The Psychobiology of Neglect

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Child neglect, the most prevalent form of child maltreatment, is associated with adverse psychological and educational outcomes. It is hypothesized that these outcomes may be caused by adverse brain development. However, there are very few published cross-sectional studies and no prospective studies that examine the neurodevelopmental consequences of neglect. In this article, the author comprehensively outlines the issues involved in the psychobiological research of child neglect. Preclinical and clinical studies will be reviewed. Throughout the article, suggestions for future research opportunities and novel ways to address methodological difficulties inherent in this field of study are offered. The results of recent neuroimaging studies of maltreated children may provide a basis for understanding the early effects of neglect on childhood brain development. The author is comprehensively examining these issues as part of the Federal Child Neglect Consortium.

Keywords: *child neglect; privation; brain development; developmental traumatology; cortisol; catecholamines; stress*

Child neglect is the most prevalent, but least empirically studied, form of child maltreatment. In 2002, 896,000 children were determined to be victims of abuse and neglect; child neglect accounted for more than 60% of these cases (U.S. Department of Health and Human Services, 2002). As will be described in this article, child neglect is associated with adverse psychological and educational outcomes (for review see Gaudin, 1999). It is hypothesized that these outcomes may be caused by adverse brain development. Psychobiological research in neglected children is inherently difficult because neglected children may suffer from different subtypes of neglect and adversities other than neglect, which may also compromise neuropsychological and psychosocial outcomes. Other adversities, such as physical or sexual abuse, prenatal exposure to substances, witnessing domestic violence, poor nutrition, poverty, and lack of educational opportunities, are only some of the important variables, which are commonly seen in neglected children, that may also confound the relationship between child neglect and outcome measures of adverse brain development. Thus, there are very few published cross-sectional studies and no prospective studies that examine the neurodevelopmental consequences of neglect. To control for all inherent confounding predictor and outcome variables, psychobiological studies of child neglect will need to involve the recruitment of either a carefully selected sample of neglected children, who may not be representative of the "real world" of neglected children or very large samples to statistically adjust for the inherent confounds in this field of research. Consequently, in this review, we will focus on the current state of the field and will also outline confounding clinical variables that need to be taken into account when undertaking psychobiological research in child neglect. Suggestions for future research opportunities and novel ways to address methodological difficulties inherent in this field of study will be offered.

One of the most profound issues in child neglect research is the development of reliable and valid operational definitions and measures of neglect, as there are few standardized instruments, which measure the absence of culturally expected parental behaviors. This article will be limited to studies of neglected children as defined by the Federal Child Abuse Prevention and Treatment Act (CAPTA; 1996) and the corresponding state laws written in accord

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with CAPTA. Thus, this article will be limited to reviews of studies of neglected children referred to Child Protective Services (CPS). Child Protective Services child neglect is defined by law as a significant omission in care by a parent or caregiver, which causes (the Harm Standard) or creates an imminent risk of (the Endangerment Standard) serious physical or mental harm to a child under 18 years of age. Child neglect is defined as physical, medical, educational, and emotional neglect (CAPTA, 1996). Physical neglect is defined as abandonment, lack of supervision, and failure to provide for a child's basic needs of nutrition, clothing, hygiene, and safety. Medical neglect is the failure to provide necessary medical or mental health treatment. Emotional neglect is defined as refusals or delays in psychological care; inadequate attentions to a child's needs for affection, emotional support, attention, or competence; exposing the child to extreme domestic violence; and permitting a child's maladaptive behaviors. Educational neglect is defined as permitted chronic truancy, failure to enroll a child in mandatory schooling, and inattention to a child's special needs. Because child neglect is defined as a criminal act, studies of CPS-referred children involve the most severe cases of neglect. Psychobiological studies of only cases of child neglect may not be practical or representative of the real world of neglected children, as various forms of neglect and abuse commonly coexist in CPS-referred samples (Kaufman, Jones, Stieglitz, Vitulano, & Mannarino, 1994; Levy, Markovic, Chaudry, Ahart, & Torres, 1995). One method of dealing with these issues is to use multiple sources of data and instruments with the best psychometric properties to obtain maltreatment information and a detailed multidimensional classification scheme for conceptualizing neglect and abuse (Zuravin, 1999). Consequently, to control for all important predictor variables, psychobiological studies of child neglect will need to involve the recruitment of very large samples to statistically adjust for the inherent confounds in this field of research.

The period from birth to adulthood is marked by progressive physical, behavioral, cognitive, and emotional development. Paralleling these stages are changes in brain maturation. Many factors can adversely impact the neurodevelopment of neglected children. Researchers will not only need to comprehensively examine the nature, age of onset, duration, and various subtypes of a potential child participant's neglect, but also must measure ecological and family factors, prenatal and postnatal physical growth, genetic or familial factors, and a neglected child's other traumatic experiences. In this article, we comprehensively outline the issues involved in the psychobiological research of child neglect. Preclinical and clinical studies, often drawing on animal models of privation and on research in maltreated children, will be reviewed. We will review what is known about the adverse developmental consequences of child neglect. Early maternal privation is an extreme stressor. Because there is little empirical data on the psychobiology of child neglect, our review comes from a variety of preclinical studies of rodents and primates and clinical studies based on different samples of maltreated children. The results of recent neuroimaging studies of maltreated children with posttraumatic stress disorder (PTSD) may provide a basis for understanding the early effects of neglect on childhood brain development. Throughout this article, we outline clinical variables that need to be taken into account when undertaking psychobiological research in the field of child neglect. Suggestions for future research opportunities and novel ways to address methodological difficulties inherent in this field of study will be offered.

