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NEURODEVELOPMENTAL BIOLOGY ASSOCIATED WITH CHILDHOOD SEXUAL ABUSE

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Abstract

Child maltreatment appears to be the single most preventable cause of mental illness and behavioral dysfunction in the US. There are few published studies examining the developmental and the psychobiological consequences of sexual abuse. There are multiple mechanisms through which sexual abuse can cause PTSD, activate biological stress response systems, and contribute to adverse brain development. This article will critically review the psychiatric problems associated with maltreatment and the emerging biologic stress system research with a special emphasis on what is known about victimization by sexual abuse.

Keywords

Sexual abuse; maltreatment; developmental traumatology; biological stress systems; brain development

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Child maltreatment appears to be the single most preventable cause of mental illness and behavioral dysfunction in the US. Child abuse and neglect can cause disrupted development leading to delays in, deficits of, or failures of multisystem achievements in motor, emotional, behavioral, language, psychosocial, social, and cognitive skills (for review see De Bellis, 2001). There is evidence that these disruptions persistent into adulthood and are accompanied by neurobiologic stress response dysregulation (DeBellis & Thomas, 2003). Individuals with child maltreatment histories are more likely to manifest multiple health risk behaviors and serious medical illnesses (Felitti et al., 1998), have greater rates of psychiatric impairment (Edwards, Holden, Felitti, & Anda, 2003) and medical utilization (Swenson & Spratt, 1999; Walker et al., 1999), higher rates of developmental disorders (Cicchetti & Lynch, 1995), impaired attachment (Hanson & Spratt, 2000), greater risk for violent crimes (Deykin & Buka, 1997), substance use disorders (De Bellis, 2002), more school discipline problems and suspensions (Eckenrode, Laird, & Doris, 1993), poor long-term intellectual

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and academic achievement (Perez & Widom, 1994), and greater likelihood of becoming a teenage parent (Anda et al., 2002; Hillis et al., 2004). Despite the fact that sexually abused children suffer adverse outcomes, there are few published studies examining the developmental and the psychobiological consequences of sexual abuse. Childhood sexual abuse is strongly associated with experiencing multiple other forms of adverse childhood experiences (Dong, Anda, Dube, Giles, & Felitti, 2003). These poor developmental outcomes may be caused by dysregulation of biological stress systems and adverse brain development (De Bellis et al., 1994a; De Bellis et al., 1999b; De Bellis et al., 1999c; De Bellis et al., 2002b; De Bellis & Keshavan, 2003; De Bellis, Lefter, Trickett, & Putnam, 1994b; see Figure 1).

This article will review the psychiatric problems associated with maltreatment and the emerging biologic stress system research with a special emphasis on what is known about victimization by sexual abuse. Childhood sexual abuse is a major public health problem that affects as many as 16.8% of women and 7.9% of men in the United States before their eighteenth birthday (Gorey & Leslie, 1997). It is clear that early and repeated sexual abuse has a devastating impact on the well-being of a young person. Although specific definitions may vary, sexual abuse most commonly refers to an activity within a spectrum that ranges from inappropriate physical touch to sexual intercourse or rape (Haugaard, 2000). Legal definitions usually include sexual contact between an adult and a minor child (Green, 1993). This discussion will include a broad definition of maltreatment (abuse and neglect), unless the data support different outcomes for various types of maltreatment. It is difficult to form clear diagnostic conclusions associated with a specific subtype of maltreatment, as many research studies examine youth with multiple types of abuse or neglect and are flawed by inconsistent diagnostic techniques, small sample groups and different outcome measures (Aber, Allen, Carlson, & Cicchetti, 1989). It is noted that for some victims child abuse and neglect are chronic conditions rather than acute events. Additionally and most importantly, various forms of abuse and neglect tend to co-exist (Cicchetti & Barnett, 1991).

Important factors found to be related to social and emotional outcomes of childhood sexual abuse include age of onset of the abuse, severity of abuse, use of force, and a victim's relationship to the perpetrator. Mothers of maltreated children who have their own child maltreatment histories, problems with social support, mental illness or current symptomatology in family of origin, such as posttraumatic stress disorder (PTSD) or substance abuse, have children with more behavior problems and poorer functioning. Thus, it is difficult to tease out factors that influence adaptation to sexual abuse. Adjustment is dependent on characteristics of the perpetrator and the victim, as well as intra- and extrafamilial factors (for review see Putnam, 2003). A better understanding of the pathophysiology associated with exposure to childhood maltreatment will lead to improved psychotherapeutic and psychopharmacologic treatment interventions and with a goal of ultimately leading to a lower prevalence of associated morbidities (see Figure 2).

Sexual Abuse and the Developmental Traumatology Model

There are multiple mechanisms through which sexual abuse can cause PTSD, activate biological stress response systems, and contribute to adverse brain development (for review see De Bellis, 2001). Developmental traumatology is the systemic investigation of the psychiatric and psychobiological impact of adversity on the developing child. It is a relatively new area of study that synthesizes knowledge from developmental 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. 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/family relationships. These adverse life circumstances usually also include socioeconomic disadvantage, perinatal insults, parental mental illness (including alcohol and substance abuse), community violence, and a lack of adequate social support and experience expected-environmental stimulation which can be thought of as emotional neglect. Additionally, these factors may contribute to poor developmental outcomes and confound clinical assessment, research and interventions inin sexually abused children The influence of sexual abuse, as well as the other noted factors, on biological stress systems regulation and brain development 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; furthermore, it will be important to determine 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. There is recognition that the primary stress systems in humans (i.e. the neuroendocrine, sympathetic nervous, and immune systems) influence brain development during critical periods for brain growth. We recognize that some areas of the brain may be more sensitive to stress than others. Although important associations are being identified, specific causality mechanisms to explain sexual abuse sequelae are difficult to establish. Based on a synthesis of the relevant literature, five basic assumptions based on Developmental Traumatology Theory (De Bellis, 2001) are made in this review:

1. 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.
2. Severe maltreatment in childhood may cause delays in, or deficits of, multisystem development of behavioral, cognitive and emotional achievements. The 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, sex of the child) in the response to the stressor, and the ability of biological stress systems to either maintain homeostasis in the face of chronic and severe stress or to permanently change in response to the stressor.
3. Maltreatment in childhood may be more detrimental than trauma experienced in adulthood. This may be due to the influence of early childhood experience on the cellular microenvironment and the effects on young brain development. The effects of abuse or neglect alone or in combination may induce a cascade of different biologic pathways that may play an essential role in child and adolescent brain development.
4. There is evidence that interpersonal stress that leads to the development of depressive and anxiety symptoms in childhood will lead to an increase risk of suffering from chronic posttraumatic stress disorder (PTSD), other psychopathology (i.e., internalizing or emotional and externalizing or behavioral disorders), and other cognitive and psychosocial consequences. Consequently, when trauma occurs during development, chronic PTSD symptoms can be seen as the trajectory to more severe co-morbid psychopathology and compromised cognitive and psychosocial functioning.
5. If the victim knows the perpetrator, the maltreatment is not only the act of maltreatment itself (e.g., sexual abuse) but also a dysfunctional and traumatized interpersonal relationship. Therefore, clinical identification of traumatic reminders may involve identification of subtleties that can sometimes be difficult to clinically

assess. 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 hard-wiring is present) but traumatized (e.g., the software is programmed to distrust and fear relationships). Consequently, the maltreated child may be more difficult to assess and treat because the establishment of a therapeutic alliance involves a process of desensitizing the maltreated individual to trust again, and this process will take moretime than in the treatment of a non-maltreated child.

Throughout this article, data on the neurodevelopmental biology associated with maltreatment, or specifically sexual abuse, will be presented and reviewed. The similarities and differences between children, adolescents and adults and the methodological difficulties and controversies inherent in this field of study will be outlined. Suggestions for future research opportunities and psychopharmacologic treatments will be offered. However, we will first discuss the mental health outcomes of maltreated children, noting that much progress has been made in the treatment of sexual abuse-related PTSD (Cohen, Mannarino, & Rogal, 2001).

Does the Diagnosis of PTSD Make a Difference in Outcomes of Maltreated Children?

