Development and Psychopathology, **13** (2001), 539–564

Developmental traumatology: The psychobiological development of maltreated children and its implications for research, treatment, and policy

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Abstract
In this review, a developmental traumatology model of child maltreatment and the risk for the intergenerational cycle of abuse and neglect using a mental health or posttraumatic stress model was described. Published data were reviewed that support the hypothesis that the psychobiological sequelae of child maltreatment may be regarded as *an environmentally induced complex developmental disorder*. Data to support this view, including the descriptions of both psychobiological and brain maturation studies in maltreatment research, emphasizing the similarities and differences between children, adolescents, and adults, were reviewed. Many suggestions for important future psychobiological and brain maturation research investigations as well as public policy ideas were offered.

Child maltreatment may be the single most preventable and intervenable contributor to child and adult mental illness in this country. Adults with child maltreatment histories are more likely to manifest multiple health risk behaviors and serious medical illnesses (Felitti, Anda, Nordenberg, Williamson, Spitz, Edward, Koss, & Marks, 1998) and greater rates of psychiatric and medical utilization (Walker, Unutzer, Rutter, Gelfand, Saunders, VonKorff, Koss, & Katon, 1999) than adults without maltreatment histories.

Multiple, densely interconnected neurobiological systems are impacted by the acute and chronic stressors associated with childhood maltreatment. These neurobiological systems significantly influence physical and cognitive development and emotional and behavioral regulation. Results from recent research suggest that the overwhelming stress of maltreatment experiences in childhood is associated with alterations of biological stress systems and with adverse influences on brain development (De Bellis, Baum, Birmaher, Keshavan, Eccard, Boring, Jenkins, & Ryan, 1999; De Bellis, Keshavan, Clark, Casey, Giedd, Boring, Frustaci, & Ryan, 1999).

Developmental traumatology is the systemic investigation of the psychiatric and psychobiological impact of overwhelming and chronic interpersonal violence (child maltreatment) on the developing child. This is a relatively new area of study in child psychiatry that synthesizes knowledge from develop-

Some of the ideas presented in this manuscript are in *Child Abuse and Neglect: A Public Mental Health Problem,* by M. D. De Bellis, master's thesis submitted in April 2000 to the Graduate Faculty of the Graduate School of Public Health in partial fulfillment of the requirements for the degree of Master of Public Health.

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mental psychopathology, developmental neuroscience, and stress and trauma research. The development of the brain is regulated by genes, which interact profoundly with life experiences, particularly early childhood experiences. Active areas of research investigate the consequences of child maltreatment and related family and psychosocial stressors and their effects on the development and regulation of major biological stress response systems and their influence on childhood brain development and function.

In developmental traumatology research, abuse and neglect are seen as a most extreme form of dysfunctional family and interpersonal functioning on a continuous spectrum of adverse life circumstances and dysfunctional interpersonal and family relationships. These adverse life circumstances include socioeconomic disadvantage, parental mental illness (including alcohol and substance abuse), community violence, and a lack of adequate social support and experience-expected environmental stimulation. The influence of maltreatment, as well as these other factors on biological stress systems regulation and brain maturation, are complicated and very difficult to disentangle. An important mission for the field of developmental traumatology research is to unravel the complex interaction between an individual's genetic constitution, unique psychosocial environment, and proposed critical periods of vulnerability for and resilience to maltreatment experiences, and how such factors may influence changes in biological stress systems, adverse brain development, and known serious consequences associated with child maltreatment. Developmental traumatology is the study of these complex interactions.

The Basic Assumptions of Developmental Traumatology Research

This review focuses on the psychobiological development of maltreated children. A mental health model, the diagnosis of posttraumatic stress disorder (PTSD), is applied to ideas arising from developmental psychopathology and developmental neuroscience. It is hypothesized that the potential psychobiological sequelae of child maltreatment may be regarded as *an environmentally induced complex developmental disorder*. Based on a synthesis of the relevant literature, a number of assumptions are made in this review.

The first assumption is that while there are an infinite number of stressors that can cause a subjective sense of overwhelming stress and distress in a child, there are finite ways that the brain and the body (i.e., biological stress systems) can respond to those stressors. Therefore, our discussion of the consequences of childhood maltreatment will purposely and nonspecifically include a broad definition of maltreatment (abuse and neglect), unless the current data support different outcomes for the various types of maltreatment. In accord with this idea, it is noted that child abuse and neglect are chronic conditions and that various forms of abuse and neglect tend to coexist (Cicchetti & Barnett, 1991). Therefore, in this review the terms maltreatment and chronic trauma are used interchangeably.

The second assumption, and the most important one in using the PTSD model in child maltreatment, involves the nature of the stressor, which is a dysfunctional and traumatized interpersonal relationship. The trauma is not only the act of maltreatment itself (e.g., physical abuse or sexual abuse) but also the relationship the victim has with the perpetrator of the trauma. Therefore, clinical identification of traumatic triggers may involve identification of subtleties that can sometimes be difficult to clinically assess. Along these lines, interpersonal stressors, such as child maltreatment, are more likely to be chronic and more severe than noninterpersonal traumas. An interpersonal stressor likely involves the maltreated child losing faith and trust in a parent or an authority figure. Thus, for the maltreated child the ability to form relationships and attachments is intact (e.g., the hardwiring is present) but traumatized (e.g., the software is programmed to distrust and fear relationships). Consequently, the maltreated child will be more difficult to treat in psychotherapy and have a harder time forming healthy social relationships, because the establishment

of a therapeutic alliance involves a process of desensitizing the maltreated individual to distrust and will take more time to progress.

The third assumption is that maltreatment in childhood may be more detrimental than trauma experienced in adulthood secondary to interactions between trauma and psychological and neurodevelopment. Hence, maltreatment in childhood may cause delays in or deficits of multisystem developmental achievements in behavioral, cognitive, and emotional regulation. The fourth assumption is that biological stress system responses will be based on several principles, including the nature of the stressor, the frequency and chronicity of the stressor, the individual differences (i.e., genetic vulnerabilities) in biological stress systems regulation and in their response to the stressor, and the ability of biological stress systems to either maintain homeostasis in the face of chronic and severe stress or permanently change in response to the stressor.

The fifth assumption is that PTSD symptoms are common responses to severe stressors. The sixth assumption is these changes in biological stress systems cause psychiatric symptoms, particularly symptoms of PTSD. Therefore, lack of PTSD symptoms after experiencing a severe stressor will be associated with little psychopathology. However, experiencing PTSD after a severe stressor in childhood will lead to an increase risk of suffering from chronic PTSD, other psychopathology (i.e., internalizing or emotional and externalizing or behavioral disorders), and other cognitive and psychosocial consequences. The seventh assumption is that when trauma occurs during development, chronic PTSD symptoms can be seen as the trajectory to more severe comorbidity and compromised cognitive and psychosocial functioning and this pathway increases the intergenerational transmission of abuse and neglect. (See Figure 1.)

Throughout this review, we will present and review data to support these ideas and descriptions of the state of research. The similarities and differences between children, adolescents, and adults, and the methodological difficulties and controversies inherent in this field of study, will be emphasized. Suggestions for future research opportunities, treatment, and policy will be offered.

Is the PTSD Model Appropriate for Studies of Maltreated Children?

The diagnosis of PTSD is made after a person experiences one or more intense, overwhelming, traumatic event and reacts with fear or disorganized behavior and with complaints of three clusters of categorical symptoms for at least 1 month (a) intrusive reexperiencing of the trauma(s), (b) persistent avoidance of stimuli associated with the trauma, and (c) persistent symptoms of increased physiological arousal (American Psychiatric Association, 1994). The diagnostic picture of PTSD in children and adolescents is similar to adults (for review, see De Bellis, 1997; Pynoos & Eth, 1985), with the exception of children less than 4 years old, where more objective criteria based on observable behaviors are warranted (Scheeringa, Zeanah, Drell, & Larrieu, 1995).

