



Child Adolesc Psychiatric Clin N Am
12 (2003) 293–317

CHILD AND
ADOLESCENT
PSYCHIATRIC
CLINICS

The neurobiology of childhood trauma and abuse

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During the past decade there has been rapid progress in the understanding of the effects of exposure to traumatic life experiences on subsequent psychopathology in children. Trauma exposure affects what children anticipate and focus on and how they organize the way they appraise and process information. Trauma-induced alterations in threat perception are expressed in how they think, feel, behave, and regulate their biologic systems.

In recent years, preclinical studies in rodents and nonhuman primates have explored the basic biology of developmental trauma, and clinical research has started to spell out the impact of one-time traumatic incidents and exposure to chronic abuse and neglect. These studies have shown that isolated traumatic incidents tend to produce discrete conditioned behavioral and biologic responses to reminders of the trauma, whereas chronic maltreatment or unavoidable recurring traumatization, such as exposure to repeated medical or surgical procedures, has pervasive effects on neurobiologic development. Child abuse, neglect, and accidents often co-occur [1,2]. For example, neglected children are at risk for developing burns, and children of alcohol and drug abusing parents are at increased risk for falling victim to physical and sexual abuse [3].

The Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) field trial for posttraumatic stress disorder (PTSD) demonstrated that the age at which children are first traumatized, the frequency of their traumatic experiences, and the degree to which caregivers contribute to the event being traumatic all have a profound impact on the extent of their psychological damage. This is expressed in problems with self-regulation, aggression against self and others, problems with

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attention and dissociation, physical problems, and difficulties in self-concept and capacity to negotiate satisfactory interpersonal relationships [4].

The developmental neurobiology of PTSD has three general areas of impact on three interrelated developmental pathways: (1) on the maturation of specific brain structures at particular ages, (2) on physiologic and neuroendocrinologic responses, and (3) on the capacity to coordinate cognition, emotion regulation, and behavior. Trauma affects children differently at different stages of development. Ornitz [5] has proposed four critical periods of major structural change in brain development: early childhood (15 months–4 years), late childhood (6–10 years), puberty, and mid-adolescence. These stages in brain growth and cortical reorganization are related to developmental shifts in cognitive and emotional function, as first outlined by Piaget. They also correspond to a progression in children's estimates of external danger and capacities to imagine protecting themselves [6].

Nadel [7] has described how the different rates of maturation of the amygdala, hippocampus, and prefrontal regions affect posttraumatic reactions in the developing child. Because the amygdala starts functioning almost immediately after birth, children rapidly are able to experience fear and assess danger. Because the hippocampus, which is necessary to put danger in a spatial context, matures only gradually over the first 5 years of life, however, children only slowly acquire the capacity to identify and organize the nature of threat. There is good evidence that early abuse and neglect significantly affect the maturation of the hippocampus, which makes children with such histories vulnerable to misinterpret sensory input in the direction of danger and threat.

Contemporary research supports the notion that prolonged alarm reactions alter limbic, midbrain, and brain stem functions through "use-dependent" modifications. Chronic exposure to fearful stimuli affects the development of the hippocampus, the left cerebral cortex, and the cerebellar vermis and alters the capacity to integrate sensory input [8]. This changes the degree to which cortical and cerebellar structures can help the growing child modulate the limbic, midbrain, and brain stem responses to danger and fear. Current research is beginning to clarify the underlying pathophysiology of the difficulties with cognition, impulse control, aggression, and emotion regulation commonly observed in severely traumatized children.

The scope of the problem

It is virtually impossible to discuss trauma in children without addressing the quality of parental attachment bond. When accidents and other environmental traumas occur in the presence of supportive, if helpless, caregivers, the child's response largely mimics that of those parents—the more disorganized the parent, the more disorganized the child [9,10]. The security of attachment bonds seems to be the most important mitigating factor against trauma-induced disorganization. In contrast, trauma that affects the safety of attachment bonds interferes with the

capacity to integrate sensory, emotional, and cognitive information into a cohesive whole and sets the stage for unfocused and irrelevant responses to subsequent stress.

In the United States, approximately 3 million children are reported for abuse or neglect each year [11]; at least 15 out of every 1000 children in the United States have substantiated histories of abuse. In a survey of 16,000 adults who belonged to an HMO in California, 22% reported having been sexually abused and 30% were physically abused as children. In a random sample of 1225 female members of an HMO, 18.4% reported a history of childhood sexual abuse, 14.2% reported physical abuse, and 24.1% reported having been emotionally abused during childhood [12]. In a national survey, Finkelhor [13] reported that 27% of women and 16% of men had a history of childhood sexual abuse. It is estimated that neglect co-occurs frequently with abuse. Approximately 80% of all child abuse occurs at the hands of children's own parents (NIS-3, 1999), while other relatives are the perpetrators of another 10% of cases. Consistent with the fact that women represent the vast majority of primary caregivers, children are twice as likely to be neglected by women than by men: 87% versus 43%, respectively (NIS-3). Girls are sexually abused three times more often than boys, whereas boys have a 24% greater risk of serious injury from abuse and are 18% more likely to be emotionally neglected.