The Diagnostic and Statistical Manual of Mental Disorders: Fourth Edition Text Revision (DSM-IV-TR) has four diagnoses for which a stressor precipitates the mental illness: posttraumatic stress disorder (PTSD), acute stress disorder, reactive attachment disorder of infancy or early childhood, and adjustment disorder(s). The essential feature (criterion A) of PTSD and acute stress disorder according to DSM-IV-TR is exposure to an extreme traumatic stressor in which the person experienced, witnessed, or was confronted with an event or events that involved actual or threatened death or serious injury, or a threat to the physical integrity of self (i.e., abuse) or others (i.e., witnessing domestic violence); furthermore, the person responded with intense fear, helplessness, or horror, or in children, disorganized or agitated behaviors. The diagnosis of PTSD is made after a person experiences a prior intense, overwhelming, traumatic event(s) and reacts with fear or disorganized behavior and with complaints of three clusters of categorical symptoms for at least one month: 1) intrusive re-experiencing of the trauma(s); 2) persistent avoidance of stimuli associated with the trauma; and 3) persistent symptoms of increased physiological arousal. The diagnostic picture of PTSD in children and adolescents is similar to adults (Pynoos & Eth, 1985), with the exception of children less than four years old, where more objective criteria based on observable behaviors are warranted (Scheeringa, Zeanah, Drell, & Larrieu, 1995). Unfortunately, a significant gap exists in our ability to accurately identify these symptoms in very young children, which may be partly attributable to the diagnostic criteria utilized. Detecting the presence of characteristic symptoms, such as hyperarousal, re-experiencing, and avoidance, may be more arduous in preverbal children, which suggests the need for clinicians and researchers to employ more developmentally sensitive diagnostic criteria. Scheeringa and colleagues (1995; 2003) developed alternate criteria that rely more heavily on behavioral observations of symptoms than on child verbalizations of symptoms. In developing alternate standards, certain criteria that were beyond the cognitive and developmental capacities of young children were no longer required (e.g., sense of a foreshortened future), while new symptoms (e.g., loss of previously acquired developmental skills) and a new cluster of commonly associated symptoms were added. The new cluster included the following symptoms: new separation anxiety, new aggression, and new fears that appeared unrelated to trauma reminders (Scheeringa et al., 2003). Furthermore, the diagnostic threshold for the number of symptoms endorsed in this cluster was lowered. These studies provided validation for developmental modifications of the DSM-IV-TR

diagnostic criteria for PTSD in preschool children. In this particular study, the resultant diagnosis rate was 26%, which distinctly contrasted to the DSM-IV rate of 0%. The 26% rate was more consistent with the PTSD rates of traumatized adults and older children (Scheeringa et al., 2003). By utilizing these alternate criteria in very young children, clinicians will be better able to identify and treat highly symptomatic children who previously would not have met diagnostic criteria for PTSD. This approach is necessary when considering the effect of trauma on development and on the child's ability to form a verbal narrative (Pynoos & Eth, 1986).

A review of the longitudinal course of PTSD suggests that PTSD symptoms are common within the first month of a trauma and that these symptoms may be a normal response to severe stress, as these PTSD symptoms usually fade within three months (Blank, 1993). However, in individuals who development chronic PTSD these symptoms do not go away. They persist and cause impairment. PTSD can also be thought of a failure to recover from these symptoms. PTSD may be better conceptualized as a dimensional process than a categorical all-or-none outcome, as complete and partial PTSD responses are seen in many forms of trauma, including 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 lasting three months or more), may provide the mechanisms for the pervasive psychopathology seen in maltreated children. The absence of PTSD symptoms after experiencing a severe stressor (i.e., lack of sleep disturbances, intrusive symptoms, or concentration impairments) may be associated with minimal psychopathology or resilience.

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; Pynoos & Nader, 1989). Only a few studies have focused on assessing PTSD in non-clinically referred maltreated children. Famularo, Fenton and Kinscherff (1993) reported a 39% incidence rate of PTSD in a non-clinically referred maltreated sample interviewed within eight weeks of abuse or neglect disclosure. About a third of the PTSD subjects re-examined from the original sample continued to meet PTSD criteria at two year follow-up (Famularo, Fenton, Augustyn, & Zuckerman, 1996). McLeer and colleagues (1998) reported prevalence rates of PTSD of 36.3% in non-clinically referred sexually abused children 60 days immediately following sexual abuse disclosure. Thus, PTSD is commonly seen in sexually-abused children, especially during the period immediately following maltreatment disclosure. Any severe trauma 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, rape, 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. Rates of PTSD in children traumatized by maltreatment are similar to those of children traumatized by war and homicide. 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 health problems (Dube, Felitti, Dong, Giles, & Anda, 2003).

Child Abuse is Associated with Dysregulation of Biological Stress Systems

The functional anatomy of PTSD anxiety or overwhelming stress is complex. Most studies to date are preclinical. These will be briefly reviewed. Multiple neurotransmitter systems

and neuroendocrine axes are activated during the acute stresses of child abuse experiences. Stress exposure affects the neurotransmitter systems, neuroendocrine system, and immune system. Necessarily, these systems are interconnected to modulate response to routine stimuli as well as acute and chronic stressors. The sympathetic nervous system (SNS) or catecholamine system, the limbic-hypothalamic-pituitary-adrenal (LHPA) axis, and the serotonin system are the three major neurobiological stress response systems implicated in mood, anxiety, and impulse control disorders (for review see Vermetten & Bremner, 2002). Arousal, stress response, behavioral and emotional regulation, and neurodevelopment are all dependent on these systems. It is highly probable that many of the acute and chronic symptoms associated with child abuse and neglect arise in conjunction with alterations of these systems. An understanding of this psychobiology may lead to early psychotherapeutic and psychopharmacological treatment(s), which in turn may lead to secondary prevention of the psychiatric chronicity and comorbidity commonly seen in maltreated children.

The Sympathetic Nervous System and the Catecholamines

Intense fear or anxiety activates the locus ceruleus, the major catecholamine containing(specifically, norepinephrine) nucleus in the brain, and the sympathetic nervous system **(**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 in the circulating catecholamines (e.g., epinephrine, norepinephrine, and dopamine). The amygdala, via the locus ceruleus, in turn stimulates the hypothalamus and release of corticotrophin-releasing hormone (CRH), also called factor CRF. CRH acts as a hormone and as a neurotransmitter. When it acts as a neurotransinitter, some investigators call it corticotrophin-releasing factor (CRF). CRH causes the pituitary to secrete adrenocorticotropin (ACTH), but CRH also stimulates cortical regions. In this manner, CRH functions as both a hormone and a neurotransmitter (Ruggiero, Underwood, Rice, Mann, & Arango, 1999). ACTH results in release of cortisol from the adrenal gland, with feedback to the SNS, causing further activation (for review see Chrousos & Gold, 1992). Cortisol, via negative feedback inhibition on the hypothalamus, pituitary, and other brain structures suppresses the HPA axis, leading to restoration of basal cortisol levels, or homeostasis.

In adult PTSD, it is hypothesized that the locus ceruleus/ SNS/ catecholamine system and LHPA axis responses to stress become maladaptive, causing long-term negative consequences (for review see Southwick, Yehuda, & Morgan, 1995). Results from adult combat-related PTSD studies suggest that there is increased sensitivity of the locus ceruleus/ SNS/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 sympathetic nervous system responses to adrenergic or traumatic reminder challenge compared to healthy combat or non-combat controls. These differences can lead to mental illness (e.g., PTSD, major depression) and cardiovascular disease in later life (Felitti et al., 1998).

The limited data published to date suggest that the locus ceruleus/SNS/catecholamine system is dysregulated in traumatized children who may suffer from PTSD and depressive symptoms, but who may or may not have a diagnosis of PTSD. Findings of elevated baseline 24-hour urinary catecholamine concentrations were seen in: 1) male children who suffer from severe clinical depression and had a history of parental neglect (Queiroz et al., 1991); 2) a pilot study of sexually abused girls, 58% of whom had histories of severely depressed mood with suicidal behavior but only one of whom had PTSD (De Bellis et al., 1994b); and 3) male and female children with abuse-related PTSD (De Bellis et al., 1999a).