HISTORICAL REVIEW OF PRECLINICAL STUDIES OF NEGLECT AND THE ROLE OF ENVIRONMENTAL STIMULATION

The social attachment between mother and infant is one of the most important experience-dependent developmental interactions in mammals (Bowlby, 1982). Frequent touching by the maternal caregiver is a biologic necessity for physical and psychological growth (Black, 1998; Hofer, 1996; Kuhn, Pauk, & Schanberg, 1990). Studies of infant rats and monkeys show that maternal deprivation results in persistent deficits in social, behavioral, and cognitive development, such as impaired executive function. Executive functions are linked to the integrity of the prefrontal cortex and consist of attention; working and delayed memory; the ability to learn, regulate emotions and behavior, and problem solve; and perform psychomotor tasks. Executive functions control the behavioral processes of planning, execution, self-regulation, maintenance, spatiotemporal segmentation, and sustained mental productivity (Daigneault, Braun, & Whitaker, 1992). Early studies of maternal deprivation have focused on infant behavior and stress chemicals as outcome measures. These studies demonstrated that maternal deprivation is associated with dysregulation of developing biological stress response systems and abnormal infant behavior (for review, see Sanchez, Ladd, & Plotsky, 2001).

The seminal studies of Harlow, Harlow, and Suomi (1971) suggested that the nature, age of onset, dura-

tion of physical neglect, and availability of an enriched environment during infancy were all important variables in the normal adult function of nonhuman primates. Rhesus monkey infants, who were reared in total social isolation (i.e., separated from their mothers, peers, and social group for their first 3 months of life and then allowed to interact with age-mates) were severely anorexic and required forced feedings to sustain life. Monkeys who underwent this relatively brief period of maternal isolation adjusted to age-mates and appeared normal as adults. However, rhesus monkey infants reared in total social isolation for their first 6 months of life were adversely affected as adults. These "isolates" spent their time primarily engrossed in autistic-like behaviors (stereotyped movements, compulsive nonnutritional sucking, and self-mutilatory behaviors when they reached puberty) and demonstrated a lack of recognition of social cues; an inability to develop normal social relationships; increased anxiety and aggression; and disoriented sexual behaviors. These autistic-like behaviors were much more severe when rhesus monkey infants were raised in total social isolation for their 1st year of life. For these 12-month-old isolates, play and exploration were nonexistent and all social interactions resulted in extremely anxious behaviors. They froze in reactions to aggression from other animals and, as a result, sustained serious injuries. An interesting finding was that monkeys reared in deprived environments were similar to monkeys reared in enriched environments in the development of some less complex intellectual processes (discrimination tasks, delayed-response tasks, and complex learning-set tasks), but the monkeys raised in enriched environments demonstrated superior scores on complex problem-oddity-learning sets (i.e., executive functions).

HISTORICAL REVIEW OF CHILD NEGLECT AND ECOLOGICAL VARIABLES

In the early 1900s, the pediatrician Henry Dwight Chapin (1917) noted that despite the improvements in food and hygiene, infants who were institutionalized in their first year of life (i.e., who experienced physical and emotional neglect) suffered death rates of 31.7% to 75% from infections or failure to thrive. In 1902, Chapin began the foster care movement in the United States by forming the Speedwell Society and boarding out orphaned infants to willing foster parents. He reported only a 2% death rate in the 266 infants his Speedwell Society boarded out, compared to the rather high institution infant death rate (Gray, 1989). Although improvements were made in hygienic and nutritional standards in the 1940s and the institutionalized infant mortality rate was under 10% (which was similar to the national rates at the time), studies continued to show that institutionalized infants suffered from an increased susceptibility to infections (Bakwin, 1942). Then, Spitz (1945) showed that as institutionalized children began to live past infancy, severe deficits in social development and behavioral and emotional regulation were noted. These were thought to be because of the lack of emotional stimulation from maternal deprivation (reviewed by Spitz, 1945). These institutionalized children suffered from progressive developmental deterioration in cognitive functioning that was felt to be irremediable if institutionalization occurred in the first 3 years of life (Bender & Yarnell, 1941). Spitz reported severe developmental retardation and evidence of symptoms which would now be described as *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.; 1994) reactive attachment disorder in these Foundling Home infants, compared to infants raised in poverty or raised by their natural young mothers, with staff assistance, in a penal institution (Spitz, 1945). Spitz concluded that fostering an adequate and satisfactory mother-child relationship in infancy would decrease the unavoidable and irreparable psychiatric consequences to children deriving from early emotional neglect. Bowlby (1982) went further to say that for an infant's development to proceed normally, a selective, noninterchangeable relationship with a single adult primary attachment figure was required and could not be provided in an institution.

In recent times, Romanian orphanages provided care similar to those of the early institutions, where children suffered from physical, emotional, and some medical neglect. Romanian orphans lived with a low staff to child ratio (1 to 60) and lacked stimulation, appropriate medical care, and nutrition. A random sample of 200 orphaned Romanian children living in these institutions suffered from physical growth delays, including smaller body size and head circumference, poor social skills, and delays in cognitive and language development, when examined at 3 years of age (Macovei, 1986). Growth delays were found in a case series of 65 Romanian children adopted in the United States (O. E. Johnson, Miller, et al., 1992). Other studies showed that Romanian adoptees suffered from growth delays (O. E. Johnson, Miller, et al., 1992), gross motor, language, cognitive delays (Miller, Kiernan, Mathers, & Klein-Gitelman, 1995), inattention and overactivity (Kreppner, O'Connor, Rutter, & the English and Romanian Adoptees Study Team, 2001), attachment disorder behavior (O'Connor, Rutter, & the English and Romanian

Adoptees Study Team, 2000), autistic-like behaviors (Beckett et al., 2002), and deficits in social functioning (Kaler & Freeman, 1994); these poor outcomes were associated with duration of institutional deprivation.