Stress regulation and attachment

The development of normal play and exploratory activity requires the presence of an attachment figure who helps modulate the child's physiologic arousal by providing a balance between soothing and stimulation. Field and Reite [14] have shown that the heart rate curves of mothers and infants parallel each other during their interactions. The capacity of caregivers to modulate physiologic arousal reinforces the child's attachment to them and allows a smooth alternation between activities that increase and reduce arousal as they go back and forth between exploring the environment and returning to their mothers. Stern [15] calls this "affect attunement" between caregivers and infants. In his studies, approximately 48% of the mothers' behaviors were described as attunements or mirroring: echoing of the infant's behavior in either the same or a different modality.

By providing soothing at the appropriate moments, caregivers not only protect children from the effects of stressful situations but also play the critical role of psychoneurobiologic regulators of the child's affective states by enabling the child to develop the biologic structures necessary to deal with future stressful experiences [16–18]. Having controllable stress reactions as an infant seems to be essential for the development of central nervous system connections that promote dealing with subsequent stresses.

Attachment researchers Bowlby and Stern have proposed that the attachment relationship creates an inner map of the world [19,20]. This map determines how the child views himself or herself, caregivers, and the way the world works. This

inner image consists of cognitive and affective knowledge of the world [17]. Emotions help interpret the meaning of the incoming stimuli by linking the present experience with past emotional reactions [21]. The emotional intensity provoked by particular stimuli determines the nature and flexibility of their behavioral responses. As long as emotions are modulated by (cognitive) awareness of what is happening, an organism is likely to be able to generate a flexible response. Emotion and cognition are important: children who only use cognitive schemes to deal with their environment and have no contact with their emotions are as disturbed as children who only use emotion [17].

In her infant studies, Mary Ainsworth has described roughly three ways in which infants organize their behavior in regard to their caregivers: secure, anxious/avoidant, and ambivalent [22]. These patterns are a function of differences in mothers' responsiveness to the signals of their children and how they subsequently cope in social settings. Secure infants tend to grow up being able to rely on their emotions and thoughts to help them determine their reactions to any given situation [17]. If children are exposed to unmanageable stress and if their caregivers do not actively help modulate their arousal, as frequently occurs when children are exposed to family violence, the children are unable to organize and categorize their experiences in a coherent fashion.

Carlson and Cicchetti have shown that 80% of traumatized children have disorganized attachment patterns [23]. When caregivers are extraordinarily inconsistent, frustrating, violent, intrusive, or neglectful, children are likely to become intolerably distressed, without a sense that the external environment will provide relief. Not being able to rely on their caregivers, these infants experience excessive anxiety, anger, and desire to be taken care of. These feelings may become so extreme as to precipitate dissociative states or self-defeating aggression. These frightened, spaced out, and hyperaroused children learn to ignore either what they feel (their emotions) or what they perceive (their cognitions) [24].

These children can neither regulate their emotional states nor compensate for their lack of affect regulation by relying on others to help them, the way children and adults usually cope with stress. This makes them vulnerable to respond with totalistic fight-or-flight or freeze reactions and keeps them from being able to learn from experience. These early patterns of attachment have powerful effects across the lifespan because they tend to establish how people process subsequent stressful information.

Neglect

Whereas almost total stimulus deprivation of infants can lead to extreme developmental delays, depression, and even death, lesser degrees of neglect have been associated with extremely poor peer relationships and the development of aggressive behaviors [25–27]. No stimulation at all actually may be even more detrimental to development than abuse. Isolation of animals during critical phases of development, an experience analogous to the neglect of human infants,

is an especially powerful predictor of subsequent aggressive behaviors [28]. The work of Spitz [29] and Bowlby [30,31] has illustrated the devastating developmental consequences of isolation for human infants [32]. Widom [33] showed that neglected children were even more dysfunctional and aggressive than children who are physically abused. One indication of the biologic underpinning of these behaviors was a study conducted by Carlson and Earls [34] of children reared in Romanian orphanages, which found that these children did not show the usual diurnal variation of cortisol levels that was found in home-reared Romanian comparison children. The orphans had significantly lower morning cortisol levels, which remained elevated relative to the lower afternoon levels of the comparison children.

The spectrum of psychopathology

Abuse, neglect, and exposure to multiple medical and surgical procedures have much more pervasive effects than single incident traumas. Whereas single trauma exposure in children occasionally precipitates the classic PTSD reactions that the DSM-III originally defined for combat veterans and burn victims, repeatedly traumatized children meet diagnostic criteria for many diagnoses [35,36], none of which capture their profound developmental disturbances or the traumatic origins of their particular clinical presentations. Symptoms of PTSD in chronically traumatized children are usually not prominent and tend to be obscured by their other cognitive, affective, social, and physical problems.

Because infants and toddlers who have been traumatized multiple times often experience developmental delays across a broad spectrum, including cognitive, language, motor, and socialization skills [36], they tend to display complex disturbances with various, often fluctuating, presentations. They generally meet numerous clinical diagnoses. In one study of 364 abused children in the United States [35], 58% met criteria for separation anxiety/overanxious disorder, 36% for phobic disorder, 35% for PTSD, 22% for attention deficit hyperactivity disorder, and 22% for oppositional defiant disorder. In prospective study by Putnam [37] of a group of sexually abused girls, anxiety, oppositional disorder, and phobia were clustered in one group, whereas depression, suicidality, PTSD, attention deficit hyperactivity disorder, and conduct disorder represented another cluster [37]. The spectrum of biologic, emotional, and cognitive abnormalities is expressed in a multitude of psychological, somatic, and behavioral problems that range from learning disabilities to aggression against self and others [38–42].