In this last study, many of the subjects had PTSD secondary to sexual abuse. Furthermore, decreased platelet alpha$_2$-adrenergic receptors and increased heart rate following orthostatic challenge were found in sexually and physically abused children with PTSD, suggesting an enhancement of SNS tone in childhood PTSD (Perry, 1994). An increase in baseline functioning of the locus ceruleus/SNS/catecholamine system in childhood PTSD is also provided by two separate, successful, open-label treatment trials of the medications clonidine (a central alpha$_2$-adrenergic partial agonist) and propranolol (a beta-adrenergic antagonist). These medications, as well as serotonin-uptake inhibitor anti-depressants, 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).

The Limbic-Hypothalamic-Pituitary-Adrenal Axis

The limbic-hypothalamic-pituitary-adrenal (LHPA) axis, the major neuroendocrine stress response system, is also involved in the pathophysiology of PTSD. Elevated levels of corticotrophin releasing hormone (CRH) or factor (CRF) has been consistently reported in traumatized individuals (Southwick, Yehuda, & Wang, 1998). Adults with PTSD, maltreated children with symptoms of mood and anxiety disorders, and pediatric patients with abuse-related PTSD evidence this dysregulation (for review see De Bellis, 2001). Accordingly, adults who suffer from combat-related PTSD have elevated levels of central CRH (Baker et al., 1999; Bremner et al., 1997). Elevated CRH and enhanced negative feedback inhibition of the pituitary for cortisol is also evidenced by infusion studies of metyrapone, which blocks the conversion of 11-deoxycortisol to cortisol and allows for the direct measure of pituitary release of ACTH (Yehuda et al., 1996). Mechanisms of down regulation of pituitary CRH receptors secondary to elevated CRH and enhanced negative feedback inhibition of the pituitary for cortisol may lead to the lower levels of 24-hour urinary free cortisol seen in adult PTSD (Yehuda, Southwick, Giller, Ma, & Mason, 1991).

However, in pediatric studies of traumatized children with symptoms of PTSD, anxiety, or depression, dysregulation of the LHPA axis with increased CFH and cortisol secretion is evidenced. Increased cortisol levels are found in most studies of traumatized young and latency age children, while most studies have shown the opposite in adults (for review see Thomas & De Bellis, 2004). Many factors account for this. For example, higher morning serial plasma cortisol levels were found in sexually abused girls ages six to 15 years within six months of disclosure compared to non-abused sociodemographically matched controls (Putnam, Trickett, Helmers, Dorn, & Everett, 1991). This suggests morning hypersecretion of cortisol in sexually abused girls. Elevated salivary cortisol levels were seen in six to12 year old children raised in Romanian orphanages for more than eight months of their lives compared to early adopted and Canadian born children six and a half years after adoption (Gunnar, Morison, Chisholm, & Schuder, 2001). In addition, elevated salivary cortisol has been described in maltreated children with depression (Hart, Gunnar, & Cicchetti, 1996) and in maltreated children with threshold and subthreshold PTSD symptoms (Carrion et al., 2002). DeBellis and colleagues (1999a) showed elevated 24 hour urine free cortisol in prepubertal maltreated children with PTSD; many of these children were sexually abused. However, another study found that Armenian adolescents who lived close to ground zero during the 1988 earthquake showed more PTSD and depressive symptoms and decreased mean salivary cortisol at baseline *five years after exposure* compared to adolescents 20 miles away from the epicenter (Goenjian et al., 1996). These results are similar to the HPA axis findings in adult PTSD and may suggest that age is one factor explaining the developmental neurobiological differences in LHPA axis regulation seen between prepubertal children and adults with PTSD.

Another factor is the normal compensatory adaptation of the LHPA axis. Chronic compensatory adaptation of the LHPA axis is seen in the studies of children with past trauma. Attenuated plasma ACTH responses to ovine CRH in sexually abused girls studied several years after abuse disclosure has been reported (De Bellis et al., 1994a). 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 HPA 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. Another study showed developmental alterations in pituitary volume in abuse-related pediatric PTSD (Thomas & De Bellis, 2004). In this study, there was a significant age-by-group effect for PTSD subjects to have greater differences in pituitary volume with age than controls. Post-hoc analyses revealed that pituitary volumes were significantly larger in pubertal and post-pubertal maltreated subjects with PTSD than control subjects, but were similar in prepubertal maltreated subjects with PTSD and controls. Age of onset of abuse that led to PTSD significantly correlated with pituitary volume in prepubertal, pubertal, and post-pubertal subjects. However, in the prepubertal group, the longer the duration of the abuse, the larger the pituitary volume. In the pubertal/post-pubertal group (Tanner stage II-V), duration of the abuse associated with the PTSD trauma negatively correlated with pituitary volume. These findings may support the hypothesis that adaptive mechanisms and developmental factors influence pituitary size in a traumatized group of children. Endogenous CRH hypersecretion likely occurred with the onset of trauma. Thus, children exposed to trauma may experience chronically elevated CRH during pituitary development. Elevated CRH may lead to pituitary hypertrophy, which may be most pronounced during puberty, possibly due to trophic factors. Chronic exposure to CRH, in turn, may result in down regulation of pituitary CRH receptors over time. This down regulation may be an adaptive mechanism that regulates pituitary hypertrophy. An adaptive response to constantly elevated CRH must be down regulation of CRH receptors, or resultant high cortisol levels would result in medical illness and gross damage to brain structures (Sapolsky, 2000). Such a mechanism could explain the complex phenomena of low ACTH but elevated cortisol levels seen in studies of abused prepubertal and latency-age children, and normal and low cortisol levels, but elevated central CRH levels exhibited in many studies of traumatized adolescents and adults. In support of this idea, low urinary cortisol secretion has been found in adults with PTSD secondary to surviving the Holocaust as youth (Yehuda et al., 1995).

However, the HPA axis functions in a complex manner in children with a history of abuse who are currently experiencing stress. 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 non-abused children, and healthy children, has been reported (Kaufman et al., 1997). This later finding may be related to ‘priming,’ or sensitization, in which responses to repeated stress increase in magnitude. 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-hour levels (De Bellis et al., 1999a). Priming may occur as a reflection of chronic compensatory adaptation of the LHPA axis long after trauma exposure. 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 an acute stress. Thus, when a new emotional stressor is experienced, LHPA axis functioning will be enhanced (i.e., higher

ACTH and higher 24-hour UFC concentrations in response to stress). This 'hyper'-response was also seen in studies of women who had experienced sexual abuse and suffered from major depression (Heim et al., 2002).

The Serotonin System

The serotonin system is a stress response system that activates both anxiogenic and anxiolytic pathways and is regarded as a master control neurotransmitter of complex neuronal communication (Lesch & Moessner, 1998). Serotonin plays important roles in the regulation of emotions (e.g., mood) and behavior (e.g., aggression, impulsivity). Serotonin is implicated in PTSD, anxiety, major depression, impulsivity, and suicidal behaviors. Low serotonin function is associated with suicidal and aggressive behaviors in adults, children, and adolescents (for review see De Bellis, 2003). In primate studies of chronic stress, serotonin levels decrease in the prefrontal cortex (Fontenot, Kaplan, Manuck, Arango, & Mann, 1995). In animal studies of unpredictable and uncontrollable stress (e.g., inescapable shock, restraint stress), serotonin turnover increases and serotonin levels decrease in the amygdala, medial prefrontal cortex, nucleus accumbens and lateral hypothalamus. This process depletes serotonin and results in "learned helplessness" (Petty, Kramer, & Wu, 1997). Dysregulation of serotonin may not only play a major role in the development of threshold and subthreshold PTSD symptoms, but also may increase the risk for co-morbid major depression and aggression in abused children. This assertion is supported by the finding that trauma-exposed individuals with the diagnosis of PTSD have a significantly higher risk for onset of major depressive disorder than trauma-exposed individuals without PTSD (Breslau, Davis, Peterson, & Schultz, 2000). Breslau, Davis, Peterson, and Schultz (2000) have shown that the prevalence of major depression is markedly increased for trauma-exposed persons who suffer from PTSD but not for trauma-exposed persons without PTSD. Thus, PTSD may lead to major depression and may be influenced by common genetic vulnerabilities to serotonin dysregulation and trauma-related factors as discussed above.