However, institutional care improved in some Western countries and institutionalized children were noted to have fewer developmental abnormalities. Tizard and colleges studied the social, behavioral, emotional and cognitive development of a group of approximately 65 institutionalized children (J. Tizard & Joseph, 1970). These children lived in small groups where staff to child ratios were high, toys and stimulating materials were abundant, and outings and weekend visits to homes of the staff were undertaken to broaden their experiences. Thus, these children did not suffer from physical neglect. The children did not have an attachment to one caregiver, but instead had been cared for on average by 50 caring adults by age 4, because these nurseries were training centers for nurses. By age 4, 24 of these children were adopted and 15 were restored to their natural parent. These authors found that these children suffered from no significant delays in cognitive function or language development by age 4 (B. Tizard & Ree, 1974). By age 8, the adopted children were found to have the highest mean IQ and reading achievements, which were above average compared to those children who stayed in the institution or those who were restored to their parent, who were average (B. Tizard & Hodges, 1977). Some of the children who were institutionalized at this early age, whether restored to their parents or adopted, did have varying degrees of significant problems in interpersonal relationships (Hodges & Tizard, 1989). Thus, the earlier described studies of institutionalization are models of severe and profound physical and emotional neglect, whereas the studies of Tizard and colleagues (e.g., B. Tizard & Hodges, 1977; J. Tizard & Joseph, 1970; B. Tizard & Ree, 1974) are less severe forms of emotional neglect than described above, but is still associated with lasting problems in emotional regulation.

Child neglect is a risk factor for psychopathology (J. G. Johnson, Cohen, Brown, Smailes, & Berstein, 1999; Widom, 1999). It is hypothesized that compromised child outcomes in neglected children may be mediated through the impact of negative environmental circumstances on biological stress response systems and brain development. Although the causes of these poor outcomes in neglected children are complex and may involve adverse environmental factors and individual's genetic vulnerability, a twin study suggests that child maltreatment is causally and independently related to an increased risk for psychopathology (Kendler et al., 2000). Age of onset and severity and duration of neglect are important variables to study. We will now review the psychobiological mechanisms that may influence the psychobiological development of neglected children.

CHILD NEGLECT AND THE DEVELOPMENTAL TRAUMATOLOGY MODEL

It can be argued that childhood neglect may be experienced by the child as traumatic—that is, causing anxiety and distress. It is hypothesized that there are multiple mechanisms through which neglect can cause anxiety and that this anxiety activates biological stress response systems and contributes to adverse brain development. Developmental traumatology is the systemic investigation of the psychiatric and psychobiological impact of adversity on the developing child (De Bellis, 2001). 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, CPS-defined neglect and abuse 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. Other adverse life circumstances that are commonly seen in neglected children may additionally contribute to and confound the relationship between child neglect and the compromised neurocognitive and psychosocial outcomes seen. The influence of neglect and these other 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 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. Most investigations in developmental traumatology focus on childhood PTSD. Psychobiological studies of child neglect are only just emerging (see Figure 1).

It is hypothesized that the degree of the traumatic experience perceived by the child may depend on the