Biology shapes perception

The biologic structures that are “on-line” to interpret the meaning of sensory input determine how children perceive, remember, and integrate new experiences into the totality of the personality. Over the course of development, structural and neurochemical changes in the brain allow for ever more complex cognitive

organization of experience: “experience and brain combine to determine how children interpret their reality in a use-dependent manner” [43].

Whereas the fundamental neuroanatomic organization of the brain is determined by the genome, the internal working models used to categorize ongoing experience—located in the limbic system and frontal lobes—develop gradually as a child matures. Research by Meaney [44], Plotsky [45], and Suomi [46] have shown that naturally occurring variations in maternal care alter the expression of genes that regulate behavioral and endocrine responses to stress. The quality of maternal care also affects hippocampal synaptic development [44]. Meaney has shown that these effects significantly contribute to the development of stable, individual differences in stress reactivity and cognitive sets. These studies have demonstrated that stressors imposed on the mother increase stress reactivity in offspring [44].

The developing brain organizes and internalizes new information in a use-dependent fashion [47]: the more children live in a disorganized physiologic state (hyperarousal or detachment), the less they are capable of dealing with stressful experiences and the more likely their development is thrown off course by exposure to traumatic experiences. Trauma-induced neurobiologic disruptions of normal development involve the areas involved in the regulation of homeostasis: the brain stem and locus coeruleus; the brain memory systems (including hippocampus, amygdala, frontal cortex), and the brain areas involved in executive functioning, including the orbitofrontal cortex, the cingulate, and the dorsolateral prefrontal cortex. Trauma also affects the neuroendocrine system, including the hypothalamic-pituitary-adrenal (HPA) axis, and every conceivable neurotransmitter system [48,49].

Analogous to the findings that muscular input shapes the organization of the motor cortex, the patterns, intensity, and frequency of neuronal information about the self in relation to its surroundings received during critical periods of brain development determine the organization of the brain structures related to emotions and interpersonal understanding in a use-dependent fashion [18]. This neuronal organization decides how a person handles subsequent information. The areas involved in neural inhibitory mechanisms [18] and long-range planning (executive function) may be most significantly impacted [50]. What are some of these long-term effects of neurobiologic dysregulation?

Loss of self-regulation

Lack of capacity for emotional self-regulation is probably the most striking feature of chronically traumatized children [51]. Their lack of self-regulatory processes leads to problems with self-definition as reflected by (1) a lack of a continuous, predictable sense of self, with a poor sense of separateness and disturbances of body image, (2) poorly modulated affect and impulse control, including aggression against self and others, and (3) uncertainty about the reliability and predictability of others, leading to distrust, suspiciousness, and problems with intimacy [41,52].

They have distinct alterations in states of consciousness, with amnesia, hypermnesia, dissociation, depersonalization, and derealization [53], flashbacks and nightmares of specific events, school problems, difficulties in attention regulation, with orientation in time and space, and they suffer from sensorimotor developmental disorders [42]. High levels of emotional reactivity in early childhood predict numerous psychiatric problems as these children grow up, including depression, poor school performance, impulsivity, and criminal behavior [54–56].

Learning and memory

Traumatized children tend to become hypervigilant (ie, they develop intense physiologic hyperreactivity to stimuli reminiscent of threat). They become preoccupied with impending danger and tend to lash out in the face of ambiguous stimuli [57]. This affects how they organize their perceptions of the world and often is associated with the development of generalized problems in learning and academic achievement [25]. Many traumatized children narrow their attention to sources of threat and feeling uninterested or numb in response to things that other children may find challenging or stimulating. Paranoid ideation and misperceptions are common in traumatized children [58,59]. The phenomena of stimulus generalization and kindling are responsible for the fact that, over time, relatively low levels of external stimuli cause excessive neural activation [60]: once they are sensitized to interpret particular stimuli as sources of threat, minor stressors can elicit full-blown emergency response patterns.

Social problems

Children with histories of exposure to violence tend to have problems accurately reading social cues and have difficulty adopting their behavioral arousal to appropriate social demands [61]. As a result they are often out of tune with others, either socially withdrawn or bullying other children. Unable to regulate their emotions, they tend to scare other children away and lack reliable playmates and chums. Emotionally neglected children have been shown to be withdrawn, inattentive, and intellectually impaired in their elementary school years [62].

Physical illness

Other studies have demonstrated that traumatized children are vulnerable to a range of physical illnesses. As adults they have between 10% and 15% increased chance of suffering from cancer, heart disease, and diabetes [12]. During adolescence they tend to engage in destructive acting out against themselves and others and have approximately a 300% greater chance than their nonabused peers to engage in drug abuse, self-mutilation, and violent and aggressive behavior against others [12].

Without early intervention there is little evidence that children outgrow these problems. As adults, they have a vastly increased chance of meeting

diagnostic criteria for borderline personality disorder [63], somatization disorder [64], and dissociative disorders [64–67] and engaging in self-destructive actions, including self-mutilation [40], anorexia and binge eating [68], and substance abuse [12].

Preclinical studies

Fifty years ago, Denenberg [69] first showed that 5 minutes of human handling during a rat's infancy led to lasting changes in their behavior and response to stress. More recently, research by Meaney and Plotsky has shown that the effects of brief handling are highly beneficial [70]. Daily handling within the first few weeks of life (picking up rat pups and then returning them to their mother) results in increased type II glucocorticoid receptor binding that persists throughout. These effects seem to be caused by "stress inoculation" from the mothers [71].