Recently, clinical studies have demonstrated strong support for the efficacy of the serotonin reuptake inhibitor antidepressant and anti-obsessive compulsive medications sertraline (Brady et al., 2000) and fluoxetine (van der Kolk et al., 1994) in adult PTSD. Practice Parameters for the treatment of pediatric PTSD, published by the American Academy of Child and Adolescent Psychiatry, state that selective serotonin reuptake inhibitors are the first line medication treatment for child and adolescent PTSD, particularly PTSD co-morbid with major depression (Cohen & and The Work Group on Quality Issues, 1998). However, it should be noted that these Practice Parameters state that the best available evidence for treating child and adolescent PTSD secondary to sexual abuse is trauma-focused psychotherapy with cognitive behavioral approaches. As very little is known about serotonin function and trauma in children, this is an important area for future research.

Physical Health and the Immune System

During chronic stress, biological stress response systems signal to the immune system via the LHPA axis and the SNS. As early as 1936, Selye showed that restraining rats produced involution of the thymus and stress-induced lymphopenia (Selye, 1936). An extensive review of the literature on the effects of stress on cellular immune response in animals concluded that a variety of acute and chronic stressors, such as inescapable noise, social isolation, and uncontrollable shock, are associated with suppression of immune responses (Weiss & Sundar, 1992). Stressed animals are at significantly greater risk for development of infections, tumors, and death after experimentally induced immune (antigenic) challenge. Adverse childhood experiences are associated with multiple and serious health problems in

adulthood (Felitti et al., 1998). In children, a significantly higher incidence of plasma antinuclear antibody titers was seen in sexually abused girls when compared with the frequency of positive antinuclear antibody titers in a sample of healthy adult women (De Bellis, Burke, Trickett, & Putnam, 1996). One may speculate that the severe stress of sexual abuse may lead to suppression of the mechanisms (T suppressor cells) that actively suppress the autoantibody-producing lymphocytes (B lymphocytes) and may thus increase the incidence of positive antinuclear antibody titers in these sexually abused girls. The influences of sexual abuse and health warrants further study in children.

A Note about Child Neglect and the Development of Biological Stress Response Systems

Emotional and physical neglect frequently co-exists with sexual abuse. The seminal studies of Harlow, Harlow and Suomi (1971) profoundly demonstrated the adverse effects of neglect in primates. Although child neglect is not abuse, neglect often co-exists with abuse, and it can be argued that childhood neglect may be perceived by the child as traumatic. For example, continuously neglected infants suffer from increased rates of infection and early death. A toddler who is not fed or supervised does not develop a “secure base” and is in a chronic state of severe anxiety (Rutter, 1981). An unsupervised non-abused young child is more likely to witness interpersonal traumas or experience traumatic accidents. Animal models demonstrate that maternal deprivation and maternal stress can alter the development of the LHPA axis of the affected offspring. Rodents exposed to maternal separation exhibit hyperresponsiveness of the LHPA axis to stress when tested as adults (for review see Caldji et al., 2001). Even brief maternal separations or trauma exposures 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 et al., 1996). Individual differences in mothering of rat pups affects their catecholamine regulation and fear response (Caldji et al., 1998). Environmental enrichment reverses some of the effects of maternal separation on stress reactivity (Francis, Diorio, Plotsky, & Meaney, 2002). Primates who were subjected to prolonged periods of maternal and social deprivation showed altered glucocorticoid (Lyons, Yang, Mobley, Nickerson, & Schatzberg, 2000) and catecholamine (Martin, Sackett, Gunderson, & Goodlin-Jones, 1988) function and impaired immune function (Lubach, Coe, & Erhler, 1995). Rosenblum and Andrews (1994) developed a primate model of non-deprivation mother-infant stress. In this paradigm, primate bonnet macaque mothers undergo variable forging demands, unpredictable periods of strenuous foraging for food with other periods where food is provided freely. The variable foraging demand manipulation altered the social behavior of these mothers and reduced the amount of time they were able to respond to their infants’ solicitations for contact and attention. Infants of these mothers demonstrated insecure patterns of attachment behaviors, such as decreased social competence and increased fearful behaviors than infants of mothers with low foraging demands (Rosenblum & Andrews, 1994). Furthermore, infant primates whose mothers underwent the variable forging demand manipulation exhibited persistent elevations in cerebrospinal fluid levels of CRF when tested as adults (Coplan et al., 1996). Cerebrospinal fluid concentrations of serotonin, dopamine and norepinephrine metabolites were also elevated in these monkeys (Coplan et al., 1998). This is similar to the elevations in cerebrospinal fluid concentrations of CRF are seen in adults with PTSD (Baker et al., 1999; Bremner et al., 1997).

The studies described above show that abuse experiences throughout the life cycle are associated with profound changes in the dynamics of the biological stress systems. These differences (increased catecholamines, CFH and cortisol) may influence brain development (see Figure 1).

Childhood Brain Development

Birth to adulthood is marked by progressive physical, behavioral, cognitive, and emotional development. Paralleling these stages are changes in brain maturation. Intracranial volume increases steadily until age 10, with 75% of adult brain weight occurring by age two (Carmichael, 1990) and near completion of adult intracranial volume by age five (Pfefferbaum et al., 1994). Human brain development takes place by an overproduction of neurons in utero and then selective elimination of many of these neurons (apoptosis) by age four and increases in myelination (Jernigan & Sowell, 1997). Early childhood is characterized by increases in synaptic neuropil (neuron size and synapses), but the process of synaptic elimination begins in late childhood and continues throughout the first three decades (Rabinowicz, 1986). Findings from cross-sectional studies suggest that the proportion of cerebral grey matter to white matter (which reflects reductions in synaptic density and pruning) decreases progressively after age four (Jernigan & Sowell, 1997). Giedd and colleagues recently demonstrated in longitudinal studies that there are regionally specific nonlinear pre-adolescent increases followed by post-adolescent decreases in cortical grey matter (Giedd et al., 1999a; Thompson et al., 2000). Neurons generally enlarge with age (Blinkov & Glezer, 1968). Axons become thicker and the number of synaptic boutons increases throughout life; axons are presumably involved in the mechanism of learning (Werry, 1991). From ages five to 18 years, myelination by oligodendrocytes is most influential in determining brain size (Giedd et al., 1996). The most dramatic increase in myelination, reflected by the corpus callosum, which connects major subdivisions of the cerebral cortex, occurs from the ages of six months to three years and continues into the third decade (Giedd et al., 1999b; Paus et al., 2001; Thompson et al., 2000). Subcortical grey matter and limbic system structures (e.g., hippocampus and amygdala), which are involved in the regulation of emotions and memory, increase in volume nonlinearly and peak at age 16.6 years in longitudinal studies (Giedd et al., 1999a). The prefrontal cortex, which subserves executive cognitive functions, also continues its development into the third decade (Alexander & Goldman, 1978; Fuster, 1989; Goldman, 1971). Interestingly, sex steroids influence neurodevelopment throughout the lifespan (for review see McEwen, 1981). However, sex differences in human brain maturation is an understudied area. In one pediatric neuroimaging study of healthy children and adolescents, boys showed significantly greater loss of grey matter volume and an increase in both white matter volume and corpus callosum area as compared to girls over a similar age range, suggesting sex differences in both cerebral grey and white matter maturational processes in childhood and adolescence (De Bellis et al., 2001). In a study of healthy adults ages 18 to 45 years, similar sex differences were seen (Gur et al., 1999). It is well known that cognitive and emotional development differs between boys and girls (for review see Nagy, Jacklin & Martin, 1999). Hence, many factors, including genetics, hormones, growth factors, nutrients and enriched environment, influence brain development (see Figure 2).

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, Harkins, Wright, & Menn, 1990; Sapolsky, 2000; Simantov et al., 1996; Smythies, 1997), delays in myelination (Dunlop, Archer, Quinlivan, Beazley, & Newnham, 1997), abnormalities in developmentally appropriate pruning (Lauder, 1988; Todd, 1992), and/or the inhibition of neurogenesis (Gould, McEwen, Tanapat, Galea, & Fuchs, 1997a; Gould, Tanapat, & Cameron, 1997b; Gould, Tanapat, McEwen, Flugge, & Fuchs, 1998; Tanapat, Galea, & Gould, 1998). Furthermore, stress decreases brain-derived neurotrophic factor expression (Smith, Makino, Kvetnansky, & Post, 1995). Thus, the overwhelming stress of child abuse experiences may have adverse influences on a child's brain maturation. Given that there are sex differences in brain development, males may be more vulnerable to adverse brain development (De Bellis & Keshavan, 2003). We will review evidence of

adverse brain development (i.e., smaller cerebral volumes and corpus callosum areas) in children and adolescents with abused-related PTSD. Note that trauma in childhood may be associated with global brain differences resulting from the experience of chronic stress at critical developmental periods and also with differences associated with brain structures (e.g., medial prefrontal regions) that are thought to be responsible for PTSD.