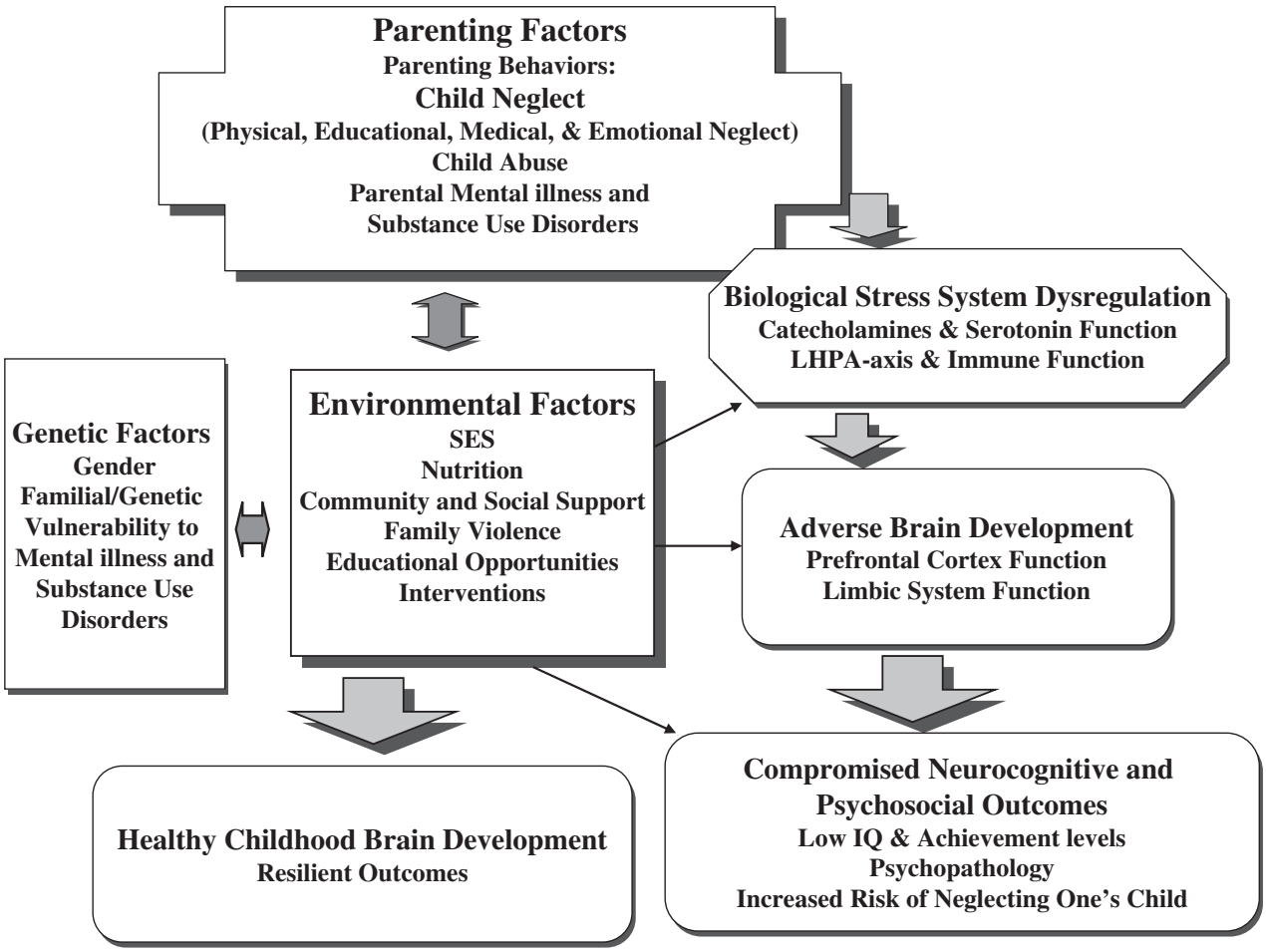

FIGURE 1: A Developmental Traumatology for the Psychobiology of Neglect
NOTE: SES = socioeconomic status; LHPA axis = limbic-hypothalamic-pituitary-adrenal axis.

age of the child at the time of neglect and the duration of neglect. For example, continuously neglected infants suffer from increased rates of infection and early death. These high rates of infection may be associated with stress-induced suppression of the immune system (for review, see De Bellis & Putnam, 1994). Infants have been known to aspirate and die from the stress of severe and continued unanswered crying. A toddler who is not fed does not develop a secure base and is in a chronic state of severe anxiety (Rutter, 1981). An unsupervised nonabused young child may be more likely to witness interpersonal traumas, experience traumatic accidents, or suffer from abuse outside of the home. Furthermore, child neglect is a chronic condition or stressor.

In developmental traumatology research, we hypothesize that although there are an infinite number of stressors that can cause anxiety and distress in a child, there are finite ways that the brain and the body (i.e., biological stress response systems) can respond to those stressors. We hypothesize that for the neglected child, the nature of the stressor is the dysfunctional parent-child interpersonal relationship. This type of a stressor is likely the failure to attain the experience-dependent trust in a parent or an authority figure and the socially expected social stimulation that follows such trust. The third hypothesis is that neglect in childhood may be more detrimental than adversity experienced in adulthood secondary to interactions between this lack of experience expected environmental stimulation with age-appropriate expected healthy neurodevelopment. The fourth hypothesis is that neglect is a chronic stressor that may influence the development of biological stress system responses and that this influence may lead to adverse brain, cognitive, and psychological development. Hence, it is hypothesized that child neglect may lead to adverse brain development through multiple

mechanisms. This process manifests itself as delays in or deficits of multisystem developmental achievements in behavioral and emotional regulation, cognitive and psychosocial function, antisocial behaviors, and poor academic achievement. The next section is organized to describe individual biological stress systems, neurobiological studies of child maltreatment, and the few neurobiological studies published to date on child neglect. The limited data to date suggest that the psychobiological research on child neglect replicates and extends studies of child abuse.

BIOLOGICAL STRESS RESPONSE SYSTEMS

The psychobiology of stress is complex. Neglect is likely perceived and processed through a child's senses as intense anxiety. Multiple neurotransmitter systems and neuroendocrine axes are activated during acute stress (De Bellis, 2003). Stress exposure affects the neurotransmitter systems, neuroendocrine system, and immune system. Necessarily, these systems are interconnected to modulate response to acute and chronic stressors. The sympathetic nervous system 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 are all dependent on these systems. Importantly, neurodevelopment is also dependent on these systems. It is highly probable that many of the mental health symptoms and learning problems associated with child neglect arise in conjunction with alterations of these biological stress systems. Although it is beyond the scope of this review, an understanding of the psychobiology of neglect may lead to early psychotherapeutic and psychopharmacological treatment(s) and academic interventions.

NEUROTRANSMITTER AND NEUROENDOCRINE SYSTEMS: THE CATECHOLAMINES, SEROTONIN, AND LHPA AXIS

Intense anxiety activates the locus coeruleus, an ancient structure in the base of the brain, and the sympathetic nervous system (SNS), leading to the biologic changes of the fight-or-flight or freeze reaction (for review, see De Bellis & Putnam, 1994). The locus coeruleus is the major norepinephrine (NE)–containing nucleus in the brain. Serotonin (5-HT), NE, and dopamine (DA) are major catecholamine brain neurotransmitters. Direct and indirect effects of this activation include increases in catecholamine turnover in the brain, the SNS, and the adrenal medulla, an endocrine gland that is located above the kidneys that secretes the stress hormones cortisol and epinephrine. This fight-or-flight or freeze reaction is manifested by increases in heart rate, blood pressure, metabolic rate, alertness and is directly caused by elevated levels of epinephrine and SNS activity. The amygdala, a brain structure involved in the regulation of emotion and anxiety, is in turn stimulated by the locus coeruleus. The amygdala then stimulates the hypothalamus, which results in release of corticotrophin-releasing hormone (CRH), also called factor (CRF). Through complex mechanisms, the amygdala also stimulates dopaminergic inputs to the medial prefrontal cortex. The CRH causes the pituitary to secrete adrenocorticotropin (ACTH), but CRH also stimulates brain regions of the cortex. In this manner, CRH functions as both a hormone and a neurotransmitter (Ruggiero, Underwood, Rice, Mann, & Arango, 1999). The 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 (hippocampus), suppresses the LHPA axis leading to restoration of basal cortisol levels so that the stress response and its effects on immune suppression are contained (homeostasis). The dopaminergic inputs to 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 may impair prefrontal cortical function, causing inattention, hypervigilance, problems in learning new material, psychotic symptoms, and paranoia in developing children.

