalamic output, alters arousal, and tunes out distracting sensory information; the midbrain regulates elements of motor activity (e.g., startle response); the limbic system modulates emotional reactivity and signalling (e.g., facial expression); and the cortex interprets the threat and develops a complex plan. Under ideal circumstances, these multiple responses are integrated and orchestrated to mobilize a host of actions that, hopefully, will be adaptive, reduce risk, and enhance survival. These responses are not always well integrated, however. Within each of the distinct neural systems responding to threat, independent responses can occur. When a Vietnam veteran jumps with an exaggerated startle response after a firecracker, despite knowing it is not gunfire, the brainstem-midbrain efferent responses have occurred before the cortex can contextualize and interpret the sound.

The specific response patterns for any individual or situation depend on many factors, including the nature, duration, severity, and history of exposure to similar threat. Age, of course, is a primary factor in determining how the individual will respond to threat. In infants and children, the higher, more complex parts of the central nervous system have yet to be organized or fully functional. The infant can still have a fear-induced startle, emotional distress, and age-appropriate reactivity in response to a traumatic experience but be unable to make a plan. Nor can the traumatized child easily use words to describe his or her terror. Adults often misunderstand the silence of maltreated or traumatized child, sometimes so badly that the child is considered resilient to trauma. It is a very common adult misperception that children are better at coping with change or stress than adults. Despite the apparent ease with which many young children survive trauma, they are much more vulnerable to trauma than adults. Indeed, it is increasingly clear that the sensitivity and organization of stress-response neurochemical systems are related to developmental experiences with stress.

Development of Stress Response Neurobiology

At birth, despite having all of its 100 billion neurons in place, the human brain is not completely organized or functional. Brain-mediated functions depend on the process of making and maintaining complex networks of neurons linked by specialized connections called synapses. During the first 6 months of life the number of synaptic connections rises dramtically. At 8 months of age, the synaptic number and density are higher than they will ever be.[89, 96] The development and organization of functionally important neuronal networks (systems) is use-dependent. Those synaptic connections that are used are maintained and strengthened, whereas those that are not are pruned out and lost. In a very concrete sense, the experiences of early childhood create patterns of neuronal activity that become the template neural networks and patterns (homeostasis) against which all future experience will be sensed, processed, and internalized.

The brain is comprised of many different systems and areas, each mediating some component of brain function. Not all of these systems and areas organize at the same time. At birth, simple regulatory functions (e.g., respiration, tempera-

ture regulation) are required and complex cognitive tasks are not. The brain organizes and neurodevelopment proceeds in a sequential fashion, starting from the lowest, most regulatory regions of the brain (i.e., brainstem) and continuing through to the higher, more complex areas (e.g., cortex). This sequential developmental process is guided by experience. As neural systems develop in a use-dependent fashion, it is critical that the specific nature, quantity, and pattern of sensory stimuli present in an infant or young child's life match this sequential development. To develop the motor systems (and, thereby, motor capabilities), the child must rock, crawl, walk, run, and dance. To organize the limbic areas and 'develop' the language of socio-emotional functioning, the child must have consistent, nurturing relationships. To organize cortical areas involved in language and cognition, the infant must be exposed to complex symbolic information (i.e., people must talk to the infant).

Timing of experience is crucial. The child who was emotionally neglected for his first 3 years and then adopted by a loving, caring, and nurturing family will still have problems with attachment, intimacy, social interactions, and other functions dependent on healthy limbic development. Sequential development requires that these optimizing experiences take place in the appropriate sequence, matching the child's developmental age. Furthermore, the healthy development of one region or capability is dependent on the healthy development of lower brain regions that takes place earlier in the process.[25, 83]

Stress-response systems develop early in life. The key neurobiologic systems that mediate the stress response are located in the brainstem and midbrain. Therefore both intrauterine and early childhood experiences play a major role in determining the sensitivity and final organization of these brainstem-mediated stress-response systems. The best characterizations of early manipulation and development of neurobiologic systems involved in stress come from animal research.[107] In animal models, very different adult stress-response neurobiology and functioning can be created using different patterns and types of intrauterine or perinatal stress.[104] In one model, for example, perinatal stress created anxious animals, whereas postnatal, moderate stress created resilient animals.[105]

In humans, studies have demonstrated the key role of the responsive, predictable caregiver in the development of a healthy stress-response neurobiology.[37–39] The infant who has a responsive and nurturing caregiver builds in the neurobiologic foundations for a flexible and maximally adaptive stress response. If the developing infant is allowed to explore his or her world and have a stable base to turn to when overwhelmed, this child is developing resilience to future stress and trauma. On the other hand, the child exposed to chaotic or threatening caregiving develops a sensitized stress-response system that affects arousal, emotional regulation, behavioral reactivity, and even cardiovascular regulation.[74, 76] These sensitized children are at risk for stress-induced neuropsychiatric problems later in life.[77]

STRESS-RESPONSE PATTERNS IN INFANCY AND CHILDHOOD

Human beings respond to stress with altered emotional, behavioral, cognitive, social, and physiologic functioning. The degree and nature of these responses varies from individual to individual in any single event, and across events for any given individual. Stress responses are heterogeneous and graded. Two primary but interactive response patterns (hyperarousal and dissociative) have been described.[83] Most individuals use various combinations of these two

distinct response patterns during any given traumatic event. The predominant response patterns appear to shift from dissociative to hyperarousal during development. Although incompletely characterized in children, these two major response patterns illustrate key principles of the neurodevelopmental perspective on trauma.