Studies of Brain Development in Abused Children

Neuroimaging studies of adults support the hypotheses that the medial prefrontal regions, which are responsible for executive functions, are hyporesponsive, and the amygdala is hyperresponsive in PTSD (Bremner et al., 1999a; Bremner et al., 1999b; Lanius et al., 2002; Shin et al., 1999; Shin et al., 2004; Shin et al., 2001). The medial prefrontal cortex and amygdala are thought to be reciprocally related (Hamner, Lorberbaum, & George, 1999; Stefanacci & Amaral, 2002). When confronted with traumatic reminders during a brain scan, medial prefrontal cortical dysfunction is seen in adults with PTSD, but not in traumatized adults without PTSD (Bremner et al., 1999a; Shin et al., 1999; Shin et al., 2004). Many of the studies in adult PTSD involved radiation using positron emission tomography (PET) scanning, a technique that is not feasible in children. In adults, PTSD is associated with specific neurostructural differences, such as a smaller hippocampus in most (Sapolsky, 2000) but not all studies (Bonne et al., 2001). However, pediatric PTSD was not associated with the predicted decrease in hippocampal volume in cross-sectional (Carrion et al., 2001; De Bellis et al., 1999c; De Bellis et al., 2002b) or longitudinal studies (De Bellis, Hall, Boring, Frustaci, & Moritz, 2001). Instead, abuse-related PTSD is associated with global adverse brain development (Carrion et al., 2001; De Bellis et al., 1999c; De Bellis et al., 2002b; Teicher et al., 1997).

Myelinated areas of the brain appear particularly susceptible to the effects of early exposure to significant levels of stress chemicals. Magnetic resonance imaging (MRI) is a non-invasive, safe method to observe and measure grey and white matter brain structure and development in children. MRI and related imaging procedures have allowed comparison of the brain structures of healthy children to those exposed to abuse. Neuroimaging is a relatively new area of study for this population of children, and a handful of studies have been published with results that indicate adverse brain structure and development as a consequence of abuse resulting in PTSD or subthreshold symptoms of PTSD. Teicher et al. (1997) provided the initial data that suggested early childhood trauma had a deleterious effect on the development of the corpus callosum, a brain structure that anatomically and functionally connects the cerebral hemispheres. The size of the corpus callosum was affected by early adverse experience, and this effect appeared to be gender dependent. These researchers found a reduction in the middle portion of the corpus callosum in children who were hospitalized at psychiatric facilities with documented histories of trauma, including abuse or neglect, as compared to psychiatric controls. Moreover, these findings were more significant in males. Sanchez and colleagues used structural brain MRI to study global brain differences in rhesus monkeys, who were separated from their mothers at 2 months of age and singly housed reared until age 12 months (Sanchez, Hearn, Do, Rilling, & Herndon, 1998). These monkeys were found to have a reduction in the midsagittal size of the corpus callosum, in parallel to a decrease in white (but not grey) matter volume in the prefrontal and parietal cortices. These decreases occurred in parallel with cognitive impairments.

In a more comprehensive study of 44 maltreated children and adolescents with PTSD and 61 age- and sex-matched controls, De Bellis (1999) extended these findings by demonstrating decreased total midsagittal area of the corpus callosum and enlarged right, left, and total lateral ventricles in PTSD-diagnosed subjects compared to controls (De Bellis et al., 1999a). Male children with PTSD had smaller measurements of the corpus callosum and a trend for

smaller total brain volume than female children with PTSD. Again, these findings suggested that males may be more vulnerable to the effects of severe stress on brain structures than females; however, adverse effects were found regardless of gender. Additionally, it was noted that the intracranial volume was decreased by 7% and total brain volume by 8% in PTSD subjects compared to controls. Earlier onset of abuse and longer duration of abuse correlated with smaller intracranial volume. Further, PTSD symptoms correlated positively with ventricular volume. Intrusive symptoms, avoidance, hyperarousal, and dissociation correlated with increased ventricular volume, decreased intracranial volume, and smaller total corpus callosum area. These findings not only suggested disrupted brain development in patients with maltreatment-related PTSD, but also indicated that adverse effects may be greater with exposure to trauma in early childhood. The correlation of lower intracranial volume with longer duration of abuse also suggested that recurrent and chronic abuse may have a cumulative, harmful effect on brain development. Many of the subjects in this study suffered from sexual abuse. Witnessing domestic violence was also a common co-abusive experience for these sexually-abused children.

Another study by Carrion and colleagues (2001) reported that children with PTSD or subthreshold PTSD showed smaller total brain and cerebral volumes when compared to healthy age- and gender-matched archival controls. In addition, attenuation of frontal lobe asymmetry in children with maltreatment-related PTSD was observed. While this study did not match for IQ or for low socioeconomic factors, which also influence brain volume, findings were consistent with the work of De Bellis (1999c).

De Bellis (2002b) replicated his work in another study of 28 psychotropic naïve children and adolescents with maltreatment-related PTSD. Again, many of the subjects were sexually abused. The PTSD subjects showed smaller intracranial, cerebral cortex, prefrontal cortex, prefrontal cortical white matter, and right temporal lobe volumes in comparison to 66 sociodemographically-matched healthy controls. Compared with these carefully matched controls, subjects with PTSD had decreased areas of the corpus callosum and subregions two, four, five, six, and seven, and larger frontal lobe cerebrospinal fluid volumes than controls, even after adjustment for total cerebral volume. Again, total brain volume positively correlated with age of onset of traumatic incident(s) leading to PTSD (i.e., smaller volumes with earlier onset of trauma), and negatively correlated with duration of abuse (i.e., longer duration of abuse with smaller volumes). Another significant gender-by-group interaction was found, with maltreated males with PTSD having larger ventricular volumes than maltreated females with PTSD.

In a secondary analyses of sex differences in the published data of De Bellis and colleagues (De Bellis et al., 1999c; De Bellis et al., 2002b), findings of larger prefrontal lobe cerebrospinal fluid volumes and smaller midsagittal area of the corpus callosum subregion seven (splenium) were seen in both boys and girls with maltreatment-related PTSD compared to their gender-matched comparison subjects (De Bellis & Keshavan, 2003). This finding suggests prefrontal deficits in maltreated children with PTSD, a finding similar to the data for adult PTSD. Child subjects with PTSD did not show the normal age-related increases in the area of the total corpus callosum and its region seven (splenium) compared to non-maltreated subjects, indicating deficits in myelination in these traumatized children. This latter finding is similar to the work in non-human primates and extends the earlier work. Interestingly, this failure of the normal age-related increases in the area of the corpus callosum was more prominent in males with PTSD (De Bellis & Keshavan, 2003). Significant sex-by-group effects demonstrated smaller cerebral volumes and corpus callosum regions one (rostrum) and six (isthmus) in males with PTSD and greater lateral ventricular volume increases in maltreated males with PTSD than maltreated females with PTSD, suggesting sex differences and more adverse brain maturation of boys compared with

girls with maltreatment-related PTSD (De Bellis & Keshavan, 2003). These sex differences were seen despite the fact that boys and girls experienced similar types and durations of maltreatments.

Hippocampal differences were not seen in these studies of pediatric PTSD cross-sectionally (Carrion et al., 2001; De Bellis et al., 1999c; De Bellis et al., 2002b) or longitudinally (De Bellis et al., 2001). A suggestion for this discrepancy between the adult and child findings is that PTSD exerts a gradual adverse effect on the structure of the hippocampus such that it may not yet be manifest in developing children. That is, stress-induced hippocampal damage may not be evident until post pubertal development, or it may be an inherent vulnerability for chronic PTSD that persists into adulthood (Gilbertson et al., 2002). Another hypothesis relates to the psychiatric comorbidity for alcohol and substance abuse/dependence, particularly in adults. This hypothesis has been supported by research on adolescent-onset alcohol abuse and dependence, which found decreased hippocampal volumes (De Bellis et al., 2000). Maltreated children are at higher risk for adolescent alcohol and substance use disorders, and these substances may be toxic to adolescent brain development (for review see De Bellis, 2002). A final suggestion for the differences in hippocampal findings between children and adults with PTSD is the capacity for primate neurogenesis in the hippocampus and frontal cortex (Gould et al., 1997a; Gould et al., 1998). Disclosure of abuse, separation from the perpetrator, and therapeutic interventions may enhance hippocampal neurogenesis, leading to no significant differences between abused children and controls. Thus, neurodevelopmental plasticity and normal developmental increases in the hippocampus may "mask" any effects of traumatic stress in maltreated children with PTSD. As such, longitudinal research of chronically stressed children is critical to understanding the complex interactions between hippocampal maturation, stress, and PTSD, with a particular focus on hippocampal neurogenesis.