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 (mood) and behavior (aggression, impulsivity). Serotonin is dysregulated in 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,

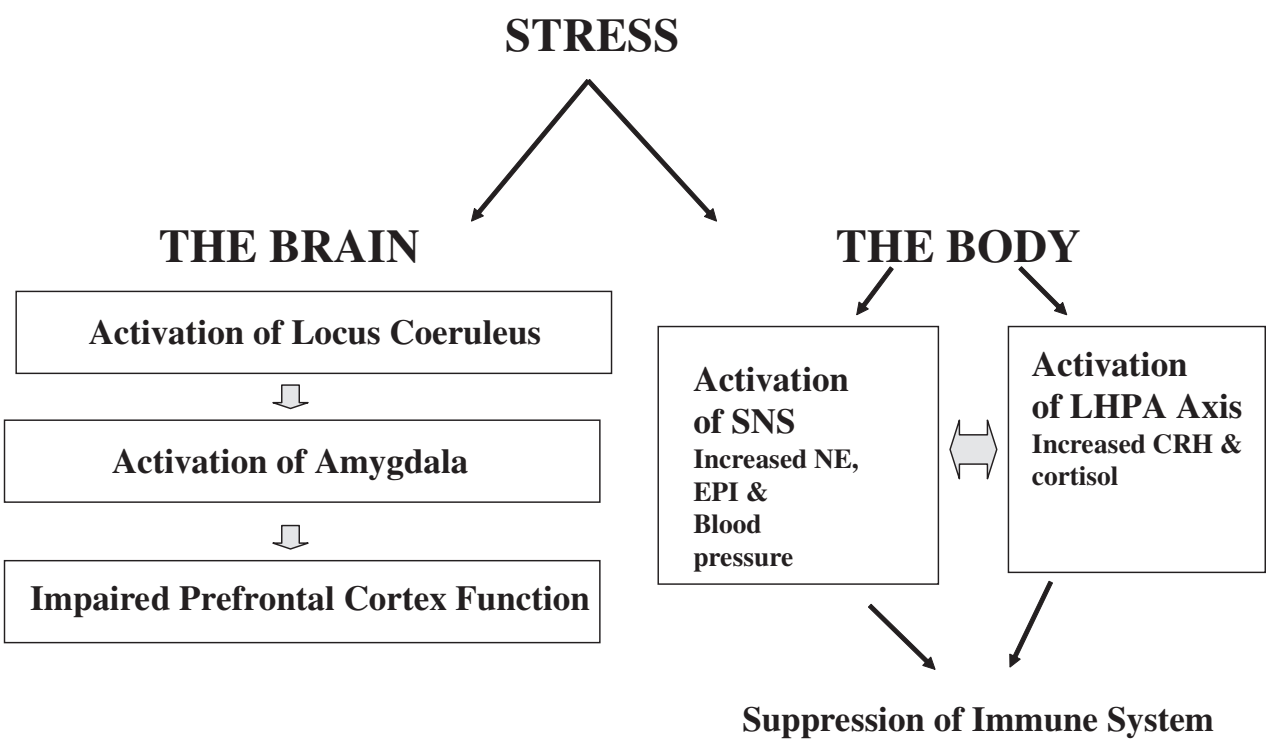

FIGURE 2: An Outline of Biological Stress Response Systems
NOTE: SNS = sympathetic nervous system; NE = norepinephrine; EPI = epinephrine; LHPA = limbic-hypothalamic-pituitary-adrenal; CRH = corticotrophin-releasing hormone.

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. These processes of serotonin depletion may result in behaviors of learned helplessness and severe behavioral dysregulation (Petty, Kramer, & Wu, 1997; see Figure 2).

NEGLECT AND THE DEVELOPMENT OF NEUROTRANSMITTER AND NEUROENDOCRINE SYSTEMS

Primates subjected to prolonged periods of maternal and social deprivation have altered catecholamine (Martin, Sackett, Gunderson, & Goodlin-Jones, 1988) and cortisol (Lyons, Yang, Mobley, Nickerson, & Schatzberg, 2000) function and impaired immune function (Lubach, Coe, & Erhler, 1995). Similarly, maltreated children with or without a diagnosis of PTSD show alterations of the development of catecholamine containing biological stress response systems (for review, see De Bellis, 2001). Specifically, maltreated children have evidence of higher catecholamine and cortisol activity compared to nonmaltreated children. For example, sexually abused girls, 58% of whom had histories of severely depressed mood with suicidal behavior, exhibited significantly greater 24-hour urinary catecholamine concentrations compared with demographically matched nonabused controls (De Bellis, Lefter, Trickett, & Putnam, 1994). Decreased platelet adrenergic receptors and increased heart rate following orthostatic challenge in physically and sexually abused children with PTSD suggest an enhancement of SNS tone in childhood PTSD (Perry, 1994). Experiencing parental neglect may, in and of itself, be associated with alterations in biological stress systems in children. In the only published study of neglected children, levels of 24-hour urinary NE were elevated in severely neglected male children who suffered from clinical depression (Queiroz et al., 1991). Abused and neglected pediatric participants with PTSD excreted significantly greater concentrations of urinary NE and DA and free cortisol concentrations within 24 hours than control participants (De Bellis, Baum, et al., 1999). Total 24-hour urinary catecholamine measures of epinephrine, NE, and DA concentrations showed positive correlations with duration of the mal-

treatment trauma and PTSD symptoms. An increase in baseline functioning of the catecholamine system in childhood PTSD is also suggested 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 these medications 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).

Similarly, maltreated children with or without a diagnosis of PTSD show alterations of the development of the LHPA axis (for review, see De Bellis, 2001). In pediatric studies of abused and neglected children, dysregulation of the LHPA axis with increased cortisol secretion is supported. Increased cortisol levels are found in most studies of maltreated young and latency-age children, whereas most studies have shown that the opposite is evidenced in adolescents and adults (for review, see De Bellis, 2001). Elevated salivary cortisol were found in 6- to 12-year-old children who were raised in Romanian orphanages for more than 8 months of their lives, compared to early adopted and Canadian-born children 6 ½ years after adoption (Gunnar, Morison, Chisholm, & Schuder, 2001). Elevated salivary cortisol has been described in maltreated children with depression (Hart, Gunnar, & Cicchetti, 1996) and in maltreated children with PTSD (Carrion et al., 2002). In addition, elevated 24-hour urine-free cortisol levels (De Bellis, Baum, et al., 1999) and greater increases in pituitary volume with age (Thomas & De Bellis, 2004) were shown in prepubertal maltreated children with PTSD compared with nonmaltreated children.