Hyperarousal: Fight or Flight Responses

The initial phase of the hyperarousal continuum is an alarm reaction that begins to activate the sympathetic nervous system. This alarm reaction is mediated by the locus coeruleus (LC). The LC is a bilateral nucleus of norepinephrine-containing neurons located on the floor of the fourth ventricle in the pons. It sends diverse axonal projections to virtually all major brain regions, enabling it to function as the primary regulator of noradrenergic tone and activity.[9, 31] The LC is important in the process of attending to novel stimuli, rank ordering the 'importance' of simultaneous sensory information, and mediating attentional and arousal states.[1, 2] In this central role of orchestrating incoming sensory information, the LC is a key mediator of the stress response.[10, 58] Other important brainstem nuclei, including the ventral tegmental nucleus (VTN), play a part in regulating the sympathetic nuclei in the pons and medulla,[66] and with the LC create the reticular activating system (RAS).[68] In addition to a role in stress response, the RAS plays key roles in regulating arousal, vigilance, affect, behavioral irritability, sleep, startle response, cardiovascular, and other regulatory functions that become dysregulated in trauma-related neuropsychiatric disorders.[8, 13, 63, 67]

The activity in the LC mirrors the degree of arousal (i.e., sleep, calm-alert, alarm-vigilant, fear and terror) related to stress or distress in the environment (internal and external). Fear increases LC and VTN activity, increasing the release of norepinephrine in all of the LC and VTN terminal fields throughout the brain. Further along in the hyperarousal continuum, alarm becomes fear. The LC tunes out noncritical information and mediates hypervigilance. This nucleus regulates the complex interactive process, which includes activation of centrally controlled autonomic nervous system tone, the immune system, and the hypothalamic-pituitary-adrenal (HPA) axis with resulting release in adrenocorticotropin and cortisol.[33] The sympathetic nervous system is further activated, increasing heart rate, blood pressure, and respiratory rate, mobilizing glucose, and increasing muscle tone. All of these actions prepare the body for defense—to fight with or run away from the potential threat. In the face of continuing threat, a full fight-or-flight response is activated. This response was first described by Cannon[20, 21] and has been the most studied, best-characterized stress-response pattern in humans.

If a child faced with threat responds with hyperarousal, there will be a dramatic increase in LC and VTN activity. The hypothalamic-pituitary-adrenal (HPA) axis is crucial to the orchestration of the peripheral response to threat. Corticotropin-releasing hormone (CRH) selectively stimulates and regulates ACTH secretions in animals.[33] ACTH, once released, in turn stimulates adrenal secretions of glucocorticoids or cortisol, which causes a myriad of peripheral adaptive responses, including gluconeogenesis, immune system mobilization, and altered cellular metabolism.

As with central neurobiologic systems, stress, distress, and trauma alter HPA regulation (i.e., a new homeostasis has been induced by the stress). Abnormalities of the HPA axis have been noted in adults with PTSD.[69] Chronic

activation of the HPA system in response to stress has negative consequences. The homeostatic state associated with chronic HPA activation wears the body out.[90, 91] Hippocampal damage, impaired glucose utilization, and vulnerability to metabolic insults[91] may result. Preliminary studies in a sample of abused children suggests similar hippocampal and limbic abnormalities.[48, 101]

Following an acute fear response, the brain creates a set of memories from the event. These memories are reactivated when the child is exposed to a specific reminder of the traumatic event (e.g., gunshots, the perpetrator). Furthermore, these memories can be reactivated when the child simply thinks about or dreams about the event. Unfortunately, one of the amazing strengths of the human brain, its capacity to make associations from the specific to the general, begins to betray the traumatized child. Specific cues from the traumatic event may generalize (e.g., gunshots to loud noises, a specific perpetrator to any strange male). In other words, despite being away from threat and the original trauma, these key parts of the child's brain are activated again and again. The memories of fear are seared into the child's neurobiology.

The use-dependent activation of these areas leads to sensitization. Sensitization of catecholamine (LC/VTN-amygdaloid) systems leads to a cascade of associated functional changes in brain-related functions.[56, 85, 106] Sensitization of the brain stem and midbrain neurotransmitter systems mediating the hyperarousal response also means that the other critical physiologic, cognitive, emotional, and behavioral functions that are mediated by these systems will become sensitized. Because the LC/VTN and its target regions (amygdaloid nuclei) also mediate a variety of other functions, sensitization of these systems by repetitive reexperience of the trauma leads to dysregulation of these functions.[5] A traumatized child may, therefore, exhibit motor hyperactivity, anxiety, behavioral impulsivity, sleep problems, tachycardia, and hypertension.[46, 72, 76, 81]

This means, of course, that the stress response itself becomes sensitized. Everyday stresses that previously may not have elicited any response are now able to elicit an exaggerated reactivity in children who are hyperreactive and overly sensitive. Simply stated, the child is in a persisting fear state. Furthermore, this means that the child's new basal homeostatic or equilibrium emotional state is a state of anxiety. This child will be more easily threatened or terrorized. Over time, these children exhibit a set of maladaptive emotional, behavioral, cognitive, social, and physiologic problems rooted in the original adaptive response to a traumatic event.