In pups, human handling provides similar benefits as licking and grooming by their mothers. In contrast, long-term isolation produces stress that has a deleterious effect on brain development. Maternally deprived rats had decreased cortisol in the hippocampus, hypothalamus, and frontal cortex [72]. Early postnatal adverse exposure induces glucocorticoid [73] and ACTH release [72].

Assuming that intense exposure to attention, licking, and grooming in rodents is equivalent to "good enough mothering" in humans and that lack of attention is equivalent to neglect, this animal model has become generally accepted as a preclinical model of the biologic consequences of neglect or abuse in children [8]. In recent years there has been a gradual growth of data in human infants and children regarding how caregivers become the "hidden regulators" of their immature endocrine and nervous systems [16], which is at least partially mediated via the regulation of the infant's hypothalamic production of corticotropin-releasing factor (CRF) [74] and inadequate development of glucocorticoid receptor feedback mechanisms.

These alterations increase the risk of an excessive stress hormone response to subsequent adversity. This is one of the factors that mediates the relationship between lack of maternal attention, heightened levels of fear, and increased norepinephrine secretion during stress. Altered corticosteroid metabolism affects immune and inflammatory responses [75], neuronal irritability, and enhanced susceptibility to seizures [8]. Still other consequences of an abnormally intense corticosterone response are reduced brain weight and DNA content, suppressed cell growth in the cerebellum and hippocampus, and interference with myelination [8].

Brain stem and midbrain

Because at birth the brain stem areas responsible for regulating cardiovascular and respiratory functions are fully functioning, infants can take care of these basic

functions without help. Most other functions require assistance from caregivers until the central nervous system is sufficiently mature to take over. Dealing with threat is mediated by the sympathetic and parasympathetic nervous systems, which originate in the brain stem. Early exposure to extreme threat and inadequate caregiving significantly affects the long-term capacity of the human organism to modulate the sympathetic and parasympathetic nervous systems in response to subsequent stress.

The sympathetic nervous system is primarily a system of mobilization; it prepares the body for emergencies by increasing cardiac output, stimulating sweat glands, and inhibiting the gastrointestinal tract. Because the sympathetic nervous system has long been associated with emotion, much work has been conducted on the role of the sympathetic nervous system in order to identify autonomic “signatures” of specific affective states. Overall, increased adrenergic activity is found in approximately two thirds of traumatized children and adults [76]. However, simple elevations in sympathetic activity do not explain the complex emotional and behavioral responses seen in traumatized children. Traumatized children have unpredictable levels of emotional reactivity: intense feelings of terror sometimes result in immobilization or freezing, while intense anxiety can lead to massive mobilization.

Catecholamines

The weight of current research suggests that early neglect and abuse lead to overstimulation of the noradrenergic system and to subsequent enzyme induction. Maltreated children with PTSD excrete significantly greater concentrations of urinary dopamine (DA) and norepinephrine (NE) over 24 hours than control subjects [77,78].

In one study [79], 12 sexually abused girls were found to secrete significantly greater amounts of homovanillic acid, a metabolite of dopamine, than a comparison group, which indicated higher catecholamine activity. The same group demonstrated that abused children who suffer from PTSD excreted significantly greater concentrations of baseline epinephrine and dopamine compared to nonabused anxious and healthy controls, measures that correlated significantly with duration of abuse [78].

The parasympathetic nervous system

The modulatory role of the parasympathetic nervous system (which plays a significant role in affect regulation [80–82]), has been much less extensively studied in traumatized children and adults, in part because of greater methodologic complexity. Vagal fibers that originate in the brain stem affect emotional and behavioral responses to stress by inhibiting sympathetic influence to the sino-

atrial node and promoting rapid decreases in metabolic output that enable almost instantaneous shifts in behavioral state [82–84].

The parasympathetic nervous system consists of two branches: the ventral vagal and the dorsal vagal systems. The dorsal vagal complex is primarily associated with digestive, taste, and hypoxic responses in mammals. Under most conditions, the dorsal vagal complex maintains tone to the gut and promotes digestive processes. If upregulated, however, the dorsal vagal complex contributes to pathophysiologic conditions, including the formation of ulcers via excess gastric secretion and colitis. In contrast, the ventral vagal complex has the primary control of supradiaphragmatic visceral organs, including the larynx, pharynx, bronchi, esophagus, and heart [55,85].

Motor pathways from the ventral vagal complex to visceromotor organs (eg, heart and bronchi) and somatomotor structures (eg, larynx, pharynx, esophagus) are myelinated to provide tight control and speed in responding [85]. The ventral vagal complex inhibits the strong mobilization responses of the sympathetic nervous system. This rapid regulation characterizes the qualities of the mammalian vagal brake that enables rapid engagement and disengagement in the environment. In mammals, the ventral vagal complex is believed to be highly reactive to input by caregivers [85]. Recovery from stress is associated with increased vagal modulation, even in the presence of residual sympathetic activation [50]. Deficient vagal modulatory capacity also has been documented in traumatized boys and in school children with internalizing problems [86,87]. Lack of ventral vagal modulation of the infantile stress response may help clarify how disrupted early attachment patterns can contribute to long-lasting problems with control of affect regulation and lack of responsiveness to interpersonal comfort.

Heart rate variability

Currently, power spectral analysis of heart rate variability provides the best available means of measuring the interaction of sympathetic and parasympathetic tone (ie, brain stem regulatory integrity) [80]. Standardized heart rate analysis of patients with PTSD at rest has demonstrated a baseline autonomic hyperarousal state in these patients. They have lower resting heart rate variability compared with controls, which suggests increased sympathetic and decreased parasympathetic tone [88].