Neglected children are at higher risk for externalizing behavioral problems and adult antisocial behavior (Luntz & Widom, 1994; Widom, 1989). Although there have been no published child studies to date, these problems are hypothesized to be the result of stress-induced serotonin dysregulation.

BIOLOGICAL STRESS SYSTEMS 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. An extensive review of the literature on the effects of stress on cellular immune response in animals concluded that a variety of 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. As discussed previously, institutionalized infants suffer from increased rates of infection and early death (Chapin, 1917). Thus, stress-induced immune dysregulation is also likely in neglected children. Although there are no child studies to date published in this area, 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 adult healthy 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 auto-antibody-producing lymphocytes (B lymphocytes) and may thus increase the incidence of positive antinuclear antibody titers in sexually abused girls. Given the complex nature of the stress response, it is likely that childhood neglect is associated with alterations of the immune system and other biological systems not addressed in this review.

THE BRAIN DEVELOPMENT OF YOUNG CHILDREN

Previous investigations of brain development focused on postmortem samples. These studies suggested that brain development during childhood is characterized by regressive and progressive maturational processes. In utero, there is an overproduction of neurons. Regressive processes, such as pruning of the connections between these neurons (synapses of dendrites and axons; Huttenlocher, 1979), occur primarily during the first 4 years of life. Synapses, dendrites, cell bodies, and unmyelinated axons, which form the brain's gray matter, thus decrease during childhood. Myelin, a fatty white substance produced by supportive glial cells, is a vital component of the brain. Myelin encases the axons of neurons, forming an insulator known as the myelin sheath and is responsible for color of white matter. Progressive maturational processes, such as myelination of newly formed neuronal networks, occur primarily during childhood and adolescence (Yakovlev & LeCours, 1967). Thus, human brain development takes place by an overproduction of neurons in utero and then by selective elimination of many of these neurons (apoptosis; Jernigan & Sowell, 1997). Early childhood is characterized by increases in synaptic neuropil (neuron size and synapses). However, the process of

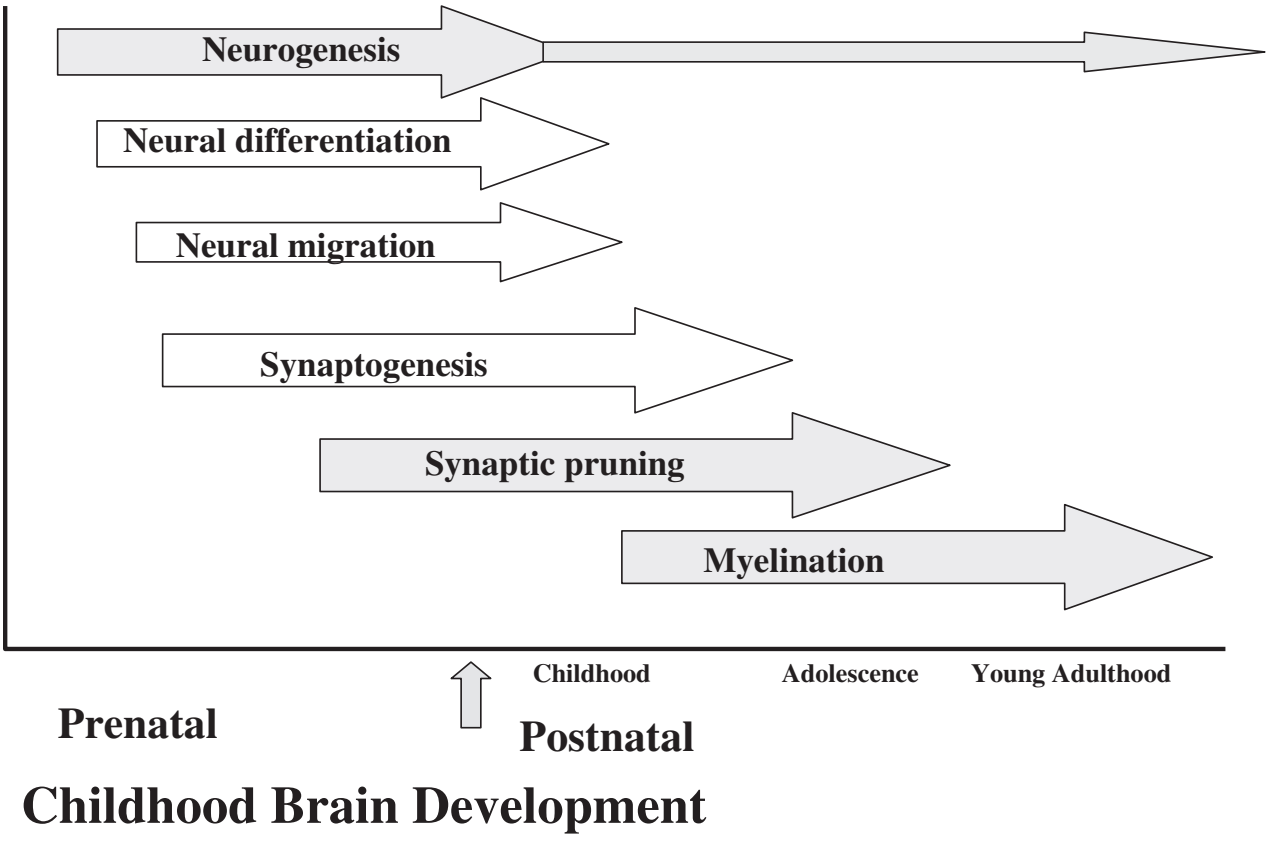

FIGURE 3: An Outline of Childhood Brain Development

synaptic elimination begins in early childhood and continues throughout the first 3 decades of life (Rabinowicz, 1986; see Figure 3).