As adverse effects on brain structure are observed in children with PTSD symptoms secondary to abuse, findings of decreased intracranial volumes and cerebral volumes in maltreated children with PTSD are worrisome and worthy of further exploration. These findings may implicate neuronal loss and disruption of neuronal and myelin growth, and may be consistent with the effects of early life stress and not necessarily the diagnosis of PTSD, as traumatized subjects without PTSD were not studied.

The Limbic System and the Prefrontal Cortex

As stated, neuroimaging studies support the hypotheses that the medial prefrontal regions are hyporesponsive and the amygdala is hyperresponsive in adult PTSD (Bremner et al., 1999a; Bremner et al., 1999b; Lanius et al., 2002; Shin et al., 1999; Shin et al., 2004; Shin et al., 2001). The medial prefrontal cortex and amygdala are reciprocally related (Hamner et al., 1999; Stefanacci & Amaral, 2002); when confronted with traumatic reminders during a brain scan, medial prefrontal cortical dysfunction is seen in adults with PTSD, but not in traumatized adults without PTSD (Bremner et al., 1999a; Shin et al., 1999; Shin et al., 2001). These studies demonstrated that when confronted with traumatic reminders, PTSD subjects show decreased activity of medial prefrontal regions and increased activity of the amygdala, while subjects without PTSD did not show the same degree of limbic activation. In a recent PET study, cerebral blood flow in the medial prefrontal regions was negatively correlated with PTSD symptom severity, while PTSD symptom severity positively correlated with cerebral blood flow in the right amygdala (Shin et al., 2004).

The amygdala, a subcortical brain structure in the limbic system, consists of several cell groups and many efferent projections involved in fear and anxiety. Direct projections from the central nucleus of the amygdala to a variety of brain regions are associated with many

fearful and anxious behaviors. In preclinical studies, electrical stimulation of the amygdaloid region of animals is associated with fearful behaviors, including increases in heart rate, blood pressure, freezing, activation of fear-related facial movements, and increases in plasma corticosteroid levels. Amygdala lesions reduce these fearful behaviors and emotional reactivity and interfere with the acquisition of conditioned fear and the rise in plasma corticosteroid levels (for review see Davis, 1997; LeDoux, 1998). In primate studies, the amygdala is involved in social inhibition (Amaral, 2002). Results from human neuroimaging studies suggest that the amygdala is activated when reading threat words (Isenberg et al., 1999), during viewing of masked fearful faces (Whalen, Rauch, Etcoff, McInerney, Lee, & Jenike, 1998), and during both conditioned fear acquisition and extinction in healthy subjects (LaBar, Gatenby, Gore, LeDoux, & Phelps, 1998). Thus, stimulation of amygdala and its associated neurotransmitter and neuroendocrine systems activates fear centers in the brain and results in behaviors consistent with anxiety, hyperarousal, and hypervigilance. These symptoms are the core symptoms of PTSD.

The Prefrontal Cortex

As reviewed, stress activates noradrenergic, serotonergic, and dopaminergic neurons in the prefrontal cortex. 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 anxiety (for review see Hamner et al., 1999). Medial prefrontal cortex inhibits activation of parts of the limbic system involved in fearful behaviors (amygdala and related nuclei and circuitry; LeDoux, 1998). The prefrontal cortex subserves executive cognitive functions such as planned behaviors (Fuster, 1989), decision making, working memory, and attention (Goldman-Rakic, 1994) and is activated during novel or dangerous situations (Posner & Petersen, 1990). However, severe stress and its associated increased activation of catecholamines (especially norepinephrine and dopamine) can “turn off” this frontal inhibition of the limbic system (Arnsten, 1998). This “turning off” of frontal inhibition to the amygdala is seen in distressed adults who were maltreated as children (Bremner et al., 1999a; Shin et al., 1999) and can likely result in inattention, inability to focus, and poor academic achievement in children. The dopaminergic inputs to the medial prefrontal cortex appear to be particularly sensitive to stress. Enhanced dopamine prefrontal cortical function in response to stress may reflect the heightened attention or cognitive processes needed to cope with the stressor (Bertolucchi-D'Angio, Serrano, & Scatton, 1990). However, chronic stress may result in more prefrontal cortical dopamine than is functionally necessary and thus may impair prefrontal cortical function, causing hypervigilance, psychotic symptoms, and paranoia in developing children. PET studies cannot be done in children as these studies involve radiation. There are only a few pediatric studies completed that examine medial prefrontal cortex and child abuse. These are neuroimaging and neurocognitive studies.

Magnetic resonance spectroscopy (MRS) is a safe approach to measure neuronal integrity in children. N-acetylaspartate (NAA) is considered to be a marker of neuronal health or integrity. Low levels of NAA are associated with neuronal damage or loss (Prichard, 1996). This phenomenon is seen in stroke and also has been examined in schizophrenia. NAA is measured via MRS. This is a measure that can be used safely in children to assess neurochemistry of the developing brain. NAA is measured via the N-acetyl signal in the proton (^{1}H) spectrum. A study of 11 children with maltreatment-related PTSD suggested that maltreated children and adolescents with PTSD have lower NAA/creatine ratios compared to controls matched for age, race, socioeconomic status, and IQ (De Bellis, Keshavan, Spencer, & Hall, 2000). These findings suggested loss of neuronal integrity in the anterior cingulate region of the medial prefrontal cortex. No sex differences were seen. Effective PTSD treatment may improve anterior cingulate functioning and alleviate PTSD

symptoms through removing the stress-mediated inhibition on the rate of medial prefrontal neurogenesis. PTSD remission may be associated with enhanced medial prefrontal neurogenesis (increase in post-treatment NAA from baseline), cognitive improvement, and down regulation of cortisol and catecholamine activity. In a case study of a seven year old boy, treatment with clonidine, an antihypertensive which centrally down regulates the catecholamine activity of the locus ceruleus, was associated with remission of PTSD, improvement of sleep efficiency and increased anterior cingulate NAA/creatine ratio from baseline (De Bellis, Keshavan, & Harenski, 2001). This case illustrates how this novel proton MRS approach can be used in treatment research to track brain maturation of specific regions of interest during treatment of pediatric PTSD.

Child Abuse, Brain Imaging and Theory of Mind

The essential symptoms of pediatric PTSD and generalized anxiety disorder are social worries and associated autonomic hyperarousal. Sexual abuse is a social trauma. Thus, trauma reminders in abused children are interpersonal in nature (e.g., raising or lowering the tone of voice, facial expressions). Social cues may trigger PTSD symptoms of hypervigilance. The amygdala and its projections to the superior temporal gyrus, thalamus, and to the prefrontal cortex are thought to comprise the neural basis of our abilities to interpret others' behavior in terms of mental states (e.g., thoughts, intentions, desires, beliefs). This process has also been called theory of mind or social intelligence (Brothers, 1990). The superior temporal gyrus and amygdala are involved in processing social information. In primate studies, the superior temporal gyrus is involved in identifying facial expressions (Desimone, 1991; Hasselmo, Rolls, & Baylis 1989). In a human functional MRI study, the amygdala, superior temporal gyrus and prefrontal cortex were activated during the performance of a social intelligence task in healthy volunteers (Baron-Cohen et al., 1999). In studies of experimental conditioning, the superior temporal gyrus is thought to be involved in higher cognitive processing of the fear experience and modulation of amygdala activity (Quirk, Armony, & LeDoux, 1997).