A review of the longitudinal course of PTSD suggested that PTSD symptoms are common within the 1st month of a trauma and that these symptoms may be a normal response to severe stress, as these symptoms usually fade within 3 months (Blank, 1993). PTSD may be better conceptualized as a dimensional process rather than a categorical all-or-none outcome, as complete and partial PTSD responses are usually seen in many forms of trauma including victims of childhood maltreatment (Armsworth & Holaday, 1993; Famularo, Fenton, & Kinscherff, 1994; Hillary & Schare, 1993; Mannarino, Cohen, & Berman, 1994; Wolfe, Sas, & Wekerle, 1994; Wolfe & Charney, 1991). Chronic PTSD symptoms may provide the mechanisms for the pervasive psychopathology seen in maltreated children. No complaints of PTSD symptoms after experiencing a severe stressor (i.e., lack of sleep disturbances, intrusive symptoms, or concentration impairments) may be associated with little psychopathology. Along these lines, children and adolescents with PTSD secondary to maltreatment may be one of the most seriously affected groups of maltreated children. These ideas

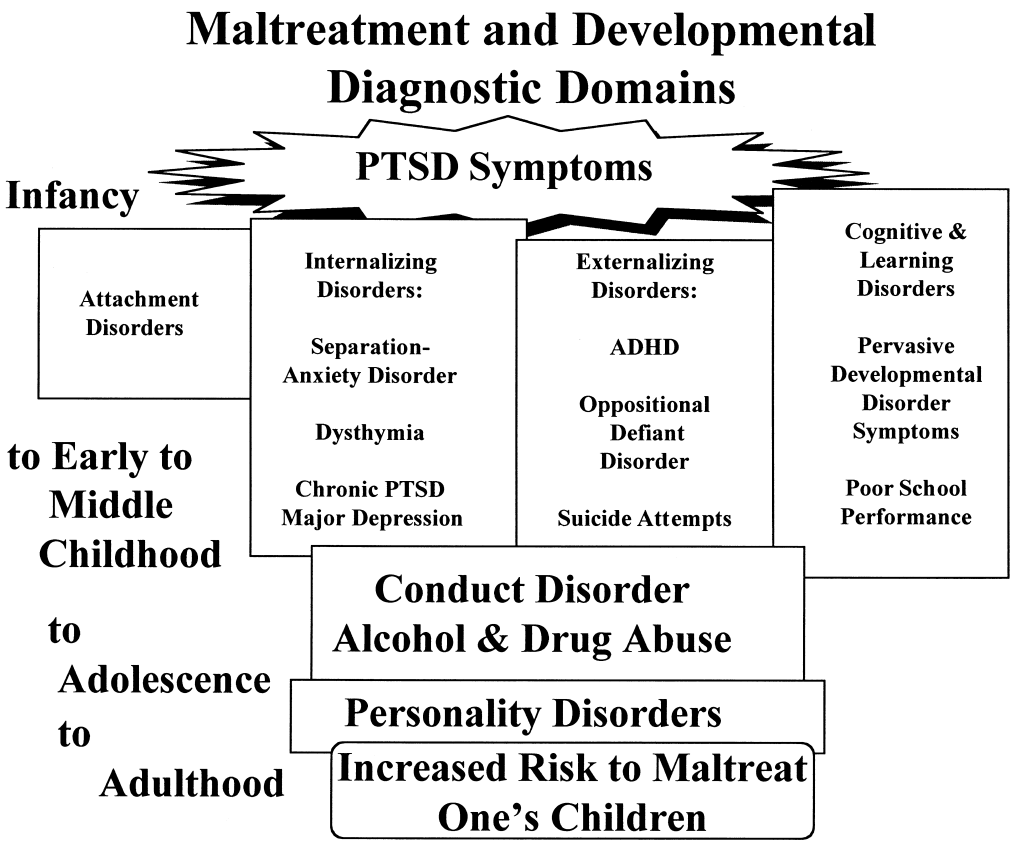

Figure 1. A developmental traumatology model for the intergenerational transmission of maltreatment. In this model the intergenerational transmission of child abuse and neglect is seen as transmitted through parental mental illness, and it is understood to be a result of (a) the impact of childhood traumatic stress on later parental biopsychosocial development, (b) consequent adverse parental brain development, (c) consequent parental mental illness, which may lead to (d) adverse parenting skills. This model is best thought of as multidetermined (i.e., genetic and environment interactions leading to outcomes).

represent an understudied area and perhaps a fruitful area for further research. However, because of the lack of "dimensional" PTSD data, the ideas presented in this review are based on the results of clinical studies, which defined PTSD as a categorical all-or-none outcome.

In clinically referred samples, the reported incidence rates of PTSD resulting from sexual abuse range from 42 to 90% (Dubner & Motta, 1999; Lipschitz, Winegar, Hartnick, Foote, & Southwick, 1999; McLeer, Callaghan, Henry, & Wallen, 1994), from witnessing domestic violence from 50 to 100% (for domestic homicide; Pynoos & Nader, 1989), and from physical abuse to as high as 50% (Dubner & Motta, 1999; Green, 1985). Only a few studies have focused on assessing PTSD in nonclinically referred maltreated children. Famularo et al. (1994) reported a 39% incidence rate of PTSD in a nonclinically referred maltreated sample interviewed within 8 weeks of abuse or neglect disclosure. About a third of the PTSD subjects reexamined from the original sample continued to meet PTSD criteria at 2-year follow-up (Famularo, Fenton, Augustyn, & Zuckerman, 1996). Recently, (McLeer, Dixon, Henry, Ruggiero, Esovitz, Niedda, & Scholle, 1998) reported prevalence rates of PTSD of 36.3% in nonclinically referred sexually abused children 60 days immediately following sexual

abuse disclosure. Thus, PTSD is commonly seen in maltreated children, especially during the period immediately following maltreatment disclosure. Identification of psychosocial and treatment-related factors which lead to remission of PTSD in maltreated children is an important area of future investigation.

To date, there are no studies which directly examine PTSD in neglected children. Although child neglect is not abuse, neglect may be perceived as traumatic. The degree of the traumatic experience perceived by the child will depend on the age and developmental attainment and the biological stress systems responses of the child at the time of the neglect. For example, continuously neglected institutionalized infants suffer from increased rates of infection and early death (Chapin, 1917). These high rates of infection may be associated with stress-induced suppression of the immune system (for review, see De Bellis & Putnam, 1994). An unsupervised nonabused young child is more likely to witness interpersonal traumas such as domestic and community violence or to experience traumatic accidents. It is estimated that one third to one half of neglected children witness domestic violence (for review, see Sassetti, 1993, or Lyon, 1999) and that at least half of these children will experience PTSD symptoms (for review, see De Bellis, 1997). Childhood victims of abuse (sexual or physical) as well as neglect were found to be at increased risk for developing a lifetime history of PTSD when assessed prospectively in young adulthood (Widom, 1999). Furthermore, these investigators found that childhood abuse and neglect predicted the number of lifetime PTSD symptoms.

Any severe traumas can result in PTSD in a susceptible individual. However, the data show that the experience of severe trauma of interpersonal origins (i.e., child abuse or neglect, sexual assault, warfare) may override any genetic, constitutional, social, or psychological resilience factors, thus heightening the risk for PTSD and its associated impairments in the majority of victims. PTSD lifetime prevalence rates for trauma of interpersonal origins in all age groups are greater than for noninterpersonal traumas and range from approximately 30 to 50%. Rates of PTSD in children traumatized by maltreatment are similar to those of children traumatized by war and homicide. Rates of PTSD in maltreated children are similar to those rates of adults traumatized by war and assault. Current prevalence rates of 50 and 47% were found in former World War II prisoners of war approximately 40 years after combat duty and prison camp confinement (Goldstein, Van Kammen, Shelly, Miller, & Van Kammen, 1987; Kluznik, Speed, Van Valkenburg, & Magraw, 1986). Rothbaum and Foa (1993) found that at 1 month 65% of rape victims met DSM-III-R PTSD criteria and that these rates remained high (41.7%) 6 months after sexual assault. In a study of Cambodian adolescents 3 years after survival of the Pol Pot regime, 50% had persistent symptoms of PTSD as well as depression and anxiety symptoms (Kinzie, Sack, Angell, & Clarke, 1989). Pynoos, Frederick, Nader, Arroyo, Steinberg, Eth, Nunez, and Fairbanks (1987) reported that 60% of school children exposed to a sniper attack continued to meet DSM-III-R criteria for PTSD 1 year later. Moreover, children are more likely to be diagnosed with PTSD, once traumatized, than their adult counterparts (Fletcher, 1996). Even if childhood trauma does not result in childhood PTSD, it increases the risk for adult PTSD (Bremner, Southwick, Johnson, Yehuda, & Charney, 1993; Widom, 1999) and adult psychiatric illness (Davidson & Smith, 1990).

The PTSD model may help us identify factors that increase the risk of experiencing PTSD secondary to maltreatment. Certain risk factors increase the probability that an individual will develop PTSD after a trauma. These factors are divided into three categories: (a) factors prior to, (b) factors relating to, and (c) factors following the traumatic experience(s). Factors that increase the risks of having PTSD prior to the traumatic experience include a prior history of poor social support and adverse life events, parental poverty, prior history of childhood maltreatment, poor family functioning, familial–genetic family history of psychiatric disorders, introversion or extreme behavioral inhibition, being female, and poor health and prior mental

illness (Davidson & Fairbank, 1993). Of these, genetics and the trauma experience may play a critical role. In a twin study, True, Rice, Eisen, Heath, Goldberg, Lyons, and Nowak (1993) found that genetic factors accounted for 13–30% of the variance in the reexperiencing cluster, 30–34% in the avoidance cluster, and 28–32% in the arousal cluster of PTSD symptoms in Vietnam veterans with combat-related PTSD. While symptoms in the reexperiencing cluster and one symptom in the avoidance and numbing cluster were strongly associated with trauma exposure, shared environment did not contribute to the development of the disorder.