In the developing brain, stress and elevated levels of stress chemicals 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), inhibition of neurogenesis (Gould, Tanapat, & Cameron, 1997; Gould, Tanapat, McEwen, Flugge, & Fuchs, 1998; Tanapat, Galea, & Gould, 1998), or a stress-induced decrease in brain growth factors (e.g., brain-derived neurotrophic factor; Smith, Makino, Kvetnansky, & Post, 1995). It is hypothesized that alterations of the development of a neglected child's major stress systems may contribute to adverse brain development and lead to psychopathology and compromised neuropsychological and psychosocial function. We will now discuss noninvasive methods to study brain structures in children.

MAGNETIC RESONANCE IMAGING IN CHILDREN

Quantitative magnetic resonance imaging (MRI) has provided a safe and novel approach to measure brain maturation in healthy children. Cross-sectional, and more recently, longitudinal MRI studies of very highly functioning children and adolescents have greatly advanced our knowledge of human brain development (for review, see Durston et al., 2001). Cortical myelination is one of the primary neurodevelopmental changes that occur during childhood (Giedd, Blumenthal, Jeffries, Rajapakse, et al., 1999). Cortical myelination, the growth of white matter, can easily be examined through MRI-based morphometry of cerebral white-matter volume and midsagittal corpus callosum area, a white matter structure compromised of axons that connects major subdivisions of the cerebral cortex. The MRI findings from cross-sectional studies suggest that the proportion of cere-

bral gray matter to white matter (which reflects reductions in synaptic density and pruning) decreases progressively after age 4 (Jernigan & Sowell, 1997). Giedd and colleagues recently demonstrated in longitudinal studies that there are regionally specific nonlinear preadolescent increases followed by postadolescent decreases in cortical gray matter (Giedd, Blumenthal, Jeffries, Castellanos, et al., 1999; Thompson et al., 2000). Neurons generally enlarge and become more myelinated with age (Blinkov & Glezer, 1968). Axons become thicker, and the number of synaptic boutons increases throughout life; myelinated axons are presumably involved in the mechanism of learning (Werry, 1991). From ages 5 to 18, myelination by oligodendrocytes is most influential in determining brain size (Giedd et al., 1996). The most dramatic increase in myelination is reflected by the corpus callosum, which peaks from the ages of 6 months to 3 years but continues linearly into the 3rd decade (Giedd, Blumenthal, Jeffries, Rajapakse, et al., 1999; Paus et al., 2001; Thompson et al., 2000).

A new MRI technique, diffusion tensor imaging (DTI), is a more sensitive MRI measure of myelination than the anatomical study of the corpus callosum (Helenius et al., 2002). The DTI is a functional neuroimaging mode that measures brain-water-diffusion characteristics. The DTI measures the apparent diffusion coefficient (ADC), a measure of linear myelination, and fractional anisotropy (FA), a measure that is negatively related to ADC. High ADCs indicate a lack of or a disruption of myelination. Age-appropriate myelination decreases ADC measures and increases FA measures (Morriss, Zimmerman, Bilaniuk, Hunter, & Haselgrove, 1999). The DTI provides information on the brain's myelin tracts and holds additional advantages than anatomical MRI morphometry. This method currently assists in the detection of stroke and transient ischemic attack in adults, but is also currently used in identifying accidental and suspected nonaccidental head trauma in infants and toddlers (Suh, Davis, Hopkins, Fajman, & Mapstone, 2001). Myelination is a process that is influenced by nutrition and environmental stimulation. Thus, DTI studies in neglected children are warranted.

During adolescence, subcortical gray matter and limbic system structures (hippocampus, amygdala)—brain structures involved in attention, emotional regulation, and memory—increase in volume nonlinearly and peak at age 16.6 in longitudinal studies (Giedd, Blumenthal, Jeffries, Castellanos, et al., 1999). The prefrontal cortex, which subserves executive cognitive functions, also continues to mature into the 3rd decade (Alexander & Goldman, 1978; Fuster, 1989; Goldman, 1971). Functional magnetic resonance imaging (fMRI), a more sensitive MRI measure of brain function that records physiological activity from localized changes in cerebral blood flow (Ogawa et al., 1992), is another new, exciting, and safe method for the study of emotion and cognitive functions in children. This method examines magnetic differences between oxygenated and deoxygenated blood. It is becoming the preferred technique for imaging normal brain activity in the typically developing child. In the past 8 years, a number of fMRI investigations have been published examining prefrontal cortical activity of healthy children during the performance of attention and working memory tasks (for review, see Casey, Davidson, & Rosen, 2002). Additionally, bilateral fMRI activation of amygdala was seen during presentation of emotional (e.g., fearful) stimuli in healthy adolescents (Baird et al., 1999). Studies utilizing fMRI methods in neglected children are warranted.

It is well known that cognitive and emotional development differs between boys and girls (for review, see Nagy Jacklin & Martin, 1999). Hence, another important area of study in healthy and maltreated children is brain maturational sex differences. Sex steroids influence neurodevelopment throughout the life span (for review, see McEwen, 1981). However, this is an understudied area in humans. In one pediatric neuroimaging study of healthy children and adolescents, boys showed significantly greater loss of gray matter volume and an increase in both white matter and corpus callosum area as compared to girls, within a similar age range; this suggests sex differences in both cerebral gray and white matter maturational processes in childhood and adolescence (De Bellis, Keshavan, Beers, et al., 2001). In another study of healthy adults aged 18 to 45 years, similar sex differences were also seen (Gur et al., 1999). Because males may be less resilient to the experience of maltreatment (McGloin & Widom, 2001), studies of brain maturational sex differences in neglected children are warranted.