It is of interest that maltreated subjects with PTSD had significantly larger, mainly right-sided, superior temporal gyrus grey matter volumes than non-maltreated controls (De Bellis et al., 2002a). These findings suggested a more pronounced right-greater-than-left asymmetry in total and posterior superior temporal gyrus volumes, but a loss of the left-greater-than-right asymmetry seen in total, anterior, and posterior superior temporal gyrus grey matter volumes (because of the relative increase in overall superior temporal gyrus grey matter) in maltreated subjects with PTSD compared to controls. Similarly, a study of healthy adult subjects with high-trait anxiety showed greater right/left ratios of cerebral metabolism than healthy subjects with low-trait anxiety (Stapleton et al., 1997). Adults with social phobia demonstrated increased right-sided EEG activation of the anterior temporal region compared to controls (Davidson, Marshall, Tomarken, & Henriques, 2000). These results are also interesting in light of a preliminary report of greater left hemispheric EEG coherence suggesting diminished left hemispheric differentiation in abused children (Teicher et al., 1997). The finding of a relatively larger superior temporal gyrus in maltreated children and adolescents with PTSD who had previously reported findings of smaller intracranial, cerebral and corpus callosum structures is interesting. Larger superior temporal gyrus grey matter volumes in maltreated children with PTSD may reflect a trauma-related increase in sensitivity to conditioned auditory and facial stimuli during development, resulting in some compensatory synaptic increase of the superior temporal gyrus. On the other hand, larger superior temporal gyrus grey matter may be the result of decreased developmentally-related input from other brain areas such as the frontal cortex resulting in decreased superior temporal gyrus pruning. Decreased input may be the result of inhibitory stress-related catecholamine inputs to the prefrontal cortex (Arnsten, 1998). A preliminary investigation

suggesting that maltreated children and adolescents with PTSD have lower N-acetylaspartate /creatine ratios that are indicative of neuronal loss in the anterior cingulate region of the medial prefrontal cortex compared to sociodemographically-matched controls (De Bellis et al., 2000) suggest differences in prefrontal lobe function in pediatric maltreatment-related PTSD compared to controls. One may speculate that these findings are due to "traumatic interference" with the developmental trajectory of the superior temporal gyrus in pediatric PTSD. The larger superior temporal gyrus in pediatric PTSD may be related to the presence of specific anxiety and mood symptoms and deficits in social intelligence that are common in abused children and not necessarily related to PTSD. In support of this idea, larger superior temporal gyrus volumes and a more pronounced right-greater-than-left asymmetry were also found in a preliminary study of children and adolescents with pediatric generalized anxiety disorder who had no history of trauma, maltreatment, or PTSD compared to healthy controls (De Bellis et al., 2002c). Thus, a relatively larger superior temporal gyrus may be a pre-existing neuroanatomical risk factor for tendencies to manifest anxiety symptoms in response to anxiety-provoking social triggers. However, the nature of the superior temporal gyrus findings differed, with PTSD children showing larger volumes of superior temporal gyrus grey matter, while children with generalized anxiety disorder demonstrated a more pronounced right-greater-than-left asymmetry in total and white matter superior temporal gyrus volumes, indicating that anxious children without trauma histories have an inherent propensity for larger right amygdala volumes and "connectivity" to larger superior temporal gyrus volumes, creating some predispositional traits, such as increased sensitivity to social cues with anxious arousal (De Bellis et al., 2000; De Bellis et al., 2002c), whereas maltreated children may be "conditioned" to be more fearful of social cues (De Bellis et al., 2002a).

Neurocognitive Studies in Abused Children

Impairments in cognitive abilities of individuals diagnosed with PTSD have been reported in adults, particularly in the areas of learning, memory, and concentration (McNally & Shin, 1995). Consistent with these findings, a growing body of literature has documented the adverse effects of early exposure to extreme stress on children's neurocognitive development, including intellectual impairment, verbal deficiencies, and poor school performance. While most studies report temporal stability of intelligence in various pediatric populations including handicapped children (Atkinson et al., 1990; Elliot & Boeve, 1987), a literature review suggests that intellectual ability, as reflected by low IQ scores, may be a consequence of child abuse. A variety of intellectual and academic impairments, with resultant poor school performance (NationalResearchCouncil, 1993; Trickett & McBride-Chang, 1995), have been consistently reported in abused children not evaluated for PTSD (Augoustinos, 1987; Azar, Barnes, & Twentyman, 1988; Kolko, 1992; NationalResearchCouncil, 1993; Trickett & McBride-Chang, 1995). Negative correlations between Verbal IQ score and severity of abuse were observed (Carrey, Butter, Persinger, & Bialik, 1995). Perez & 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). However, cognitive function, as indexed by performance on standardized neuropsychological instruments, has not been extensively evaluated in children with PTSD. It is critical to characterize these deficits, as they are likely to have broad ramifications across domains of development and general academic and social functioning.

In one of the few studies conducted to date with children with PTSD, Beers and De Bellis (2002) found that 14 children with maltreatment-related related PTSD showed more deficits in attention and abstract reasoning/executive functions than a group of socio-demographically matched controls (Beers & De Bellis, 2002). These children demonstrated

deficits on measures designed to assess frontal executive functioning (e.g., Wisconsin Card Sorting Test, Controlled Oral Word Association Test), and they were more susceptible to distraction, showed higher rates of impulsivity, and exhibited greater problems with sustained attention. Although based on a small number of subjects, these findings were consistent with neuroimaging studies indicating CNS changes in the frontal cortex in individuals with PTSD. Relatedly, Moradi and colleagues (1999) found general memory deficits in children with PTSD. Further research is necessary to ascertain how psychiatric symptoms interact with neuropsychological deficits.

In a brain imaging study, IQ was positively correlated with intracranial volume and negatively correlated with duration of maltreatment (De Bellis et al., 1999c). Specifically, Verbal IQ, Performance IQ, and Full Scale IQ negatively correlated with duration of child abuse that led to PTSD in maltreated children. Koenen and colleagues (2003) extended these findings by focusing specifically on the relationship between domestic violence and cognitive/intellectual ability as measured by IQ. Limitations of previous studies included the inability to partial out potential genetic effects on the domestic violence-IQ association. This large-scale twin study, which utilized 1,116 monozygotic and dizygotic five year old twin pairs, was aimed at assessing whether domestic violence had environmentally-mediated effects on young children's intelligence. Domestic violence was found to be associated with delayed intellectual development, and the size of the association was significant. The negative effect on IQ increased in a dose-response relationship. On average, children exposed to high levels of domestic violence had IQ scores, as measured by an abbreviated version of the Wechsler Preschool and Primary Scale of Intelligence-Revised (WPPSI-R), that were eight points lower than children who were not exposed. This effect did not differ by gender. This is a revolutionary study, as it revealed that domestic violence is linked to an environmental effect on suppression of children's IQ that is independent of possible confounding genetic effects on IQ. Moreover, this environmental effect was speculated to be specific to domestic violence, as it persisted even after controlling for maltreatment, which is the larger source of extreme childhood stress. The impact of maltreatment types on more specific cognitive functions in children will require further investigation.

Is There a Protective Psychobiology?

In this review, data show that the effects of traumatic stress on the developing brain may be severe and persistent and lead to adverse brain development. However, there appear to be some factors that may be protective against this response. It is still not clear if some of the biological differences seen in abused children are adaptive or maladaptive. There is a capacity for primate neurogenesis in the hippocampus and frontal cortex (Gould & Gross, 2002; Gould, Reeves, Graziano, & Gross, 1999). Environmental stress and adrenal steroids inhibit this neurogenesis (Gould et al., 1997a; Gould et al., 1997b; Tanapat et al., 1998). Since we now know that there is neurogenesis in the primate brain (Gould et al., 1999), effective psychosocial and medical treatments of abuse-related disorders and therapeutic reversibility are important areas for future investigations. Early interventions may theoretically attenuate these changes. Social support during times of upheaval may also buffer biological stress systems responses. Quality of preschool childcare and child temperament are associated with a buffering of LHPA axis to stress (Gunnar, 1998). For children in settings with a lower quality of focused attention and stimulation, there was a rising pattern of cortisol over the day, indicating that cortisol activity in young children is sensitive to the social context (Dettling, Parker, Lane, Sebanc, & Gunnar, 2000). When rescued from extremely neglectful and abusive environments, some profoundly developmentally delayed maltreated children were capable of accelerated rates of catch-up growth, including remission of severe psychopathology and normalization of cognitive function (Koluchova, 1972, 1976; Money, Annecillo, & Kelly, 1983). In theory, early

interventions with maltreating parents, loving adoptive families (Johnson, 2002), cognitive behavioral therapy, and medications (De Bellis et al., 1999a) may improve global brain functioning and alleviate PTSD and depressive symptoms by removing the stress-mediated inhibition on the rate of cortical neurogenesis. This can, in theory, lead to therapeutic reversibility of the adverse brain developmental effects of abuse. Brain maturation studies in maltreated children are non-invasive and timely. These studies 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 sexually-abused children, clinical intervention research for abused children and their families is markedly underfunded. Young professionals who choose to specialize in child maltreatment can greatly alleviate this type of profound human suffering and consequently decrease the intergenerational transmission of abuse.