Several studies have found that patients with PTSD, unlike patients with panic disorder and controls, may not respond to reminders of their trauma with increases in heart rate and low frequency components of heart rate variability and with autonomic correlates of distress [89]. In these studies, traumatized subjects who did not develop PTSD exhibited significant autonomic responses to a reminder of their trauma, whereas patients with PTSD showed almost no autonomic response to the recounting of the triggering stressful event. One study [89] found that patients with PTSD had a similar degree of autonomic dysregu-

lation at rest as did control subjects in response to a personal stressor. Patients with PTSD overreacted to nonthreatening stimuli the way others reacted to reminders of traumatic incidents. Adults and children with PTSD have less vagal control over their heart rate in response to such mental challenges as an arithmetic task than nontraumatized controls [90]. These data support the notion that PTSD is associated with a fundamental dysregulation of arousal modulation at the brain stem level.

Decreased autonomic reactions in traumatized children with compromised vagal inhibition may contribute to their well-documented problems misreading social cues and responding inappropriately in peer relationships [91]. A recent cross-sectional study of 122 children aged 6 to 7 years examined sympathetic and parasympathetic reactivity to standardized field laboratory stressors as predictors of parent- and teacher-reported mental health symptoms. Measures of autonomic reactivity discriminated between children with internalizing and externalizing behavior problems. Internalizing children showed high reactivity relative to low-symptom children, principally in the parasympathetic branch, whereas externalizing children showed low reactivity in both autonomic branches [92].

The hypothalamic-pituitary-adrenal axis

Corticotropin-releasing factor

Nemeroff et al have proposed that the relationship between early life stress and the development of psychiatric disorders is mediated by persistent changes in CRF neurotransmission and alterations in other neurotransmitter systems involved in the regulation of the stress responses [93]. CRF is the major coordinator of the behavioral, autonomic, immune, and endocrine components of the mammalian stress response and a central component of the HPA axis, the major neuro-endocrine stress response system.

Administration of CRF produces effects that mimic stress, depression, and anxiety, including increases in peripheral catecholamine secretion, heart rate, and arterial pressure, changes in gastrointestinal activity, decreased reproductive behavior, decreased appetite, disruption of sleep, increased grooming behavior, increased locomotor activity in familiar environments, suppression of exploratory behavior in novel environments, potentiation of acoustic startle responses, facilitation of fear conditioning, and enhancement of shock-induced freezing and fighting behavior [93,94].

The neocortex and the central nucleus of the amygdala contain an abundance of CRF neurons and receptors. The CRF neurons of the central nucleus of the amygdala are directly and indirectly connected to brain stem nuclei, including the locus coeruleus and the raphe nuclei [95]. CRF controls the synthesis of ACTH, a hormone that facilitates imprinting. CRF also regulates the production of β -endorphin.

Cortisol

Although increased glucocorticoid secretion is critical to the adaptation of an organism to stress, prolonged or excessive exposure to glucocorticoids may damage the central nervous system and physical organs [97].

High levels of glucocorticoids are associated with deficits in new learning and damage to the hippocampus [96]. Circulating glucocorticoids exert a wide range of metabolic and immunomodulating effects that counterregulate the neuroendocrine stress response by negative feedback at pituitary, hypothalamic, and hippocampal levels.

The HPA axis has been implicated in the pathophysiology of PTSD in children [34,98]. In general (and in contrast to the cortisol studies of adults with PTSD), traumatized children show significantly elevated cortisol levels compared with control groups. Even infants with disorganized or disoriented attachment responses were found to have higher cortisol levels during the Strange Situation Test [99]. A study of children with PTSD living in stable situations [77] showed increased levels of 24-hour urinary cortisol in comparison to healthy controls. These findings have been ascribed to a lack or immaturity of adaptation of the HPA axis.

As children grow older, a different picture emerges, probably a function of the organisms' downregulation of an overly challenged HPA axis. A longitudinal study of sexually abused girls [100] found dysregulation of the HPA axis with a blunted ACTH response to ovine corticotropin-releasing hormone (oCRH), but without increased cortisol secretion. It is assumed that this is the result of adaptive down regulation of the HPA axis in response to stress-related hypersecretion of CRF.

The limbic system

The limbic system is the area of the brain dedicated to the regulation of self-preservation and procreation, parenting, and play. It fine tunes the regulatory functions of the hypothalamus and brain stem and serves as a filter that determines what sensory input is relevant for further mental processing. The amygdala, in particular, rapidly appraises complex information for its existential relevance and organizes self-protective behavior by signaling the emotional intensity that particular stimuli evoke. Signals from the amygdala initiate autonomic responses, such as increased heart rate and blood pressure, and activate defense (eg, fight-or-flight and freeze) reactions. The limbic appraisal system circuit bypasses cortical evaluation, which allows for quick (but "irrational") emergency responses.

The amygdala makes the initial interpretation of whether an incoming stimulus constitutes a threat and initiates emotional responses by transforming sensory stimuli into emotional and hormonal signals [101]. Projections from the amygdala to the rostral ventral medulla and the lateral hypothalamus initiate sympathetic and parasympathetic nervous system responses. Projections from the amygdala to the

brain stem activate a startle responses and initiate defensive behaviors that do not require direct action of the sympathetic nervous system, whereas projections from the amygdala to the solitary tract initiate the parasympathetic responses, which may constrain autonomic arousal. Projections from the central amygdala to the bed nucleus of the stria terminalis initiate the HPA axis response.