Thus, important risk factors for PTSD associated with the trauma are the degree of trauma exposure and an individual's subjective sense of danger, and other related traumatic events (e.g., witnessing domestic violence; Pynoos & Nader, 1990). Chronicity of psychiatric impairment also increases with the dose of traumatic exposure(s) (Pynoos et al., 1987; Pynoos & Nader, 1990).

Risk factors associated with PTSD after the trauma include lack of social supports and continued negative life events and lack of posttrauma interventions such as secondary stressors including change of school, change of residence, destruction of a home, repeated threats and fear of the perpetrator (of child abuse), and financial problems (Pynoos & Nader, 1993). Although genetics may play an important role in the development of PTSD, PTSD is a common disorder, affecting 30 to 60% of the most severely exposed population. Thus, the genetic variants involved in PTSD are most probably common to all humans.

The Impact of Maltreatment on Developmental Achievements

Trauma in childhood may be more detrimental than trauma experienced in adulthood because of the interactions between trauma and psychological and neurodevelopment (De Bellis, Keshavan, et al., 1999; De Bellis & Putnam, 1994). Maltreatment in children and adolescents may disrupt developmental achievements and may cause delays in, deficits of, or failures of multisystem developmental achievements in motor, emotional, behavioral, language, psychosocial, social, and cognitive skills (Cicchetti & Lynch, 1995; Trickett & McBride–Chang, 1995). Trauma in childhood may also impact psychosexual and moral development. The developmental consequences of PTSD and PTSD symptoms can lead to failures in behavioral and emotional regulation as well as cognitive consequences resulting in the comorbid psychopathology commonly seen in maltreated children (Pynoos, Steinberg, & Wraith, 1995).

Thus, failure to self-regulate behavior and emotion may lead to externalizating (e.g., acting out behaviors, explosive anger, suicide attempts) and internalizing (e.g., chronic depressive disorders, suicidal ideation) symptoms in the same individual that continue to adulthood (for review, see De Bellis, 1997). Most studies find significantly increased rates of internalizing disorders (especially major depression–dysthymia and suicidal ideation) and externalizing disorders (oppositional defiant behaviors, attention deficit hyperactivity disorder, self-destructive behaviors) in maltreated children and adolescents (for review, see National Research Council, 1993). It is well known that histories of child maltreatment are associated with poor parenting skills and a higher risk of intergenerational transmission of substance abuse, problematic parent–child interactions, domestic violence, and child maltreatment (Center for Substance Abuse Treatment, 1997). These poor outcomes may be mediated through these traumatic maltreatment associated developmental consequences and negative effects on biological stress systems and on brain development (De Bellis, Keshavan, et al., 1999).

The categorical clusters of symptoms which form the diagnosis of PTSD (Cluster B, reexperiencing and intrusion; Cluster C, avoidance; Cluster D, hyperarousal) may each individually contribute to delays in or deficits of multisystem developmental achievements in behavioral, cognitive, and emotional regulation in traumatized children and lead to comorbidity. Thus, if we choose to examine PTSD as a dimensional diagnosis encompassing a range of pathological reactions to severe stress, rather than as a dichotomous variable,

then we may better understand the psychobiological consequences of these broad range of symptoms humans experience across development.

Is Childhood PTSD a "Gateway Illness" to Serious Comorbid Disorders?

Cluster B reexperiencing and intrusive symptoms can best be conceptualized as a classically conditioned response. An external or internal conditioned stimulus (e.g., the traumatic trigger) activates unwanted and distressful recurrent and intrusive memories of the traumatic experience(s) (the unconditioned stimulus). Intrusive phenomena take the form of distressing intrusive thoughts and nightmares or night terrors, dissociative flashback episodes, and psychological distress and physical reactivity on exposure to traumatic reminders. In young children, these intrusive thoughts may be part of repetitive play or trauma-specific reenactment(s) or compulsive rituals. These compulsive rituals resemble symptoms of pervasive developmental disorders. Intrusive symptoms such as hearing the voice of a threatening perpetrator can be easily misdiagnosed as psychotic behavior (auditory hallucinations). Thus, intrusive symptoms most closely resemble another psychiatric disorder, obsessive–compulsive disorder, which is characterized by intrusive and recurrent and persistent thoughts, impulses, or images and is a disorder of serotonin regulation (for review, see Rosenberg & Keshavan, 1998).

The serotonin system is a stress response system. Serotonin plays important roles in compulsive behaviors and the regulation of emotions (mood) and behavior (aggression, impulsivity) and is also implicated in major depression, impulsivity, and suicidal behaviors (Benkelfat, 1993; Siever & Trestman, 1993). In animal studies of unpredictable and uncontrollable stress (e.g., inescapable shock), serotonin levels decrease in the brain (Southwick, Krystal, Johnson, & Charney, 1992). Drugs that increase brain serotonin (serotonin agonists) prevent some of these behavioral changes. Low serotonin function is associated with suicidal and aggressive behaviors in adults, children, and adolescents (Benkelfat, 1993; Siever & Trestman, 1993). These are common behaviors seen in child victims of childhood maltreatment and in adults with PTSD secondary to an interpersonal stressor. Because of serotonin's interdependence with the noradrenergic system (Sulser, 1987), another stress response system that is involved in the psychobiology of adult and child mood disorders, dysregulation of serotonin may not only play a major role in Cluster B symptoms but also may also increase the risk for comorbid major depression and aggression in maltreated children. Consequently, Breslau, Davis, Peterson, and Schultz (2000) have shown that the onset of major depression is markedly increased for trauma-exposed persons who suffer from PTSD but not for trauma-exposed persons who did not suffer from PTSD. Thus, PTSD may lead to major depression and be influenced by common genetic vulnerabilities to serotonin dysregulation and trauma related factors as discussed above. However, as very little is known about serotonin function and trauma in developing humans, this is an important area for future research. Given that studies show strong support for the efficacy of serotonin reuptake inhibitor antidepressant and anti-OCD medications in adult PTSD (Brady, Pearlstein, Asnis, Baker, Rothbaum, Sikes, & Farfel, 2000; van der Kolk, Dreyfuss, Michaels, Shera, Berkowitz, Fisler, & Saxe, 1994), psychopharmacological studies of PTSD in maltreated children are sorely needed.

Cluster C symptoms represent both avoidant and dissociative behaviors and can be thought of as ways to control painful and distressing reexperiencing of symptoms. These include efforts to avoid thoughts, feelings, conversations, activities, places, people, and memories associated with the trauma; amnesia for the trauma; diminished interest in others; feelings of detachment from others; a restricted range of affect; and a sense of a foreshortened future. Emotional numbing and diminished interest in others, particularly during development, may result in lack of empathy, comorbid dysthymia, and an increased risk for self-mutilation (van der Kolk, Greenberg, Orr, & Pitman, 1989), personality disorders (Johnson, Cohen, Brown, Smailes, &

Berstein, 1999), or antisocial behaviors (Luntz & Widom, 1994). For example, Johnson et al. (1999) prospectively assessed personality disorders in young adults who were maltreated as children and found that documented child abuse and neglect were associated with increased risk for antisocial, borderline, dependent, depressive, narcissistic, paranoid, and passive–aggressive personality disorders after controlling for parental education and parental psychiatric disorders. Furthermore, (Steiner, Garcia, & Matthews, 1997) found that in a sample of incarcerated juvenile offenders, 32% fulfilled and another 20% met partial criteria for PTSD. The most commonly reported PTSD traumas involved interfamilial violence including abuse.

Dissociative symptoms are commonly seen in traumatized individuals. These symptoms are defined as disruptions in the usually integrated functions of consciousness, memory, identity, or perception of the environment that interfere with the associative integration of information (Putnam, 1997). Avoidant and dissociative symptoms are thought to be mediated by dysregulation of endogenous opiate system (for review, see Southwick et al., 1992, or Bremner, Davis, Southwick, Krystal, & Charney, 1993). However, higher concentrations of urinary dopamine are associated with avoidant symptoms in adult PTSD (Yehuda, Southwick, Giller, Ma, & Mason, 1992) and with avoidant and dissociative symptoms in maltreated children with PTSD (De Bellis, Baum, et al., 1999). Endogenous opiate systems and their links with dopamine systems have not been studied in maltreated children. These systems may be contributory to the constricted affect and high incidence of self-injury and violent behaviors reported in maltreated children and in adults who have experienced maltreatment as children (van der Kolk et al., 1989; van der Kolk, Perry, & Herman, 1991; Yeo & Yeo, 1993). The corpus callosum, the major interconnection between the two hemispheres, connects homologous areas of the cortex structure and functions to facilitate cortical communication and integration of input (Ramaekers & Njiokiktjien, 1991). A significant negative correlation with the Child Dissociative Checklist score and corpus callosum area was seen in a recently published neuroimaging study of maltreated children and adolescents (De Bellis, Keshavan, et al., 1999). Perhaps dissociative symptoms are the result of less "connectivity" in the corpus callosum. However, very little is known about the links between endogenous neurotransmitter function, neuroanatomy, and Cluster C symptoms or between the psychobiology of childhood trauma, Cluster C symptoms, and adult personality and antisocial behaviors in developing humans. Examination of these issues are not only paramount but also should lead to clinical interventions.