The few research studies examining catecholamine systems in children following trauma suggest a dysregulated, sensitized stress-response neurobiology. In a pilot study, sexually abused girls exhibited greater total catecholamine synthesis as measured by the sum of the urinary concentration of epinephrine, norepinephrine, and dopamine when compared with matched controls.[27, 28] In a group of 60 children with PTSD, altered cardiovascular regulation (e.g., increased resting heart rate) has been demonstrated, suggesting altered autonomic regulation at the level of the brainstem.[76, 82] In other studies, clonidine, an α_2-adrenergic receptor partial agonist, has been demonstrated to be an effective pharmacotherapeutic agent.[76] The presumed therapeutic site of action is the LC. These indirect studies all support the hypotheses of a use-dependent alteration in the brainstem catecholamine systems following childhood trauma.

The Dissociative Continuum

Infants, of course, are not capable of fight or flight. Their threat response patterns are unique and, in the initial stages of distress, are characterized by a

precursor form of a hyperarousal response. In these pre-alarm and alarm stages, the infant will use his or her limited behavioral repertoire to attract the attention of a caregiver. These behaviors include changes in facial expression, body movements, and, most important, vocalization (i.e., crying). This is a successful adaptive strategy if the caretaker comes to feed, warm, sooth, fight for, or flee with the infant.

Unfortunately, for many infants and children these strategies are not effective. Indeed, millions of children, if they are fussy, difficult, or weepy, are maltreated by the very adults who should be protecting them. In the absence of an appropriate caregiver reaction to the initial alarm outcry, the child will abandon this behavior. Furthermore, if the infant or child has few if any positive responses and negative responses, he or she will abandon this set of adaptations; the converse of use-dependent development occurs, disuse-related behavior extinction. This defeat response is well-characterized in animal models of stress reactivity and learned helplessness.[65] This defeat reaction is a common element of the presenting emotional and behavioral phenomenology of many neglected and abused children.[22, 24, 32, 65, 98, 99] Indeed, adults, professional or not, often puzzle over the emotional nonreactivity, passivity, and compliance of many abused children. All too often this defeat reaction is mistaken for resilience: "Can you believe how easy it is for her to talk about all those horrible things they did to her, and she is so easy to have around, so compliant. What a tough little girl! But I guess kids are just resilient, right?" Wrong. Children are malleable. Children become resilient if they incorporate a stress-response neurobiology that mirrors their experiences of predictable and nurturing caregiving.

In the face of threat, with no adequate response forthcoming from the initial alarm, the infant or young child will be forced to activate other responses to adapt. If the child is old enough, this may involve moving further along the hyperarousal continuum (the child's version of fight or flight); for infants, however, this will involve activation of dissociative adaptations. Dissociation is a broad descriptive term that includes a variety of mental mechanisms involved in disengaging from the external world and attending to stimuli in the internal world. It can involve distraction, avoidance, numbing, daydreaming, fugue, fantasy, derealization, depersonalization, and, in the extreme, fainting or catatonia. In our experiences with young children and infants, the predominant adaptive responses during the trauma are consistent with dissociative mechanisms. Children report going to a "different place," assuming persona of heroes or animals, a sense of "watching a movie that I was in" or "just floating"—classic depersonalization and derealization responses. Observers report these children as numb, robotic, nonreactive, daydreaming, "acting like he was not there," and staring off in a glazed look. The younger the child the more likely there will be primary dissociative adaptations. Immobilization, unavoidability, or pain will increase the dissociative components of the stress response patterns at any age.

In animals, the defeat response is mediated by different neurobiologic mechanisms than the fight or flight response. What little is known about the neurobiology and phenomenology of dissociation appears to most approximate the defeat reaction described in animals.[14, 41, 44, 65] As with the hyperarousal response, there is brainstem-mediated CNS activation that results in increases in circulating epinephrine and associated stress steroids.[34, 43, 45] A major difference in the CNS, however, is that vagal tone increases dramatically, decreasing blood pressure and heart rate (occasionally resulting in fainting) despite increases in circulating epinephrine.

Dopaminergic systems, primarily mesolimbic and mesocortical, play an important role in defeat reaction models in animals.[4, 41, 42, 49, 50, 51] These dopamin-

ergic systems are intimately involved in the reward systems, affect modulation (e.g., cocaine-induced euphoria), and, in some cases, are colocalized with endogenous opioids that mediate pain and other sensory processing.[19] The opioid systems are clearly involved in altering perception of painful stimuli, sense of time, place, and reality. Opioids appear to be major mediators of the defeat reaction's dissociative behaviors.[3] Indeed, most opiate agonists can induce dissociative responses in humans.

Little research on the neurobiology of dissociation in children exists. In our preliminary studies, traumatized children with dissociative symptoms demonstrated lower heart rates than traumatized children with hyperarousal symptoms. Cue-specific increases in heart rate were seen in the children with persisting hyperarousal symptoms.[82] In a recent case series with 10 children suffering from severe dissociative symptoms (e.g., fainting, catatonia, bradycardia), naltrexone, an opioid antagonist, improved dissociative symptoms.[80] The hypothesized therapeutic site of action is the opioid receptors regulating LC activity.[3]

The capacity to dissociate in the midst of terror appears to be a differentially available adaptive response; some people dissociate early in the arousal continuum, and some people dissociate only in the state of complete terror. The determinants of individual differences in the specific stress response to threat have yet to be well characterized. One important observation is a clear gender difference. Women tend to dissociate much more frequently than men. This is likely due to multiple factors, but it is a persistent observation across all ages and cultures. In its most common form, however, the child and adult response to trauma is a mixture of these two primary adaptive patterns. Mixture of hyperarousal with a partial dissociative response confers tremendous adaptive advantages (it is what allows the soldier to fight without panic). This advantage is age-dependent; for example, little adaptive advantage is conferred to a young child using only a hyperarousal response. Children's mixture of response preference changes with maturity. The older a child becomes, the more viable is a full-blown fight or flight response.