Numerous studies have reported activation of the amygdala during early phases of aversive conditioning, which shows that the amygdala is necessary for the establishment of conditioned fear [102]. Most of these studies have focused on fear perception and show that the amygdala is important for the recognition of cues of threat or danger. For example, the amygdala is activated in response to facial expressions of fear, compared with neutral, happy, or disgusted control faces [103,104], even when subjects are exposed to masked-fear faces that were not consciously perceived [105].

The author's research on traumatized adults showed increased activation of the right amygdala in people who suffer from PTSD, when reminded of their trauma, accompanied by decreased activation of the speech center of the brain, Broca's area changes [106]. When amygdala activation in response to sensory stimuli reminiscent of a trauma causes the misinterpretation of an innocuous stimulus as a threat, this precipitates inappropriate fight/flight/freeze responses. This causes this system to react to minor irritations in a stereotyped, totalistic manner, preventing learning from experience. These immediate responses are so difficult to extinguish that LeDoux has called the memories associated with these limbic circuits "indelible" [107].

The hippocampus and trauma

The hippocampus plays a significant role in the capacity to recall specific life events consciously (ie, in context-dependent memory) [108]. Its role in emotion has received less attention. When an animal is exposed to a cue-conditioning procedure in which a discrete cue is paired with an aversive outcome, the animal also learns to associate the context in which the learning occurs with the aversive outcome. Lesions to the hippocampus abolish this context-dependent form of memory but have no effect on learning cue-punishment contingencies [109].

The high density of glucocorticoid receptors in the hippocampus supports the idea that it plays an important role in emotion regulation. Glucocorticoids have a powerful impact on hippocampal neurons [97,110]. Exogenous administration of large doses of hydrocortisone to humans impairs explicit memory [111], whereas more moderate amounts of cortisol may facilitate memory [1].

Several PTSD studies have reported significantly decreased hippocampal volume in patients with PTSD [112,113]. Bremner et al [112] compared MRI scans of 17 adult survivors of childhood physical or sexual abuse with PTSD with 17 healthy controls. The left hippocampus of abused patients with PTSD was 12% smaller than the hippocampus of the healthy controls, but the right hippocampus was of normal size, as were other brain regions, including the

amygdala, caudate nucleus, and temporal lobe. Consistent with the role of the hippocampus in memory, these patients also had lower verbal memory scores than the nonabused group.

Stein et al [114] also found left hippocampal abnormalities in women who had been sexually abused as children. Their left hippocampal volume was significantly reduced, but the right hippocampus was relatively unaffected. Fifteen of the 21 sexually abused women had PTSD; 15 had a dissociative disorder. They suffered a reduction in the size of the left hippocampus proportionate to the severity of their symptoms. These subjects also exhibit neuropsychological abnormalities that can be associated with impaired hippocampal functioning, such as difficulty learning from negative experiences, despite extreme emotional and biologic reactivity to reminders of their traumas.

Several well-controlled studies have failed to replicate these findings in acutely traumatized children [115] or adults [116]. The weight of the evidence suggests that subjects with histories of severe childhood trauma are vulnerable to developing smaller hippocampi over time. In the studies in which hippocampal atrophy has been found, investigators have proposed that excessively high levels of cortisol caused hippocampal cell death, resulting in hippocampal atrophy.

Davidson et al [109] have proposed that the impact of hippocampal involvement in psychopathology may be most apparent in the processing of emotional information and that in individuals with compromised hippocampal function, the normal context-regulatory role of this brain region would be impaired. Consequently, children with hippocampal damage would be prone to display emotional behavior in inappropriate contexts.

The prefrontal cortex

Learning from experience means that incoming input must be registered in consciousness, compared with what the child already knows, and evaluated for an appropriate response. These are all functions of the frontal cortex: the capacity for representational memory, a cornerstone for the development of a delayed response, depends on the maturation of the frontal cortex. Traumatized kids tend to have serious problems carrying out a host of these functions. Excessive subcortical activation, combined with decreased cortical inhibition, would make them vulnerable to disregard the precise nature of incoming information.

Children must develop “object permanence” to modulate an emotional expression through cognitive processes, (ie, be able to recognize that an object has continuity in time and space when they cannot actually see it) [74]. This represents what Bowlby [19] called the development of “internal working models.” These working models are defined largely by the child’s internalization of the affective and cognitive characteristics of their primary relationships. “Children learn to regulate their impulsive behavior by being able to anticipate the mother’s response to it” [74]. Neural development and social interaction are inextricably intertwined. As Tucker [117] states: “For the human brain, the most

important information for successful development is conveyed by the social rather than the physical environment. The baby brain must begin participating effectively in the process of social information transmission that offers entry into the culture.”

To respond adaptively to his or her environment, a child must feel calm enough to form an accurate perception of incoming stimuli. Arousal is mediated, at least in part, by elevated norepinephrine. This is associated with impaired function of the prefrontal cortex [118], planning and organizing, using “working memory”, and inhibiting inappropriate responses and attention to distractions (“executive functions”). The interaction between the capacity to modulate autonomic arousal and frontal lobe (executive) function was illustrated by a study by Mezzacappa et al [86], which showed that executive control is associated with vagal modulation of respiratory driven, high-frequency heart-rate variability, whereas motivational control is associated with sympathetic modulation of posturally driven, low-frequency heart-rate variability. Competence in executive control is associated with greater vagal modulation. This is consistent with the observation that traumatized boys have deficient executive control and vagal modulatory capacity and do not improve on these dimensions as they mature [86,87].