Cluster D hyperarousal symptoms consist of persistent symptoms of increased physiological arousal (difficulty falling or staying asleep, irritable mood or angry outbursts, difficulty concentrating, hypervigilance, and exaggerated startle response). These symptoms are thought to be mediated by dysregulation of three catecholamine systems—norepinephrine (NE), epinephrine (EPI), and dopamine (DA)—and the limbic–hypothalamic–pituitary–adrenal (LHPA) axis (Charney, Deutch, Krystal, Southwich, & Davis, 1993; De Kloet, Vreugdenhil, Oitzl, & Joes, 1998). These neurotransmitter systems and neuroendocrine axis interact with the serotonin system and are also implicated in mood and anxiety disorders. Since noninvasive peripheral measures of the catecholamine systems and the LHPA axis are relatively easy to undertake in children, there is more published data available to investigate these systems in maltreated children and adolescents. Hence, these systems will be discussed in more detail below.

A Brief Review of Biological Stress Systems

A brief review of the major biological stress systems is important because (a) these are the major systems implicated in mood, anxiety, and impulse control disorders (Goodwin & Jamison, 1990); (b) there are pharmacological treatments to target these systems; (c) alcohol and various illicit substances will also "self-medicate" or target these systems by damping down hyperarousal or dysregulated stress system(s); and (d) a hyperaroused or primed

stress system may lead to behavioral manifestations of motor restlessness and learning and memory deficits that may be secondary to anxiety.

Multiple neurotransmitter systems and neuroendocrine axes are activated during acute stress (reviewed by Charney et al., 1993). Traumatic stress may have negative effects on the development of these systems (De Bellis & Putnam, 1994). Since there is little research on the neurobiological effects of maltreatment and PTSD in developing children, studies of the neurobiological effects of overwhelming stress in animal models and of the psychobiology of adult PTSD provide comparative models. Most investigators have focused on two of the body's major stress systems—the catecholamine system (i.e., the locus ceruleus–NE and sympathetic nervous system [SNS]) and the LHPA axis—and brain morphology and function. Although this article will focus mainly on these two biological stress systems, there are multiple, densely interconnected neurobiological systems that are likely impacted by childhood maltreatment (De Bellis & Putnam, 1994). These neurobiological systems significantly influence physical and cognitive development and behavioral and emotional regulation. It is highly probable that many of the acute and chronic symptoms associated with maltreatment arise in conjunction with alterations of these systems. An understanding of the psychobiology of maltreatment may lead to early psychotherapeutic and psychopharmacological treatment(s). This may lead to secondary prevention of the psychiatric chronicity and comorbidity commonly seen in maltreated children.

Animal studies show that traumatic stress activates the locus coeruleus, the major catecholamine (specifically NE) containing nucleus in the brain, and the SNS, leading to the biologic changes of the "fight-or-flight reaction" (for review, see De Bellis & Putnam, 1994). Direct and indirect effects of this activation include increases in catecholamine turnover in the brain, the SNS, and adrenal medulla which lead to increases in heart rate, blood pressure, metabolic rate, alertness, and the circulating catecholamines (EPI, NE, and DA). During stress, the locus coeruleus stimulates the LHPA axis via indirect connections through the brain's limbic system and hypothalamic corticotropin releasing hormone (CRH) is released. CRH activates the LHPA axis by stimulating the pituitary to secrete adrenocorticotropin hormone (ACTH). These events promote cortisol release from the adrenal gland, stimulate the SNS, and centrally cause behavioral activation and intense arousal (for review, see Chrousos & Gold, 1992). Cortisol, via negative feedback inhibition on the hypothalamus, pituitary, and other brain structures (hippocampus) suppresses the HPA axis, leading to restoration of basal cortisol levels (homeostasis). Activation of the catecholamine system and CRH results in animal behaviors consistent with anxiety, hyperarousal, and hypervigilance, which are the core symptoms of PTSD.

Is Adult PTSD a Risk Factor for Alterations in Biological Stress Systems and Brain Morphometry?

In adult PTSD, it is hypothesized that the catecholamine system and LHPA axis responses to stress become maladaptive, causing long-term negative consequences (reviewed by Charney et al., 1993, and Southwick, Yehuda, & Wang, 1998). Results from adult combat-related PTSD studies suggest that there is increased sensitivity of the catecholamine system that is most clearly evident under experimental conditions of stress or challenge. These findings include increased heart rate, systolic blood pressure, skin conductance, and other SNS responses to adrenergic or traumatic reminder challenge compared to healthy combat or noncombat controls. Although most baseline studies of single or multiple time point plasma catecholamines found no significant differences between adult PTSD and controls, *elevated levels of catecholamines* were found in 24-hr urinary excretions in three of five studies (for review, see Southwick, Yehuda, & Morgan, 1995). Single time point measures of catecholamines and cortisol may not provide an accurate measure of baseline functioning because these neurotransmitters have circadian influences (i.e., a 24-hr diurnal rhythm) and the stress of a single-stick

venipuncture may result in elevations of cortisol and catecholamine concentration alone, obscuring any baseline differences. Cortisol, which reflects LHPA axis activity, and essentially all catecholamines and their metabolites, which reflect SNS activity, are excreted into urine (Chrousos & Gold, 1992; Maas, Koslow, Davis, Katz, Frazer, Bowden, Berman, Gibbons, Stokes, & Landis, 1987). *Rather than randomly timed urine measures, timed 24-hr measures of urinary free cortisol (UFC) and catecholamine concentrations are a better way to noninvasively evaluate for alterations in baseline activity of the LHPA axis and catecholamine system.* Thus, in adult PTSD elevated 24-hr urinary excretion of catecholamines provides evidence of an increase in baseline functioning of the catecholamine system.

Unlike the increased sensitivity to stress of the catecholamine system seen in adult PTSD, results from baseline and challenge studies of the LHPA axis appear to show that this system functions in a more complicated manner. In adult combat-related PTSD, elevated levels of central CRH were found (Baker, West Nicholson, Ekhator, Kasckow, Hill, Bruce, Orth, & Geracioti, 1999; Bremner, Licinio, Darnell, Krystal, Owens, Southwick, Nemeroff, & Charney, 1997). Infusion studies of metyrapone, which blocks the conversion of 11-deoxycortisol to cortisol and allows for the direct measure of pituitary release of ACTH, suggested that there is down-regulation of anterior pituitary CRH receptors presumably secondary to elevated central CRH and enhanced negative feedback inhibition of the pituitary for cortisol (Yehuda, Levengood, Schmeidler, Wilson, Guo, & Gerber, 1996). Further evidence for enhanced negative feedback inhibition includes findings of increased number of glucocorticoid receptors on lymphocytes presumably secondary to decreased circulating cortisol, suppression of cortisol with low dose dexamethasone, and lower 24-hr UFC concentrations in three of four studies of adult combat-related PTSD compared with controls (Mason, Giller, Kosten, Ostroff, & Podd, 1986; Yehuda, Southwick, Giller, Ma, & Mason, 1991; Yehuda et al., 1992). Low 24-hr UFC levels were also found in one study of male and female adults with PTSD who survived the Holocaust during childhood compared to survivors without PTSD (Yehuda, Kahana, Binder–Brynes, Southwick, Mason, & Giller, 1995). In two other studies, 24-hr UFC concentrations were higher in male combat veterans with PTSD compared to combat veterans without PTSD (Pittman & Orr, 1990) and in women with PTSD secondary to childhood sexual abuse compared to women abused as children without PTSD and healthy nonabused controls (Lemieux & Coe, 1995).

These discrepant findings may be related to a mechanism called "priming." A possible long-term consequence of the trauma experience may be to prime the LHPA axis so that ACTH and cortisol secretion are set at lower 24-hr levels (De Bellis, Baum, et al., 1999). Priming may occur as a reflection of chronic compensatory adaptation of the HPA axis long after trauma exposure or be more likely after maturation. LHPA axis regulation is affected by other hormones that are stress mediated such as arginine vasopressin and the catecholamines, both of which act synergistically with CRH (Chrousos & Gold, 1992). A "primed system" will "hyper"-respond during acute stress because of the interactive neuroendocrine and neurotransmitter effects activated by current life stressors on the HPA axis. Thus, when a new emotional stressor is experienced LHPA axis functioning will be enhanced (higher ACTH and higher 24-hr UFC). Since the adult PTSD studies focus on past trauma, the latter hypothesis may best explain the data in childhood PTSD studies (see below) and is our working hypothesis in developmental traumatology studies. However, this is only a suggestive hypothesis and perhaps another area of worthwhile investigation.