Freezing

One of the most common behavioral presentations seen in the combined hyperarousal-dissociation response pattern is freezing. The teleologic adaptive advantage of freezing is clear. Freezing makes it harder for movement-dependent predators to localize the prey. In the animal kingdom, freezing is a very common predecessor of flight. In some animals such as the opossum, the freezing response is the primary adaptive response to threat. For humans, freezing is only a component of a more complete set of possible responses. Fear impairs thinking, a human's best defense, and freezing can allow the escalating anxiety to plateau and give the person a chance to mentally regroup.

Children who have been traumatized and who have developed a sensitized hyperarousal or sensitized dissociative pattern often use freezing when they feel anxious. Typically this freezing behavior is labeled *oppositional-defiant*. The child with a history of maltreatment will feel threatened owing to an evocative stimulus that has tapped into emotional and state memories of previous threat (e.g., a family visit). Children rarely understand why they are anxious. In this state, they are less capable of processing complex information and are easily overwhelmed. They feel out of control and will cognitively, and often physically, freeze. Caregivers or teachers, unaware of this internal process, may ask the child to do something, but the child is 'frozen' and refuses. Typically, the adult—a teacher, a parent, a counselor—persists, and these directives involve more threat: "If you don't do this, I will . . ." The nonverbal and verbal character of this threat makes the child feel more anxious, threatened, and out of control.

The more anxious the child feels, the quicker the child will move from being anxious to threatened to terrorized. As the child becomes threatened and terrorized, the freezing may escalate into fight or flight, becoming aggressive or combative. Conversely, the child may dissolve into a regressed, near-psychotic dissociative state, a condition familiar to too many staff working with maltreated children.

Maladaptive Persistence of Stress Response Patterns and Neuropsychiatric Disorders

The use-dependent nature of neural systems ensures that the changes in homeostasis (i.e., memories) resulting from a traumatic event will be in those neural systems that mediated the stress response during the event. It will be in those neural systems that the altered homeostasis manifest as dysregulation and dysfunction.

If a child dissociates in response to a severe trauma and stays in that dissociative state for a sufficient period of time, he or she will alter the homeostasis of the systems mediating the dissociative response (i.e., opioid, dopaminergic, HPA axis). A sensitized neurobiology of dissociation will result and he or she may develop prominent dissociative-related symptoms (withdrawal, somatic complaints, dissociation, anxiety, helplessness, dependence) and disorders (dissociative disorders, somatoform disorder, anxiety disorders, major depression). Children may find artificial ways to facilitate soothing and reinforce opioid-mediated dissociation when they suffer from anxiety or other distress. Rocking, head banging, self-mutilation, and "cutting" are all distorted self-soothing activities related to the capacity of painful stimuli to activate the brain's opioid systems.

If a child is traumatized later in life and uses a predominately hyperarousal response, the altered homeostasis will be in different neurochemical systems (adrenergic, noradrenergic, HPA axis). This child will be vulnerable to developing persisting hyperarousal-related symptoms (hypervigilance, anxiety, impulsivity, sleep problems) and disorders (PTSD, ADHD, conduct disorder). Both groups are vulnerable to substance abuse and dependence: alcohol serves to reduce anxiety in both groups, opiates to induce soothing dissociation, and psychostimulants (cocaine) to activate dopaminergic "reward" areas in mesolimbic areas for the empty, "defeated" child.

When examining the epidemiologic data of neuropsychiatric disorders in children, there is a 3:1 male-to-female ratio of childhood psychiatric problems that tends to disappear in adolescence. In early adulthood, this ratio shifts to become 2:1 female-to-male. The childhood ratio reflects the nature and pattern of the gender distribution of primary preference in response to stress. Boys tend to use hyperarousal responses whereas girls are much more likely to dissociate. In childhood, more boys meet the diagnostic criteria for externalizing disorders such as ADHD, conduct disorder, and oppositional-defiant disorder. In girls there is a higher incidence of internalizing disorders such as depression, anxiety, and dissociative disorders.

Young boys typically come to the attention of the clinician because of their externalizing symptoms. There will be reports of aggression, inattentiveness,

and noncompliance. Typically these inattentive boys are diagnosed with ADHD. Young girls who have been similarly traumatized are not brought to the clinician by the parents (thus, perhaps, the 3:1 male-to-female ratio). The maltreated, dissociating girl daydreaming in the classroom is less bothersome to caregivers and teachers than the hyperactive, impulsive, and noncompliant boy. Girls are maltreated as much, if not more, than boys. Girls' brains process trauma with the same principles of neurodevelopment and neurophysiology as boys. Girls are damaged by trauma as much as boys, yet they are much less likely to get our help.