When children feel threatened and activate their noradrenergic alarm system, the fast tracts of the limbic system are activated before the slower prefrontal cortex has a chance to evaluate the stimulus [119]. Hyperarousal interferes with the activation of the orbitofrontal cortex, which is needed for subtle stimulus discrimination, learning, and problem solving [120]. Bremner [121] and Shin [122] found a relative failure of orbitofrontal activation with traumatic imagery in patients with histories of childhood trauma-related PTSD.

Evidence from neuropsychological, neurologic, and brain imaging studies suggests that antisocial and aggressive behavior is related to functional deficits in the prefrontal area. It has been proposed that the social and executive function demands of late adolescence, in particular, are likely to overload the late developing prefrontal cortex, giving rise to prefrontal dysfunction and a lack of inhibitory control over the antisocial, violent “acting out” that peaks at this age [123].

Difficulties in responding appropriately to different levels of stress do not depend on deficits in a specific brain structure but generally involve distributed brain systems that include increased subcortical sensitivity combined with decreased frontal lobe functioning. A recent analysis of positron emission tomographic activation during the performance of a working memory task specifically studied distributed brain systems in PTSD [124]. Patients with PTSD suffered from abnormal working memory updating. This was correlated to an abnormal functional connectivity pattern characterized by relatively more activation in the bilateral inferior parietal lobes and less activation in the inferior medial frontal lobe, bilateral middle frontal gyri, and right inferior temporal gyrus.

Adults with PTSD are known to have problems on tests of sustained attention, mental manipulation, initial acquisition of information, and retroactive interfer-

ence. Their performance also is characterized by errors of commission and intrusion [125]. Similar findings recently were documented in children with abuse-related PTSD [126]. Compared with healthy controls, children with PTSD performed more poorly on measures of attention and abstract reasoning/executive function and were more distracted and impulsive than controls. The Stroop and the Wisconsin Card sort tests, measures of frontal lobe function, revealed significant deficits.

Altered hemispheric lateralization

In Rauch et al's first neuroimaging study of adults with PTSD [106], the authors found marked hemispheric lateralization in patients with PTSD exposed to traumatic reminders. Subsequently, Teicher [127] found clinically significant left-sided electroencephalographic abnormalities in most patients with a history of early trauma, whereas in the nonabused group, left-sided electroencephalographic abnormalities were rare. In the psychologically abused group, all the electroencephalographic abnormalities were left-sided.

Teicher [8] measured hemispheric activity in adults during recall of a neutral memory and then during recall of an upsetting childhood memory. Patients with a history of child abuse seemed to use predominantly their left hemispheres when thinking about neutral memories and their right hemispheres when recalling an early disturbing memory. Persons in the control group had a more integrated bilateral response. Measures of electroencephalographic coherence indicated that the left cortex of the healthy controls was more developed than the right cortex, which is consistent with the anatomy of the dominant hemisphere. The abused patients, however, were notably more developed in the right than the left cortex, although all were right-handed. The right hemisphere of abused patients had developed as much as the right hemisphere of the controls, but their left hemispheres lagged substantially, as though arrested in their development. Another recent neuroimaging study of 24 children with a history of trauma and PTSD demonstrated a similar frontal lobe asymmetry [128].

This finding of left cortex underdevelopment is consistent with Teicher's earlier finding that abused patients had increased left-hemisphere electroencephalographic abnormalities and left-hemisphere (verbal) deficits on neuropsychological testing. The left hemisphere is specialized for perceiving and expressing language, and the right hemisphere is for processing spatial information and processing and expressing negative emotions.

Because childhood abuse is associated with diminished right-left hemisphere integration, two different investigators [8,116] studied whether there was a deficiency in the corpus callosum, the primary pathway that connects the two hemispheres. They found that the middle portions of the corpus callosum were significantly smaller in boys with histories of severe abuse or neglect than in the control groups. In boys, neglect exerted a far greater effect than any other type of maltreatment; physical and sexual abuse exerted relatively small effects. In girls,

however, sexual abuse was a more powerful factor and was associated with a major reduction in size of the middle portions of the corpus callosum.

The cerebellum, corpus callosum, and integration of experience

In his early studies in the Wisconsin Primate Laboratory, Harry Harlow examined the effects of monkeys being raised with their mothers compared with monkeys raised with wire or terrycloth surrogate mothers. Monkeys raised with the surrogates became socially deviant and highly aggressive adults [8,46]. Subsequently, other investigators found that the adverse effects of surrogate rearing were attenuated if the surrogate mother swung from side to side. This type of movement is associated with the cerebellum, particularly to the cerebellar vermis, which integrates sensory information with motoric action [8]. Similar to the hippocampus, the cerebellum develops gradually over the course of human development and continues to create new neurons after birth. It also has a high density of cortisol receptors, which makes it vulnerable to stress, similar to the hippocampus [8].

Teicher et al [8] found that the vermis plays a role in controlling and quelling electrical irritability in the limbic system. It seems that the cerebellar vermis not only is important for postural, attentional, and emotional balance but also plays a role in regulating emotional instability. Teicher proposed that stimulation of the vermis through exercise, rocking, and movement may exert calming effects on traumatized children and adolescents.