Elevated levels of glucocorticoids during traumatic stress may have neurotoxic effects and lead to learning and concentration impairments secondary to damage to the brain's hippocampi (Edwards, Harkins, Wright, & Menn, 1990), a principal neural target tissue of glucocorticoids (Sapolsky, Uno, Rebert, & Finch, 1990). Hippocampal degeneration was noted in monkeys after sustained social stress (Uno, Tarara, Else, Suleman, & Sapolsky, 1989). El-

evated levels of cortisol during traumatic stress may have neurotoxic effects on the hippocampus through the *N*-methyl-D-aspartate (NMDA) excitotoxicity (Armanini, Hutchins, Stein, & Sapolsky, 1990). Smaller hippocampal volumes were reported in adults with Cushing syndrome (Starkman, Gebarksi, Berent, & Schteingart, 1992), combat veterans with PTSD (Bremner, Randall, Scott, Bronen, Southwick, Seibyl, Delaney, McCarthy, Charney, & Innis, 1995; Gurvits, Shenton, Hokama, Ohta, Lasko, Gilbertson, Orr, Kikinis, Jolesz, McCarley, & Pitman, 1996), adult PTSD secondary to child abuse (Bremner et al., 1997), and female adult survivors of childhood sexual abuse (Stein, Koverola, Hanna, Torchia, & McClarty, 1997).

The anterior cingulate cortex, a region of the medial prefrontal cortex, is involved in the extinction of conditioned fear responses and is implicated in the pathophysiology of PTSD (for review, see Hamner, Lorberbaum, & George, 1999). The anterior cingulate region is part of an executive attention system, as it is activated during decision making and novel or dangerous situations (Posner & Petersen, 1990). Since intrusive thoughts of trauma (danger) and poor concentration are core symptoms of PTSD, anterior cingulate integrity may be affected in PTSD. LeDoux (for review, see LeDoux, 1998) has shown that medial prefrontal cortex may inhibit activation of parts of the limbic system involved in fearful behaviors (amygdala and related nuclei and circuitry).

Recent neuroimaging studies provide evidence for anterior cingulate dysfunction in adult PTSD. Positron emission tomography investigations comparing women who had been sexually abused as children and who had PTSD with women with similar history who did not have PTSD found a lower level of anterior cingulate blood flow during traumatic script-driven imagery (Shin, McNally, Kosslyn, Thompson, Rauch, Alpert, Metzger, Lasko, Orr, & Pitman, 1999) and during memories of sexual abuse (Bremner, Narayan, Staib, Southwick, McGlashan, & Charney, 1999). A lower level of anterior cingulate blood flow has also been seen in Vietnam combat veterans with PTSD compared to those without PTSD during exposure to combat-related traumatic stimuli (Bremner, Staib, Kaloupek, Southwick, Soufer, & Charney, 1999). In these studies, subjects with PTSD activated the amygdala, while subjects without PTSD did not show the same degree of limbic activation. Thus PTSD symptoms may represent an impairment of medial prefrontal cortex functioning (Zubieta, Chinitz, Lombardi, Fig, Cameron, & Liberzon, 1999). Exposure to mild to moderate uncontrollable stress impairs prefrontal cortical function in studies of humans and animals (for review, see Arnsten & Goldman–Rakic, 1998). This impairment may be catecholamine mediated (for review, see Arnsten, 1998). Thus, animal and adult studies show that severe stress and PTSD are associated with alterations in biological stress systems and brain morphology and function.

Is Childhood Trauma a Risk Factor for Alterations of Biological Stress Systems?

Since there is little data on childhood PTSD, studies of traumatized children are reviewed broadly and also focus on outcomes of anxiety or depression. Findings of elevated baseline 24-hr urinary catecholamine concentrations suggest an increase in baseline functioning of the catecholamine system in traumatized children. In a pilot study, sexually abused girls, 58% of whom had histories of severely depressed mood with suicidal behavior (but only one of whom had PTSD), exhibited significantly greater 24-hr urinary catecholamine concentrations compared with demographically matched nonabused controls (De Bellis, Lefter, Trickett, & Putnam, 1994). When given a detailed sexual abuse trauma interview five years later, these subjects continued to not complain of PTSD, but mood and PTSD symptoms persisted (F. Putnam, personal communication, February 2000). Levels of 24-hr urinary NE were elevated in male children who suffer from severe clinical depression and had a history of parental neglect (Queiroz, Lombardi, Santos Furtado, Peixoto, Soares, Fabre, Basquez, Fernandes, & Lippi, 1991). Perry (1994) found decreased platelet adrenergic receptors and increased heart rate following orthostatic challenge in physically

and sexually abused children with PTSD, suggesting an enhancement of SNS tone in childhood PTSD. An increase in baseline functioning of the catecholamine system in childhood PTSD is also provided by two separate, open-label treatment trials of the medications clonidine (a central alpha$_2$-adrenergic partial agonist), and propranolol (a beta-adrenergic antagonist), both of which dampen catecholamine transmission. Clonidine treatment was associated with general clinical improvement and decreases in the arousal cluster of PTSD symptoms and basal heart rate (Perry, 1994). Propranolol treatment was associated with decreases in aggressive behaviors and insomnia (Famularo, Kinsherff, & Fenton, 1988).

Results from investigations of the LHPA axis and childhood trauma are similar to those of adult studies in that the data also suggest that this system functions in a complex manner. Results fall into a predictable pattern when addressed as a reflection of a chronic compensatory adaptation of the LHPA axis long after trauma exposure. This compensatory adaptation may involve the "priming" mechanism.

In studies of children undergoing current adversity, evidence of elevations of cortisol or ACTH and "priming" are seen. Augmented mean morning serial plasma cortisol levels were found in sexually abused girls *recruited within 6 months of disclosure* compared with nonabused sociodemographocally matched controls. This suggests morning hypersecretion of cortisol in sexually abused girls (Putnam, Trickett, Helmers, Dorn, & Everett, 1991). Maltreated young children with major depression failed to show the expected diurnal decrease in cortisol secretion from morning to afternoon (Hart, Gunnar, & Cicchetti, 1996; Kaufman, 1991). Increased ACTH response to human CRH, but normal cortisol secretion in maltreated prepubertal depressed children undergoing current psychosocial adversity compared to depressed children with prior histories of maltreatment, depressed nonabused children, and healthy children, were reported (Kaufman, Birmaher, Perel, Dahl, Moreci, Nelson, Wells, & Ryan, 1997). This result of an increase in ACTH secretion may be related to "priming."

In studies of children with past trauma, chronic compensatory adaptation of the HPA axis is seen. Attenuated plasma ACTH responses to ovine CRH in sexually abused girls *studied several years after abuse disclosure* were reported (De Bellis, Chrousos, Dorn, Burke, Helmers, Kling, Trickett, & Putnam, 1994). The abused subjects had histories of severely depressed mood with suicidal behavior, but only one had a diagnosis of PTSD. The abused girls exhibited reduced evening basal, ovine-CRH-stimulated, and time-integrated total plasma ACTH concentrations compared with controls. Plasma total and free cortisol responses to ovine CRH stimulation did not differ between the two groups. Thus, sexually abused girls manifest a dysregulatory disorder of the LHPA axis, associated with hyporesponsiveness of the pituitary to exogenous CRH and normal overall cortisol secretion to CRH challenge. CRH hypersecretion may have led to an adaptive down-regulation of CRH receptors in the anterior pituitary which is similar to the mechanism suggested in adult PTSD (Baker et al., 1999; Bremner et al., 1997). Armenian adolescents who lived close to the epicenter of the 1988 earthquake and experienced a significant direct threat to life had greater PTSD and comorbid depressive symptoms, lower baseline mean salivary cortisol levels, and greater afternoon suppression of cortisol by dexamethasone, *5 years after exposure,* when compared to Armenian adolescents who lived 20 miles from the epicenter (Goenjian, Yehuda, Pynoos, Steinberg, Tashjian, Yang, Najarian, & Fairbanks, 1996). These results are similar to the LHPA axis findings in adult PTSD. These studies show that elevated secretion of ACTH or cortisol is seen initially, and enhanced negative feedback inhibition of the pituitary for cortisol is seen as a compensatory adaptation of the LHPA axis long after trauma exposure. However, if an individual child, who has a history of severe stress (maltreatment) is restressed, there is evidence for "priming" or hyper-responding of the LHPA system.

To further study this issue, we recently completed a cross-sectional investigation of medically healthy clinically referred prepubertal medication naive maltreated children

with chronic PTSD studied within a year of disclosure and nontraumatized healthy controls (De Bellis, Baum, et al., 1999). PTSD trauma for most of these children was sexual abuse. Maltreated subjects with PTSD excreted significantly greater concentrations of urinary DA and NE over 24 hr than nonmaltreated overanxious disorder and control subjects and greater concentrations of 24-hr UFC than control subjects. Childhood PTSD was associated with greater comorbid psychopathology including depressive and dissociative symptoms, lower global assessment of functioning, and increased incidents of lifetime suicidal ideation and attempts. Urinary catecholamine and UFC concentrations showed positive correlations with duration of the PTSD trauma and severity of PTSD symptoms. These data suggest that maltreatment experiences are associated with alterations of biological stress systems in maltreated children with PTSD. Because we did not study maltreated children without PTSD, we do not know if these results are related to PTSD or abuse. However, the limited data published to date and discussed above suggest *that biological stress systems are dysregulated in maltreated children who may suffer from depressive and PTSD symptoms but who may or may not have a diagnosis of PTSD.*

Is Childhood Trauma (i.e., Maltreatment) a Risk Factor for Adverse Brain Development?