SUMMARY AND FUTURE DIRECTIONS: THERAPEUTIC AND POLICY IMPLICATIONS

All experiences change the brain, but not all experiences have an equal impact on the brain. Because the brain is developing and organizing at such an explosive rate in the first years of life, experiences during this period have more potential to influence the brain in positive and negative ways. Traumatic experiences and therapeutic experiences affect the same brain and are limited by the same principles of neurophysiology. Traumatic events disrupt homeostasis in the multiple areas of the brain that are recruited to respond to the threat. Use-dependent internalization of elements of the experience create memories that influence future functioning. To heal (i.e., alter or modify memories of trauma), therapeutic interventions must activate those portions of the brain that have been altered by the trauma. Understanding the persistence of fear-related emotional, behavioral, cognitive, and physiologic patterns can lead to focused therapeutic experiences that modify those parts of the brain affected by trauma.

A neurodevelopmental view of childhood trauma provides novel directions for assessment, intervention, and policy. Primary among these is the clear neurobiologic rationale for early identification and aggressive, proactive interventions that will improve our ability to protect, heal, educate, and enrich traumatized and neglected children. Future clinical and research efforts in this area must begin to define and use child-specific and developmentally informed models to guide assessment, intervention, education, therapeutics, and policy.

References

1. Abercrombie ED, Jacobs BL: Single-unit response of noradrenergic neurons in the locus coeruleus of freely moving cats. I. Acutely presented stressful and non-stressful stimuli. J Neurosci 7:2837–2843, 1987
2. Abercrombie ED, Jacobs BL: Single-unit response of noradrenergic neurons in the locus coeruleus of freely moving cats. II. Adaptation to chronically presented stressful stimuli. J Neurosci 7:2844–2848, 1987
3. Abercrombie ED, Jacobs BL: Systemic naloxone administration potentiates locus coeruleus noradrenergic neuronal activity under stressful but not non-stressful conditions. Brain Res 441:362–366, 1988
4. Abercrombie ED, Keefe KA, DiFrischia DS, et al: Differential effects of stress on in vivo dopamine release in striatum, nucleus accumbens and medial frontal cortex. J Neurochem 52:1655–1658, 1989
5. Adell A, Garcia-Marquez C, Armario A, et al: Chronic stress increases serotonin and noradrenaline in rat brain and sensitizes their responses to a further acute stress. J Neurochem 50:1678–1681, 1988

6. Adler A: Neuropsychiatric complications in victims of Boston's Coconut Grove disaster. JAMA 123:1098–1101, 1943
7. Amaya-Jackson L, March JS: Post-traumatic stress disorder. *In* March JS (ed): Anxiety Disorders in Children and Adolescents. New York, The Guilford Press, 1995, pp 276–300

7a. American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, ed 4. Washington, DC, American Psychiatric Association, 1994

8. Aston-Jones G, Chiang C, Alexinsky T: Discharge of noradrenergic locus coeruleus neurons in behaving rats and monkeys suggests a role in vigilance. *In* Barnes CD, Pomeiano O: Progress in Brain Research. Amsterdam, Elsevier Science Publishers, 1991, pp 501–519
9. Aston-Jones G, Ennis M, Pieribone J, et al: The brain nucleus locus coeruleus: Restricted afferent control over a broad efferent network. Science 234:734–737, 1986
10. Aston-Jones G, Valentino RJ, Van Bockstaele EJ, et al: Locus coeruleus, stress and post traumatic stress disorder: Neurobiological and clinical parallels. *In* Murberg M (ed): Catecholamine Function in Post-Traumatic Stress Disorder: Emerging Concepts. Washington, DC, American Psychiatric Press, 1996, pp 17–62
11. Bartanusz V, Jezova D, Bertini LT, et al: Stress-induced release in vasopressin and corticotropin releasing factor expression in hypophysiotropic paraventricular neurons. Endocrinology 132:895–902, 1993
12. Bennett EL, Diamond ML, Krech D, et al: Chemical and anatomical plasticity of the brain. Science 146:610–619, 1964
13. Bhaskaran D, Freed CR: Changes in neurotransmitter turnover in locus coeruleus by changes in arterial blood pressure. Brain Res Bull 21:191–199, 1988
14. Blanchard DC, Sakai RR, McEwen B, et al: Subordination stress: behavioral, brain and neuroendocrine correlates. Behav Brain Res 58:113–121, 1993
15. Bremmer J, Southwick S, Johnson D, et al: Childhood physical abuse and combat-related posttraumatic stress disorder in Vietnam veterans. Am J Psychiatry 150:235–239, 1993
16. Brown JW: Morphogenesis and mental process. Dev Psychopathol 6:551–563, 1994
17. Browne A, Finkelhor D: Impact of child sexual abuse: A review of the literature. Psychol Bull 99:66–77, 1986
18. Butler PD, Weiss JM, Stout JC, et al: Corticotropin-releasing factor produces fear-enhancing and behavioral activating effects following infusion into the locus coeruleus. J Neurosci 10:176–183, 1990
19. Caggiula AR, Antelman SM, Aul E, et al: Prior stress attenuates the analgesic response but sensitizes the corticosterone and cortical dopamine responses to stress 10 days later. Psychopharmacology (Berlin) 99:233–237, 1989
20. Cannon WB: Bodily Changes in Pain, Hunger, Fear and Rage. New York, Appleton, 1929
21. Cannon WB: The emergency function of the adrenal medulla in pain and the major emotions. Am J Physysiol 33:356–372, 1914
22. Carlson V, Cicchetti D, Barnett D, et al: Disorganized/disoriented attachment relationships in maltreated infants. Dev Psychol 25:525–531, 1989
23. Castro-Alamancos MA, Connors BW: Short-term plasticity of a thalamocortical pathway dynamically modulated by behavioral state. Science 272:274–276, 1996
24. Chisholm K, Carter MC, Ames EW, et al: Attachment security and indiscriminately friendly behavior in children adopted from Romanian orphanages. Dev Psychopathol 7:283–294, 1995
25. Courchesne E, Chisum H, Townsend J: Neural activity-dependent brain changes in development: Implications for psychopathology. Dev Psychopathol 6:697–722, 1994
26. Davis M: The role of the amygdala in conditioned fear. *In* Aggleton JP (ed): The Amygdala: Neurobiological Aspects of Emotion, Memory, and Mental Dysfunction. New York, Wiley-Liss, 1992, pp 255–306
27. De Bellis MD, Chrousos GP, Dorn LD, et al: Hypothalamic-pituitary-adrenal axis dysregulation in sexually abused girls. J Clin Endocrinol Metab 78:249–255, 1994
28. De Bellis MD, Lefter L, Trickett PK, et al: Urinary catecholamine excretion in sexually abused girls. J Am Acad Child Adolesc Psychiatry 33:320–327, 1994