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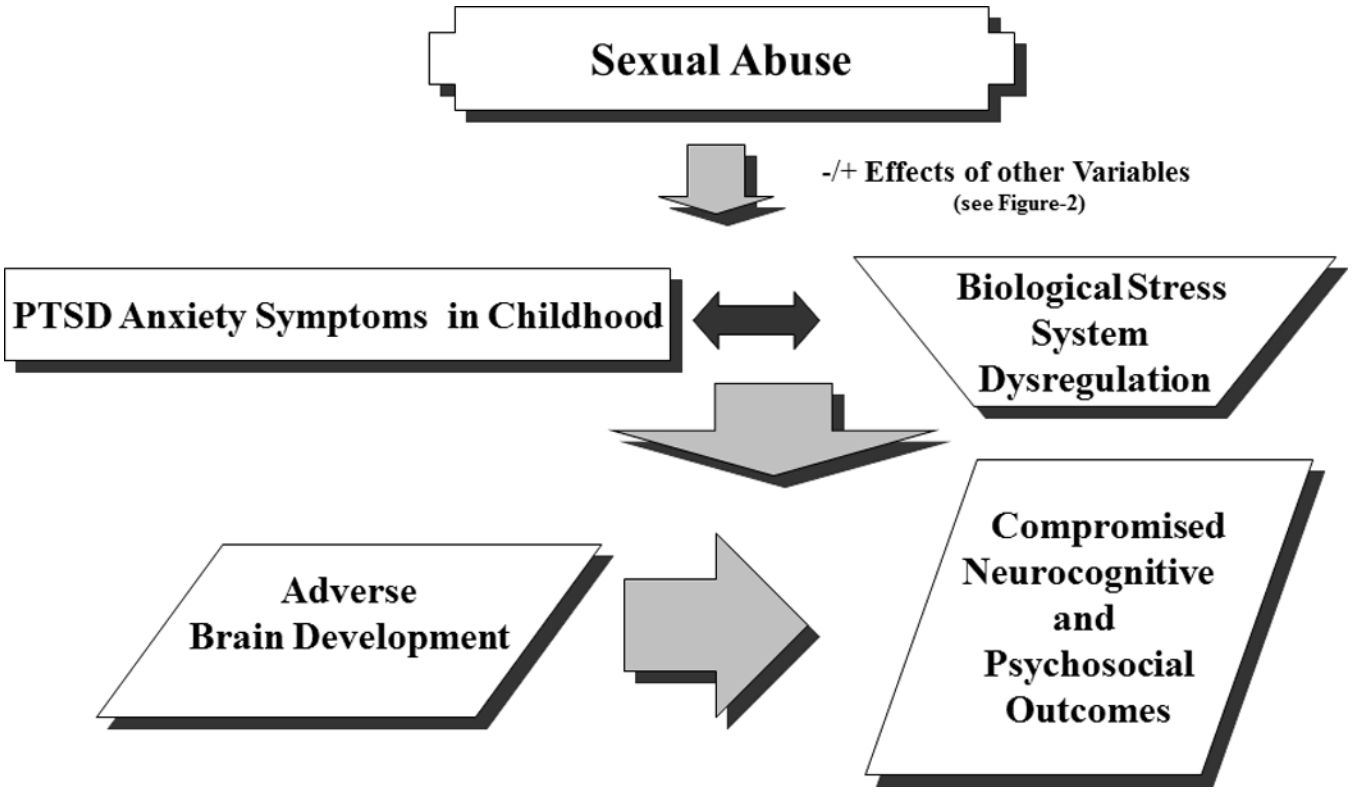

Figure 1.
Proposed Model of the Psychobiology of Sexual Abuse: Adverse Conseqences

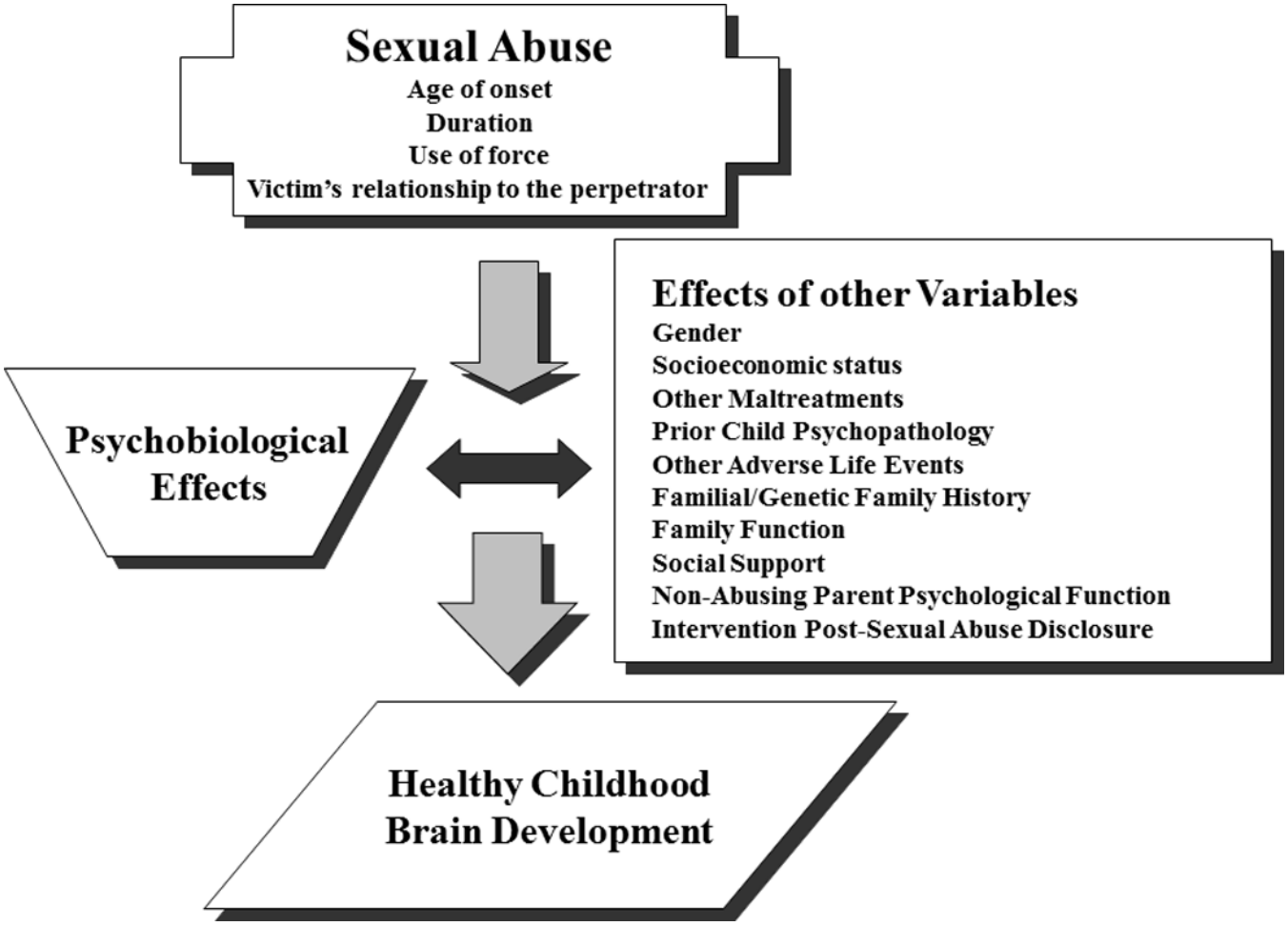

Figure 2.
Proposed Model of the Psychobiology of Sexual Abuse: Intervention and Resilience