Birth to adulthood is marked by progressive physical, behavioral, cognitive, and emotional development. Paralleling these stages are changes in brain maturation. Findings from cross-sectional studies suggested that the proportion of cerebral gray matter to white matter (which reflects reductions in synaptic density and pruning) decreases progressively after age 4 years (Jernigan & Sowell, 1997). Using anatomical magnetic resonance imaging (MRI) technology to noninvasively investigate the child and adolescent brain, Giedd and his colleagues have recently demonstrated in longitudinal studies that there are regionally specific nonlinear preadolescent increases followed by postadolescent decreases in corticol gray matter (Giedd, Blumenthal, Jeffries, Castellanos, Liu, Zijdenbos, Paus, Evans, & Rapoport, 1999; Thompson, Giedd, Woods, MacDonald, Evans, & Toga, 2000). The most dramatic increase in myelination, reflected by the corpus callosum, which connects all major subdivisions of the cerebral cortex, occurs between the ages of 6 months and 3 years and continues into the 3rd decade (Giedd, Blumenthal, Jeffries, Castellanos, et al., 1999; Giedd, Blumenthal, Jeffries, Rajapakse, Vaituzis, Liu, Tobin, Nelson, & Castellanos, 1999; Giedd, Castellanos, Casey, Kozuch, King, Hamburger, & Rapoport, 1994). Subcortical gray matter and limbic system structures (septal area, hippocampus, amygdala) increase in volume nonlinearly and peak at age 16.6 years according to longitudinal studies (Giedd, Blumenthal, Jeffries, Castellanos, et al., 1999). The prefrontal cortex also continues its development into the 3rd decade (Alexander & Goldman, 1978; Fuster, 1980; Goldman & Rosvold, 1970). The prefrontal cortex subserves executive cognitive functions such as planned behaviors (Fuster, 1980) and working memory (Goldman–Rakic, 1994). The anterior cingulate region of the medial prefrontal cortex is part of an executive attention system and involved in the extinction of conditioned fear responses. It may be involved in the pathophysiology of PTSD symptoms (for review, see Hamner et al., 1999).

That experience affects brain structure and function has been established in animal studies. Studies of infant rats and monkeys show that early deprivation of frequent touching by the maternal caregiver results in persistent deficits in social, behavioral, and cognitive development and concluded that this caregiving is a biologic necessity for physical and psychological growth (Black, 1998; Kuhn, Pauk, & Schanberg, 1990). Parental care affects many physiological variables in animals (Hofer, 1996). Even brief maternal separations or trauma exposure during infancy have been shown to affect the functioning of the LHPA axis and glucocorticoid receptor gene expression in the hippocampus and frontal cortex in rats (Francis & Meaney, 1999; Meaney, Diorio, Francis, Widdowson, LaPlante, Caldji,

Sharma, Seckl, & Plotsky, 1996). Individual differences in mothering of rat pups affects their catecholamine regulation and fear response (Caldji, Tannenbaum, Sharma, Francis, Plotsky, & Meaney, 1998). In the developing brain, elevated levels of catecholamines and cortisol may lead to adverse brain development through the mechanisms of accelerated loss (or metabolism) of neurons (Edwards et al., 1990; Sapolsky et al., 1990; Simantov, Blinder, Ratovitski, Tauber, Gabbay, & Porat, 1996; Smythies, 1997), delays in myelination (Dunlop, Archer, Quinlivan, Beazley, & Newnham, 1997), abnormalities in developmentally appropriate pruning (Lauder, 1988; Todd, 1992), or by inhibiting neurogenesis (Gould, McEwen, Tanapat, Galea, & Fuchs, 1997; Gould, Tanapat, & Cameron, 1997; Tanapat, Galea, & Gould, 1998).

To further examine changes in brain development in maltreated children, MRI technology is being used. This method provides a noninvasive and safe way to examine differences between maltreated and nonmaltreated subjects in brain morphology, physiology, and function. To investigate this issue, we recently completed a cross-sectional investigation of brain development in medically healthy clinically referred children and adolescents with chronic PTSD secondary to maltreatment and nontraumatized healthy controls (De Bellis, Keshavan, et al., 1999). Most PTSD subjects experienced multiple types of maltreatment particularly experiences of sexual abuse and witnessing domestic violence. Most PTSD subjects had comorbid disorders with many subjects also complaining of comorbid mood disorders (major depression, dysthymia), oppositional defiant disorder, or attention deficit hyperactivity disorder (mainly inattentive subtype).

Maltreated children and adolescents with PTSD had smaller MRI-based brain structural measures of intracranial volumes, cerebral volumes, midsaggital corpus callosum areas, and larger lateral ventricles than controls after adjustment for intracranial volumes and socioeconomic status (SES; De Bellis, Keshavan, et al., 1999). Intracranial volumes positively correlated with abuse age of onset and negatively with abuse duration and PTSD symptoms. The positive correlation of intracranial volumes with age of onset of PTSD trauma suggests that traumatic stress is associated with disproportionately negative consequences if it occurs during early childhood. The negative correlation of intracranial volumes with abuse duration suggests that childhood maltreatment has global and adverse influences on brain development that may be cumulative. Symptoms of intrusive thoughts, avoidance, hyperarousal, dissociation, and abuse duration correlated negatively with corpus callosum regional measures. There was some indication that maltreated males with PTSD may show more evidence of adverse brain development than maltreated females with PTSD. A significant sex-by-diagnosis effect revealed greater total corpus callosum area reduction and trends for smaller cerebral volume and corpus callosum Region 6 (isthmus) in maltreated males with PTSD compared with maltreated females with PTSD. Thus, our findings may suggest that males are more vulnerable to the effects of severe stress in global brain structures than females. However, both males and females showed findings of adverse brain development.

Our findings of decreased intracranial volumes (ICVs) and cerebral volumes in maltreated children with PTSD are intriguing. The positive correlation of ICV with age of onset of PTSD trauma and negative correlation with the duration of the maltreatment that led to a PTSD diagnosis suggest that there may be critical periods and dose effects for stress-related alterations in brain development. Findings of lateral ventricular enlargement that also correlated positively with abuse duration may be indicative of neuronal loss associated with severe stress. This stress-induced enhancement of neuronal loss may be the mechanism causing such pervasive problems in maltreated children and adolescents with PTSD and is an important area for future investigations. (See Figure 2.)

Magnetic resonance spectroscopy (MRS), a safe and novel approach, can be used to further study the in vivo neurochemistry of such neurobiological alterations in the brains of living children. The *N*-acetyl signal in the proton