Teicher's work on abnormal cerebral lateralization in traumatized children confirms the existence of inadequate development of the corpus callosum and hippocampus [8].

Implications for treatment

Traumatized children tend to communicate what has happened to them not in words but by responding to the world as a dangerous place and by activating neurobiologic systems geared for survival, even when they objectively are safe. At the core of posttraumatic symptomatology is the tendency to remain biologically "fixated" on reliving the traumatic past and shut oneself down for new experiences that might provide restitution and resolution. Learning from experience is only possible when children are in a physiologic state that allows them to consider new possibilities.

Much of the impact of trauma is on subcortical structures and on the degree to which cortical and cerebellar structures can help the growing child modulate his or her limbic, midbrain, and brain stem responses to danger and fear. Traditional therapies have relied either on words and meaning making or on medications to help modulate these neurobiologic systems. Parents and teachers do not necessarily help children deal with extreme stress by talking or drugs, however, but by providing a physical sense of safety, including holding and rocking, and

demonstrating that when the child's own resources fail, someone else is there to take over to reestablish a sense of safety and predictability. In the absence of such soothing presences, children are likely to demonstrate difficulties with cognition, impulse control, aggression, and emotion regulation.

Having controllable stress reactions seems to be essential for the development of central nervous system connections that promote neural inhibitory mechanisms and long-range planning (executive function), generally, to coordinate cognition, emotion regulation, and behavior. When treating traumatized children, it is essential to establish safe conditions, such as shielding them from potential dangers, including human perpetrators. It also is critical to provide boundaries, rules, and predictability to promote the capacity to inhibit impulses. Because traumatized children are prone to experience novel stimuli, including rules and other protective interventions, as sources of threat, they easily respond to their teachers and therapists as perpetrators [42].

Faced with their aggression, withdrawal, shyness, and inability to read social cues, caregivers have a tendency to deal with their frustration by retaliating in ways that often uncannily repeat the children's earlier traumas.

Clinical experience shows that children's are unlikely to give up their primitive self-protective behaviors until they learn how to feel physically competent and secure. Actual experience with safety and predictability is essential to establish the capacity to regulate physiologic arousal that is indispensable for observing what is going on, process the information, and initiate the appropriate motor responses (ie, for the establishment of executive functioning). Only after acquiring an internal sense of personal competence and gaining a feeling of predictability are children likely to gain sufficient physiologic control over their arousal to start learning from new experiences and learn to respond flexibly to new challenges.

Traumatized children must be helped actively to overcome their habitual fight/flight/freeze reactions by engaging their attention in actions that (1) are not related to trauma triggers and (2) provide them with a sense of mastery and pleasure [42].

Once children develop the capacity to focus on activities without becoming disorganized, they are in a position to develop skills and engage in nondisruptive play with other children. Without these basic capacities for executive functioning (ie, observing before reacting), they are not capable of remembering their traumatic experiences without becoming disorganized and working through their traumatic experiences without becoming hopelessly disorganized.

Children must learn to know what they feel, put those feelings into words, or find some other symbolic expression (drawing, play acting) that can allow them to gain distance from the traumatic events and help them imagine alternative outcomes.

Mastery is most of all a physical experience: the feeling of being in charge, being calm and able to engage in focused efforts to accomplish the goals one sets for oneself. Trauma does not primarily affect cognitive functions; the entire organism is affected; trauma-related hyperarousal and numbing is experienced on a physical level. Children's somatic hyperarousal is observable in their irritability

and their inability to relax or in their numbness and spaciness in situations in which other children are focused and interested. Traumatized children must learn to tolerate trauma-related bodily sensations and emotional states.

Children with “frozen” reactions must be helped to reawaken their curiosity and explore their surroundings. Many have deficient pain perceptions [42] and must work on reestablishing proper tactile perceptions. They tend to avoid engagement in activities because any task may unexpectedly turn into a traumatic trigger. As long as they remain numb and dependent on others, they are unable to accumulate restitutive experiences. Neutral, enjoyable tasks and physical games can provide them with knowledge of what it feels like to be relaxed and enjoy a sense of physical mastery. This serves as an essential antidote to feeling frozen or hyperaroused.

Body-focused therapies, including theater groups [128], can help children coordinate and integrate perceptions with motor actions to accomplish appropriate actions. These therapies include such simple exercises as holding piece of a paper in the one hand and cutting it with the other, learning to read a line from right to left without getting stuck on the midline, working on keeping their equilibrium on balance beams or on large inflatable balls to help them overcome problems with their vestibular system, and helping them find a sense of calm by swinging on a hammock and learning to focus on bodily sensations that signify safety and control [42].

At the center of the therapy with terrified children is helping them understand the connections between their experience and their emotions and reactions [42,129]. It has become common in child psychiatry to substitute medications for teaching children skills to deal with their uncomfortable physical sensations. The weight of treatment outcome research suggests that processing the trauma is essential and necessarily involves the controlled experiencing of the sensations and emotions associated with traumatic memories.

As long as children are unable to talk about their traumatic experiences, they simply have no story, and instead, the trauma is likely to be expressed as an embodiment of what happened. The body tells the story—with striated muscles—in action or smooth muscles—as psychosomatic problems. The task of therapy is to help these children develop a sense of physical mastery and awareness of who they are and what has happened to them to learn to observe what is happening in present time and physically respond to current demands instead of recreating the traumatic past behaviorally, emotionally, and biologically.

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