29. Drell M, Siegel C, Gaensbauer T: Post-traumatic stress disorder. *In* Zeanah CH (ed): Handbook of Infant Mental Health. New York, Guilford Press, 1993, pp 291–304
30. Famularo R, Fenton T: Early developmental history and pediatric post-traumatic stress disorder. Arch Pediatr Adolesc Med 148:1032–1038, 1994
31. Foote SL, Bloom FE, Aston-Jones G: Nucleus locus coeruleus: New evidence of anatomical and physiological specificity. Physiol Rev 63:844–914, 1983
32. George C, Main M: Social interactions of young abused children: Approach, avoidance and aggression. Child Dev 50:306–318, 1979
33. Giller EL, Perry BD, Southwick S, et al: Psychoneuroendocrinology of post-traumatic stress disorder. *In* Wolf ME, Mosnaim AD (eds): Post-traumatic Stress Disorder: Etiology, Phenomenology and Treatment. Washington, DC, American Psychiatric Press, 1990, pp 158–170
34. Glavin GB: Stress and brain noradrenaline: A review. Neurosci Biobehav Rev 9:233–243, 1985
35. Goelet P, Kandel ER: Tracking the flow of learned information from membrane receptors to genome. Trends Neurosci 9:492–499, 1986
36. Goldstein DS: Stress, Catecholamines and Cardiovascular Disease. New York, Oxford University Press, 1995, pp 120–168
37. Gunnar MR: Human developmental psychoneuroendocrinology: A review of research on neuroendocrine responses to challenge and threat in infancy and childhood. *In* Lamb ME, Brown LA, Rogoff B, (eds): Advances in Developmental Psychology. Hillsdale, NJ, Lawrence Erlbaum, 1986, pp 51–103
38. Gunnar MR, Brodersen L, Krueger K: Dampening of adrenocortical responses during infancy: Normative changes and individual differences. Child Dev 67:877–889, 1996
39. Gunnar MR, Hertsgaard L, Larson M, et al: Cortisol and behavioral responses to repeated stressors in the human newborn. Dev Psychobiol 24:487–505, 1991
40. Haddad P, Garralda M: Hyperkinetic syndrome and disruptive early experiences. Br J Psychiatry 161:700–703, 1992
41. Heinsbroek RPW, van Haaren F, Feenstra MPG, et al: Controllable and uncontrollable footshock and monoaminergic activity in the frontal cortex of male and female rats. Brain Res 551:247–255, 1991
42. Heinsbroek RPW, van Haaren F, Feenstra MPG, et al: Sex differences in the effects of inescapable footshock on central catecholaminergic and serotonergic activity. Pharmacol Biochem Behav 37:539–550, 1990
43. Henry JP, Liu YY, Nadra WE, et al: Psychosocial stress can induce chronic hypertension in normotensive strains of rats. Hypertension 21:714–723, 1993
44. Henry JP, Stephens PM, Ely DL: Psychosocial hypertension and the defence and defeat reactions. J Hypertension 4:687–697, 1986
45. Herman JP, Guillonneau R, Dantzer R, et al: Differential effects of inescapable footshocks and of stimuli previously paired with inescapable footshocks on dopamine turnover in cortical and limbic areas of the rat. Life Sci 30:2207–2214, 1982
46. Hoffman WH, DiPiro JT, Tackett RL, et al: Relationship of plasma clonidine to growth hormone concentrations in children and adolescents. J Clin Pharmacol 29:538–542, 1989
47. Horowitz K, Weine S, Jekel J: PTSD symptoms in urban adolescent girls: Compounded community trauma. J Am Acad Child Adolesc Psychiatry 34:1353–1361, 1995
48. Ito Y, Teicher MH, Glod CA, et al: Increased prevalence of electrophysiological abnormalities in children with psychological, physical, and sexual abuse. J Neuropsychiatry 5:401–408, 1993
49. Kalivas PW: Sensitization to repeated enkephalin administration into the ventral tegmental area of the rat, II: Involvement of the mesolimbic dopamine system. J Pharmacol Exp Ther 235:544–550, 1985
50. Kalivas PW, Duffy P, Dilts R, et al: Enkephalin modulation of A 10 dopamine neurons: A role in dopamine sensitization. Ann NY Acad Sci 537:405–414, 1988
51. Kalivas PW, Richardson-Carlson R, Van Orden G: Cross sensitization between foot shock stress and enkephalin-induced motor activity. Biol Psychiatry 21:939–950, 1986
52. Kandel ER: Genes, nerve cells and remembrance of things past. J Neuropsychiatry Clin Neurosci 1:103–125, 1989