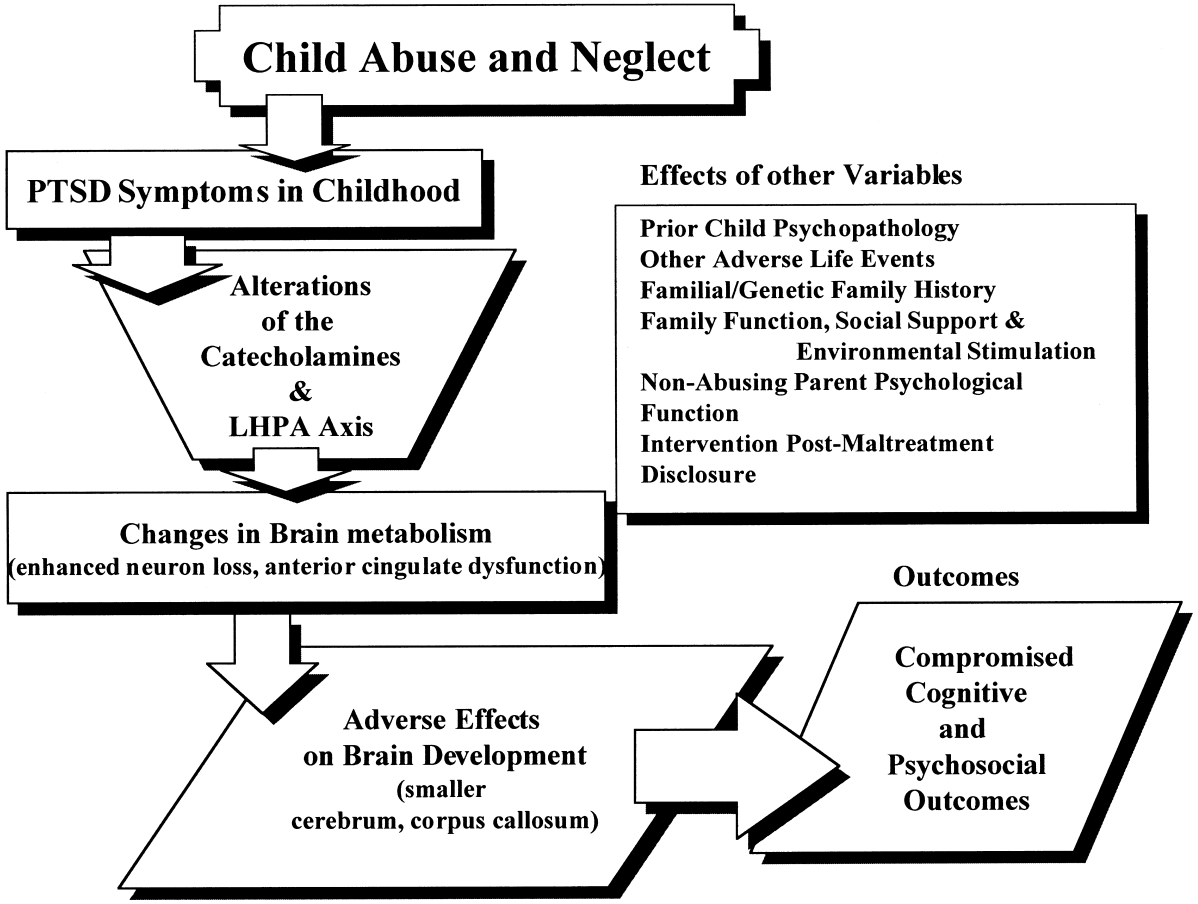

Figure 2. A developmental traumatology model of biological stress systems and brain maturation in maltreated children. In this model compromised neurocognitive and psychosocial outcomes are understood as being a result of adverse brain development.

(^{1}H) spectrum mainly comprises of *N*-acetyl-aspartate (NAA) and is considered to be a marker of neural integrity. Decreased NAA concentrations are associated with increased metabolism and loss of neurons (for review, see Prichard, 1996). We recently completed a preliminary investigation suggesting that maltreated children and adolescents with PTSD have lower NAA-to-creatine ratios that are suggestive of neuronal loss in the anterior cingulate region of the medial prefrontal cortex compared to sociodemographically matched controls (De Bellis, Keshavan, Spencer, & Hall, 2000). These results were not specific to gender. These findings may reflect global neuronal loss in childhood PTSD, a possibility supported by our previous findings discussed above. Neuronal loss in the anterior cingulate of pediatric PTSD patients agree with the recent adult neuroimaging studies, which provide evidence for anterior cingulate dysfunction in adult PTSD. Thus, dysfunction of the anterior cingulate cortex, which is involved in the extinction of conditioned fear responses, may be implicated in the pathophysiology of both adult and child PTSD.

PTSD is an anxiety disorder and anxiety disorders have been associated with dysregulation of growth hormone secretion (Pine, Cohen, & Brook, 1996). Stress-related abnormalities in growth hormone may affect brain and body maturation (for review, see De Bellis & Putnam, 1994). We undertook a pilot study comparing measures of brain regions in nontraumatized, nonmaltreated children and adolescents with DSM-IV generalized anxiety disorder with sociodemographically matched controls. Right and total amygdala volumes were significantly larger in subjects with generalized anxiety disorder compared to controls (De Bellis, Casey, Dahl, Birmaher, Williamson, Thomas, Axelson, Frustaci, Boring, Hall, & Ryan, 2000). Intracranial, cerebral, cerebral gray and white matter, temporal lobe, hippocampal and basal ganglia volumes, and measures of the midsagittal area of the corpus callosum did not differ between groups. The amygdala and its related circuits are important in fear-related behaviors (Davis, 1997; LeDoux, 1998). These results are consistent with the idea that alterations in the amygdaloid structure and function, but not of global brain measures, may be associated with pediatric generalized anxiety disorder. Increased amygdala volume may index some genetic trait such as increased sensitivity to threat cues, which could create a vulnerability for pediatric generalized anxiety disorder. Unlike children with pure anxiety disorders, maltreated children and adolescents with PTSD showed global adverse brain development and no anatomical changes in limbic (hippocampal or amygdala) structures (De Bellis, 1999). These results provide indirect evidence that PTSD in maltreated children may be regarded as a *complex environmentally induced developmental disorder. This provides further evidence for the need to study brain maturation in traumatized children and carefully characterize trauma histories when studying the psychobiology of psychiatric disorders that share symptoms in common with PTSD, throughout the life span. The safety and availability of MR methods make this an exciting time to disentangle these challenges.*

Our results of lack of hippocampal findings are in contrast to the adult PTSD literature. *We did not find the predicted decrease in hippocampal volume.* Subcortical gray matter structures that include the limbic system (septal area, hippocampus, amygdala) actually show an increase in volume during adolescence (Jernigan & Sowell, 1997). This increase may "mask" any effects of traumatic stress in maltreated children with PTSD. *Since our subjects had less comorbid histories of alcohol and substance abuse* (*four of 43 subjects*), our maltreated PTSD subjects differed in the degree of psychiatric comorbidity from the adult PTSD studies. High rates of comorbid lifetime alcohol dependence were seen in adult MRI studies of PTSD secondary to combat exposure (Bremner et al., 1995; Gurvits et al., 1996), adult PTSD secondary to child abuse (Bremner et al., 1997), and female adult survivors of childhood sexual abuse (Stein et al., 1997). Although these investigators attempted to control for lifetime alcohol consumption, these studies may not have controlled for adolescent onset alcohol abuse. Results from animal studies show that the hippocampus is susceptible to the effects of chronic

alcohol administration (Lescaudron, Jaffard, & Verna, 1989). The additional negative impact of excessive alcohol consumption on the regulation of NMDA receptors (Breese, Freedman, & Leonard, 1995) in persons with trauma history may lead to more profound excitotoxic neuronal damage in alcoholic adults comorbid for PTSD.

Furthermore, maltreated children are at increased risk for adolescent alcohol and substance use disorders (Clark, Lesnick, & Hegedus, 1997; Dembo, Williams, Wothke, Schmeidler, & Brown, 1992; Deykin & Buka, 1997). In community adult samples, sexual abuse histories have been found to be associated with increased alcohol consumption and related problems (Widom, Ireland, & Glynn, 1995; Wilsnack, Vogeltanz, Klassen, & Harris, 1997). Childhood abuse has been found to moderate the relationship between parental alcohol abuse or dependence and young adulthood offspring alcohol abuse or dependence (Sher, Gershuny, Peterson, & Raskin, 1997). Dysregulation of biological stress systems and self-medication of chronic PTSD symptoms may constitute the mechanisms for the association between maltreatment and alcohol and substance abuse and dependence disorders. Maltreatment experiences in childhood and adolescence may increase the likelihood of alcoholism and substance abuse through attempts to use alcohol and other drugs to reduce symptoms of PTSD and its common comorbid symptoms of depression (Labouvie, 1986; Newcombe & Harlowe, 1986) and to dampen the effects of dysregulated biological stress systems (Higley, Hasert, Suomi, & Linnoila, 1991). On the other hand, adolescent onset alcohol and substance abuse and dependence may cause further dysregulation of biological stress systems (Groote Veldman & Meinders, 1996; Rivier, 1996). (See Figure 1.)

Adolescent onset alcohol abuse and dependence may be neurotoxic to the hippocampus. MRI measures of hippocampal volumes were significantly smaller in 12 subjects with adolescent onset alcohol abuse or dependence compared with 24 sociodemographically matched controls (De Bellis, Clark, et al., 2000). These findings were not explained by comorbid PTSD in the adolescent onset alcohol group. Global brain regions did not differ between groups. Adolescent alcohol abuse and dependence may be major confounds when studying adults who were maltreated as children. *These issues need to be addressed in future research designs involving maltreatment studies.*

Cognitive Functioning in Maltreated Children and Adolescents

Adult studies reported cognitive changes in individuals with PTSD (Wolfe & Charney, 1991), particularly concentration, learning, and memory problems (Boulanger, 1985; Sutker, Winstead, Galina, & Allain, 1990, 1991). One study suggested that premorbid lower IQ may increase the risk for combat-related PTSD (Macklin, Metzger, Litz, McNally, Lasko, Orr, & Pitman, 1998), but these subjects were not screened for child abuse history. Child abuse history is a risk factor for later onset PTSD in combat veterans (Bremner, Southwick, et al., 1993).

PTSD symptoms associated with child maltreatment experiences may have broad developmental ramifications. While most studies report temporal stability of intelligence in various pediatric populations including handicapped children (Atkinson, Bowman, Dickens, Blackwell, Vasarhelyi, Szep, Dunleavy, MacIntyre, & Bury, 1990; Elliot & Boeve, 1987), a literature review suggests that intellectual ability, as reflected by IQ score, may be a consequence of child maltreatment. A variety of intellectual and academic impairments, with resultant poor school performance (National Research Council, 1993; Trickett, McBride–Chang, & Putnam, 1994), have been consistently reported in abused children not evaluated for PTSD (Augoustinos, 1987; Azar, Barnes, & Twentyman, 1988; Kolko, 1992). Carrey, Butter, Persinger, and Bialik (1995) noted negative correlation between Verbal IQ score and severity of abuse. Perez and Widom (1994) reported lower IQ and reading ability in a large sample of adult survivors of child maltreatment who were followed in a long-term, well-controlled prospective study of early onset abuse or neglect (before age 11 years). Investigations re-

ported changes in IQ in high-risk samples that are related to the quantity of parent–child interaction and home environment and to the degree of maternal depression (Money, Annecillo, & Kelly, 1983; Pianta, Egeland, & Erickson, 1989). In one case control study (Money et al., 1983), low and persistent impairment of IQ were associated with abuse disclosure, while IQ elevations were significantly correlated with duration of "rescue" (in years) from an abusive upbringing. There is a positive relationship in adults between IQ and brain size (Andreasen, Flaum, Swayze, O'Leary, Alliger, Cohen, Ehrhardt, & Yuh, 1993). In our MRI study, the known positive correlations between IQ scales and intracranial volume were seen for Verbal ($r = .24$; $p = .01$), Performance ($r = .25$; $p < .01$), and Full Scale ($r = .29$; $p < .003$) IQ. However, Verbal ($r = -.36$; $p < .0001$), Performance ($r = -.42$; $p < .0001$), and Full Scale ($r = -.43$; $p < .0001$) IQ showed negative correlations with abuse duration (in years) that led to PTSD (De Bellis, Keshavan, et al., 1999). These findings lead us to hypothesize that these smaller intracranial volumes may be associated with permanent neuronal loss leading to lower IQ. To date, cognitive function, as indexed by performance on standardized neuropsychological instruments, has not been evaluated in maltreated children with and without PTSD. *Given that maltreated children tend to do poorly in school and our current lack of understanding of cognitive development in maltreated children, this is another extremely important area for future research.*

Is There a Psychobiology of Hope?

In this review, data show that the effects of traumatic stress on the developing brain may be severe and persistent and may lead to adverse brain development. However, neurobiological development is regulated by the complex interactions of genes and experiences. Quality of childcare is associated with a buffering of HPA axis to stress (Gunnar, 1998). This buffering should lead to fewer psychosocial impairments. Neuronal loss may not be permanent. There is a capacity for primate neurogenesis in the hippocampus and frontal cortex (Gould, Reeves, Graziano, & Gross, 1999; Gould, Tanapat, McEwen, Flugge, & Fuchs, 1998). Environmental stress and adrenal steroids inhibit this neurogenesis (Gould, McEwen, et al., 1997; Gould, Tanapat, & Cameron, 1997; Tanapat et al., 1998). When rescued from extremely neglectful and abusive environments, some profoundly maltreated children are capable of accelerated rates of catch-up growth, including remission of severe psychopathology and normalization of cognitive function (Koluchova, 1972, 1976; Money et al., 1983). *Brain maturation studies in maltreated children will help the field begin to understand these processes in humans. Yet, despite the clinical and recent neurobiological data showing that there is hope for maltreated individuals, clinical intervention research for maltreated children and their families is markedly underfunded.*

A Psychobiological Model for the Intergenerational Cycle of Maltreatment

Some of the factors that contribute to the difficulty in understanding the etiology of child maltreatment are (a) the relatively low prevalence of child abuse and neglect, (b) the extreme socially deviant nature of these parenting behaviors, (c) the presence of other confounding factors (i.e., poverty and family violence), and (d) the changing political and historical definitions of child abuse and neglect (for review see National Research Council, 1993).

There is an unequivocal relation between parental poverty and child maltreatment (Garbarino, 1982; Pelton, 1981; Russell & Trainor, 1984). While poverty may expose parents to more stressors and risk factors for child abuse and neglect, it is clear that most poor parents do not maltreat their children (Besharov & Laumann, 1997). A ecological–transactional model suggests that maltreatment exists when multiple risk factors outweigh protective, compensatory, and buffering factors (Cicchetti & Lynch, 1993; Cicchetti & Rizley, 1981). Approximately one quarter to one third of maltreated children grow up to repeat the cycle of abuse and neglect (Kaufman & Zigler, 1987; Widom, 1989). How-

ever, the majority of parents involved in a child maltreatment disclosure had a personal history of abuse or neglect (Kaufman & Zigler, 1987).

It is proposed that child abuse and neglect and the associated factors of substance abuse and family violence may be the result of "untreated" psychopathological (signs and symptoms of PTSD) and developmental consequences of growing up with traumatic stress. It is further proposed that these negative developmental consequences are mediated by PTSD symptoms and its trajectory to serious and comorbid adult mental disorders (see Figure 1). Recent studies have found increased rates of major depression, PTSD substance abuse–dependence, and antisocial behaviors in parents of maltreated children recruited from child protective service samples (Famularo, Kinscherff, & Fenton, 1992; Kaplan, Pelkovit, Saltzinger, & Ganeles, 1983; Taylor, Norman, Murphy, Jellinek, Quinn, Poitrast, & Groshko, 1991) and from epidemiological samples (Bland & Orn, 1986; Dinwiddie & Bucholz, 1993; Egami, Ford, Greenfield, & Crum, 1996). Furthermore, maltreatment in families involves acts of commission (the abuse or neglect) and omission (not protecting the child from abuse and neglect). Certain symptoms of untreated mood disorders (hopelessness, low self-worth) make these individuals more likely to commit these acts of omission, which put their child at risk for abuse and neglect. Other symptoms of untreated mood disorders (poor concentration, anhedonia) make learning effective parenting skills and enjoying one's child a difficult task. Mood, posttraumatic stress, substance abuse, and personality disorders are treatable illnesses. Persons with these disorders require long-term clinical attention to alleviate their suffering and to become "good enough" parents. However, one must note that some serious mental disorders are less likely to be amendable to conventional community outpatient or inpatient clinical interventions (i.e., schizophrenia, severe substance abuse–dependence, antisocial personality disorder, and violent and criminal behaviors) and that even adequately treated individuals with these disorders may never be able to adequately care for a child. *Given that maltreating parents are likely to have serious but treatable comorbid mental disorders and our current lack of understanding of their treatment needs and mental health resources for these individuals, this is another extremely important area for future prevention and intervention research.*

Can a Psychobiological Model for the Intergenerational Cycle of Maltreatment Inform the Nation About Maltreatment Policy?

This model described in Figure 1 suggests several mechanisms for therapeutic intervention to break the intergenerational cycle of abuse and neglect. However, research on childhood maltreatment is often viewed as addressing social rather than scientific public health problems. Given how common PTSD is in maltreated children, it is sad that there is no U.S. national policy for mental health screening of all parents and children involved with child protection services. Furthermore, the assessment and management of parents involved in maltreatment and their maltreated children will, more often than not, require clinical skills in interviewing persons with PTSD symptoms. Consequently, licensed mental health professionals from multidisciplinary fields have much to offer our nation's child protective services. Public Law 104-235, the Child Abuse Prevention and Treatment Act Amendment of 1996, established federal guidelines to execute and coordinate various functions and activities aimed at the prevention and treatment of child abuse and neglect. Public Law 105-89, the Adoption and Safe Families Act of 1997, clarified federal guidelines for the establishment of reasonable efforts to maintain a maltreated child in his and her home and for a child's reunification with his and her family of origin. This law also established safety requirements for foster care and adoptive placements and guidelines for the termination of parental rights. However, these laws do not comprehensively address the complexities of the mental health issues involved in child maltreatment. Since an essential way to secure secondary prevention of maltreatment and to break the intergenera-

tional cycles of abuse and neglect in already existing maltreating families is to identify and treat PTSD and related comorbid psychiatric diagnoses of caregivers involved in maltreatment and their maltreated children, express language concerning the mental health needs of maltreating families would greatly strengthen the existing laws and should help decrease future incidences of child maltreatment. *Regarding child abuse and neglect from a public health perspective rather than a social problem would open up opportunities for treatment research which would rationally inform these important life decisions and is an essential way to break the intergeneration cycle of abuse and neglect.*

Summary

Child maltreatment has a traumatic impact on biological development and is a negative life altering experience for children. Data were reviewed that support that the psychobiological sequelae of child maltreatment may be regarded as *an environmentally induced complex developmental disorder*. In this review, a developmental traumatology model of child maltreatment and the risk for the intergenerational cycle of abuse and neglect using a mental health or posttraumatic stress model was described. Data to support this view and descriptions of the state of the psychobiology of maltreatment research, emphasizing the similarities and differences between children, adolescents, and adults, were reviewed. Many suggestions for important future research opportunities as well as public policy ideas were offered. These questions should be of interest to basic scientists, clinical and policy researchers, and therapists who have long struggled with this difficult area. Although trauma in childhood may have profound and long-lasting impacts on development, it is always helpful to note that individual children strive toward growth and that there is a psychobiology of hope.

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