53. Kandel ER, Schwartz JH: Molecular biology of an elementary form of learning: Modulation of transmitter release by cyclic AMP. Science 218:433–443, 1982
54. Kaufman J: Depressive disorders in maltreated children. J Am Acad Child Adolesc Psychiatry 30:257–265, 1991
55. Kiser L, Heston J, Millsap P: Physical and sexual abuse in childhood: Relationship with post-traumatic stress disorder. J Am Acad Child Adolesc Psychiatry 30:776–783, 1991
56. Kleven MS, Perry BD, Woolverton WL, et al: Effects of repeated injections of cocaine on D-1 and D-2 dopamine receptors in rat brain. Brain Res 532:265–270, 1990
57. Konarska M, Stewart RE, McCarty R: Sensitization of sympathetic adrenal medullar responses to a novel stressor in chronically stressed laboratory rats. Physiol Behav 46:129–135, 1989
58. Korf J: Locus coeruleus, noradrenaline metabolism and stress. *In* Usdin E, Kvetnansky R, Kopin IJ (eds): Catecholamines and Stress. New York, Pergamon, 1976, pp 105–111
59. Lauder JM: Neurotransmitters as morphogens. Prog Brain Res 73:365–388, 1988
60. Leakey R: The Origins of Humankind. New York, Basic Books, 1994
61. LeDoux JE, Cicchetti P, Xagoraris A, et al: The lateral amygdaloid nucleus: Sensory interface of the amygdala in fear conditioning. J Neurosci 10:1062–1069, 1990
62. LeDoux JE, Romanski L, Xagoraris A: Indelibility of subcortical emotional memories. J Cogn Neurosci 1:238–243, 1989
63. Levine ES, Litto WJ, Jacobs BL: Activity of cat locus coeruleus noradrenergic neurons during the defense reaction. Brain Res 531:189–195, 1990
64. McFarlane AC: Post-traumatic phenomena in a longitudinal study of children following a natural disaster. J Am Acad Child Adolesc Psychiatry 26:764–769, 1987
65. Miczek KA, Thompson ML, Tornatzky W: Subordinate animals: Behavioral and physiological adaptations and opioid tolerance. *In* Brown MR, Koob GF, Rivier C (eds): Stress: Neurobiology and Neuroendocrinology. New York, Marcel Dekker, 1990, pp 323–357
66. Moore RY, Bloom FE: Central catecholamine neuron systems: Anatomy and physiology of the norepinephrine and epinephrine systems. Ann Rev Neurosci 2:113–153, 1979
67. Morilak DA, Fornal CA, Jacobs BL: Effects of physiological manipulations on locus coeruleus neuronal activity in freely moving cats. I. Thermoregulatory challenge. Brain Res 422:17–23, 1988
68. Munk MHJ, Roelfsema PR, Konig P, et al: Role of reticular activation in the modulation of intracortical synchronization. Science 272:271–273, 1996
69. Murberg MM, McFall ME, Veith RC: Catecholamines, stress and post-traumatic stress disorder. *In* Giller EL (ed): Biological Assessment and Treatment of Post-Traumatic Stress Disorder. Washington, DC, American Psychiatric Press, 1990, pp 27–65
70. National Clearinghouse on Child Abuse and Neglect Information WC: Child Abuse and Neglect Fact Sheet. Washington, DC, National Clearinghouse Brochure on Child Abuse and Neglect, 1993
71. Ogata SN, Silk KR, Goodrich S, et al: Childhood sexual and physical abuse in adult patients with borderline personality disorder. Am J Psychiatry 147:1008–1013, 1990
72. Ornitz EM, Pynoos RS: Startle modulation in children with post-traumatic stress disorder. Am J Psychiatry 147:866–870, 1989
73. Pelcovitz D, Kaplan S, Goldenberg BA, et al: Post-traumatic stress disorder in physically abused adolescents. J Am Acad Child Adolesc Psychiatry 33:312–319, 1994
74. Perry BD: Incubated in terror: Neurodevelopmental factors in the "cycle of violence." *In* Osofsky JD: Children in a Violent Society. New York, The Guilford Press, 1997, pp 124–149
75. Perry BD: Memories of fear: How the brain stores and retrieves physiological states, feelings, behaviors and thoughts from traumatic events. *In* Goodwin JM, Attias R (eds): Images of the Body In Trauma. New York, Basic Books, 1998
76. Perry BD: Neurobiological sequelae of childhood trauma: Post-traumatic stress disorders in children. *In* Murberg M (ed): Catecholamines in Post-traumatic Stress Disorder: Emerging Concepts. Washington, DC, American Psychiatric Press, 1994, pp 253–276

77. Perry BD: Neurodevelopment and the neurophysiology of trauma I: Conceptual considerations for clinical work with maltreated children. The APSAC Advisor 6:1–18, 1993
78. Perry BD: Neurodevelopmental aspects of childhood anxiety disorders: Neurobiological responses to threat. *In* Coffey CE, Brumback RA (eds): Textbook of Pediatric Neuropsychiatry. Washington, DC, American Psychiatric Press, 1988b
79. Perry BD: Placental and blood element neurotransmitter receptor regulation in humans: Potential models for studying neurochemical mechanisms underlying behavioral teratology. Prog Brain Res 73:189–206, 1988
80. Perry BD, Arvinte A, Pollard RA, et al: Syncope, bradycardia, catplexy and paralysis: Evidence of a sensitized opioid-mediated dissociative response following childhood trauma. Submitted, 1997
81. Perry BD, Pate JE: Neurodevelopment and the psychobiological roots of post-traumatic stress disorders. *In* Koziol LF, Stout CE (eds): The Neuropsychology of Mental Illness: A Practical Guide. Springfield, IL, Charles C Thomas, 1994
82. Perry BD, Pollard RA, Baker WL, et al: Continuous heartrate monitoring in maltreated children [abstract]. *In* Proceedings of the Annual Meeting of the American Academy of Child and Adolescent Psychiatry New Research, 1995
83. Perry BD, Pollard RA, Blakley TL, et al: Childhood trauma, the neurobiology of adaptation and use-dependent development of the brain: How states become traits. Infant Mental Health Journal 16:271–291, 1995
84. Perry BD, Southwick SM, Giller EL: Adrenergic receptors in post-traumatic stress disorder. *In* Giller EL (eds): Biological Assessment and Treatment of Post-traumatic Stress Disorder. Washington, DC, American Psychiatric Press, 1990, pp 89–114
85. Perry BD, Stolk JM, Vantini G, et al: Strain differences in rat brain epinephrine synthesis and alpha-adrenergic receptor number: Apparent 'in vivo' regulation of brain alpha-adrenergic receptors by epinephrine. Science 221:1297–1299, 1983
86. Phillips RG, LeDoux JE: Differential contribution of amygdala and hippocampus to cued and contextual fear conditioning. Behav Neurosci 106:274–285, 1992
87. Pynoos RS: Post-traumatic stress disorder in children and adolescents. *In* Garfinkel B, Carlson G, Weller E (eds): Psychiatric disorders in children and adolescents. Philadelphia, WB Saunders, 1990, pp 48–63
88. Pynoos RS: Traumatic stress and developmental psychopathology in children and adolescents. American Psychiatric Press Review of Psychiatry 12:205–238, 1995
89. Rakic P: Development of cerebral cortex in human and non-human primates. *In* Lewis M (ed): Child and Adolescent Psychiatry: A Comprehensive Textbook. New York, Williams and Wilkins, 1996, pp 9–30
90. Sapolsky RM, Plotsky PM: Hypercortisolism and its possible neural bases. Biol Psychiatry 27:937–952, 1990
91. Sapolsky RM, Uno H, Rebert CS, et al: Hippocampal damage associated with prolonged glucocorticoid exposure in primates. J Neurosci 10:2897–2902, 1990
92. Scheeringa MS, Zeanah CH, Drell MJ, et al: Two approaches to the diagnosis of post-traumatic stress disorder in infancy and early childhood. J Am Acad Child Adolesc Psychiatry 34:191–200, 1995
93. Schwab-Stone ME, Ayers TS, Kasprow W, et al: No safe haven: A study of violence exposure in an urban community. J Am Acad Child Adolesc Psychiatry 34:1343–1352, 1995
94. Schwarz E, Kowalski J: Malignant memories: Post-traumatic stress disorder in children and adults following a school shooting. J Am Acad Child Adolesc Psychiatry 30:937–944, 1991
95. Schwarz ED, Perry BD: The post-traumatic response in children and adolescents. Psychiatric Clin North Am 17:311–326, 1994
96. Shore R: Rethinking the Brain: New Insights into Early Development. New York, Families and Work Institute, 1997
97. Singer W: Development and plasticity of cortical processing architectures. Science 270:758–764, 1995
98. Spitz R: Hospitalism: An inquiry into the genesis of psychiatric conditions in early childhood. Psychoanal Study Child 1:53–74, 1945

99. Spitz RA, Wolf KM: Anaclitic depression: An inquiry into the genesis of psychiatric conditions in early childhood. II. Psychoanal Study Child 2:313–342, 1946
100. Taylor L, Zuckerman B, Harik V, et al: Exposure to violence among inner city parents and young children. Am J Dis Child 146:487–487, 1992
101. Teicher MH, Glod CA, Surrey J, et al: Early childhood abuse and limbic system ratings in adult psychiatric outpatients. J Neuropsychiatry 5:301–306, 1993
102. Terr L: Childhood traumas: An outline and overview. Am J Psychiatry 148:1–20, 1991
103. Terr LC: Chowchilla revisited: The effects of psychic trauma four years after a schoolbus kidnapping. Am J Psychiatry 138:1543–1550, 1983
104. Vaid RR, Yee BK, Shalev U, et al: Neonatal nonhandling and in utero prenatal stress reduce the density of NADPH-diaphorase-reactive neurons in the fascia denata and Ammon's Horn of rats. J Neurosci 17:5599–5609, 1997
105. Vallee M, Mayo W, Dellu F, et al: Prenatal stress induces high anxiety and postnatal handling induces low anxiety in adult offspring: Correlation with stress-inducing corticosterone secretion. J Neurosci 17:2626–2636, 1997
106. Vantini G, Perry BD, Gucchait RB, et al: Brain epinephrine systems: Detailed comparison of adrenergic and noradrenergic metabolism, receptor number and 'in vivo' regulation in two inbred rat strains. Brain Res 296:49–65, 1984
107. Weinstock M, Fride E, Hertzberg R: Prenatal stress effects on functional development of the offspring. Prog Brain Res 73:319–333, 1988

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