We will now discuss brain structures likely to be of interest in child neglect research.

THE FRONTAL CORTEX, COGNITIVE DEVELOPMENT, AND CHILD NEGLECT

Stress activates NE, 5-HT, and DA 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, Lorberbaum, & George, 1999).

Medial prefrontal cortex inhibits activation of the parts of the limbic system involved in anxiety (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 NE and DA) 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., 1999; Shin et al., 1999). Although other brain regions clearly are involved in the deployment of executive functions, the prefrontal cortical regions are primarily responsible (Denckla, 1994). It is hypothesized that neglect interferes with the effective development of prefrontal cortical regions and, thus, executive functions. This process can likely result in inattention, inability to focus, and poor academic achievement in neglected children.

In support of these ideas, it has been demonstrated that maternal deprivation of infant primates is associated with deficits in prefrontal functions of attention and motivation (Beauchamp & Gluck, 1988; Beauchamp, Gluck, & Lewis, 1991; Gluck & Sachiltz, 1976). Recently, Sanchez, Hearn, Do, Rilling, and Herndon (1998) used structural brain MRI to study brain differences in rhesus monkeys. One group of infant rhesus monkeys was separated from their mothers at 2 months of age and another group was not separated at this age. The separated monkeys demonstrated a reduction in the midsagittal size of the corpus callosum. This decrease occurred in parallel to a decrease in white (but not gray) matter volume in the prefrontal and parietal cortices and impairment in cognitive function. Thus, primates who suffer physical and emotional neglect have deficits in prefrontal functions and in normal age-related myelination.

Of the little research on brain and cognitive development in neglected children, most studies have focused on the broadly defined outcomes of intellectual ability and academic function. In prospective studies, child neglect is associated with significantly delayed cognitive development and head growth in young children (Strathearn, Gray, O'Callaghan, & Wood, 2001) and lower IQ and academic achievement in adulthood (Perez & Widom, 1994). Chugani et al. (2001) reported that previously institutionalized Romanian adoptees exhibited deficits on tasks dependent on prefrontal function (i.e., attentional and social deficits). These children showed significantly decreased metabolism in the brain structures involved in cognitive function, social intelligence, and anxiety (orbital frontal gyrus, temporal cortex, prefrontal cortex, amygdala, and brain stem) compared to children with chronic epilepsy and healthy adults. Recent studies applying neuropsychological methods suggest that maltreated children and adolescents with PTSD show deficits in executive functioning, including abstract thinking and attention (Beers & De Bellis, 2002) and in everyday memory (Moradi, Doost, Taghavi, Yule, & Dalgleish, 1999). We recently reported lower cognitive functioning in medically healthy neglected children, who had no history of severe physical abuse, sexual abuse, prenatal substance exposure, or perinatal insults compared to a group of nonmaltreated control children on all cognitive domains of the NEPSY, a standardized neuropsychological battery tapping attention and executive functions, language, memory and learning, visual-spatial abilities, and sensorimotor functions (De Bellis et al., 2003). All neglected child participants witnessed domestic violence. An interesting finding was that those with PTSD from domestic violence performed significantly worse on measures of attention and executive functions and visual-spatial functions than those neglected children without PTSD, suggesting that neglected children with PTSD may also have specific deficits in attention and executive functions and visual-spatial functions. Thus, preliminary studies suggest that neglected children have deficits in prefrontal cortex function and difficulty with executive functions.

Investigations of executive functioning comprising the functions of initiating, sustaining, and regulating behaviors (Denckla, 1996), as well as other cognitive domains, including language development, memory, learning, visual-spatial abilities, sensorimotor functions, and laterality, are warranted in neglected children. Studies of neglect that incorporate neurocognitive measures and fMRI methods of prefrontal function are needed, as these investigations will help to identify the academic and vocational needs of neglected children.

THE AMYGDALA AND ANXIETY

The amygdala, a subcortical brain structure in the limbic system, consists of several cell groups and many efferent projections involved in anxiety. Direct projections from the central nucleus of the amygdala to a variety of brain regions are associated with many anxious behaviors. In preclinical studies, electrical stimulation of the amygdaloid region of animals is asso-

ciated with fearful behaviors, including increases in heart rate, blood pressure, freezing, activation of fear-related facial movements, and increases in blood cortisol levels (for review, see Davis, 1997; LeDoux, 1998). Stimulation of the amygdaloid region of animals also inhibits the proper function of the prefrontal cortex (Arnsten, 1998). In primate studies, the amygdala is involved in social inhibition or watchfulness rather than approach behaviors (Amaral, 2002). This means that 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-related anxiety. 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 et al., 1998), and during both conditioned fear acquisition and extinction in healthy participants (LaBar, Gatenby, Gore, LeDoux, & Phelps, 1998). Neuroimaging studies support the hypotheses that the medial prefrontal regions are hyporesponsive and that the amygdala is hyperresponsive in adult PTSD, which is secondary to child abuse (Bremner et al., 1999; Lanius et al., 2002; Rauch et al., 1996; Rauch et al., 2000; Shin et al., 1999). Medial prefrontal regions and amygdala are thought to be reciprocally related (Hamner et al., 1999; Stefanacci & Amaral, 2002). Thus, it is hypothesized that in neglected children, chronic amygdala activation impairs the development of the prefrontal cortex leading to problems with the normal age-related acquisition of behavioral and emotional regulation including the inhibition of impulsive behaviors. To date, there are very few published functional neuroimaging studies of prefrontal lobe function in maltreated children. Most of these studies focus on quantitative measures of cerebral damage in children with head injury (Ewing-Cobbs et al., 1998; Suh et al., 2001). There is only one published study of children who experience severe institutionalization (Chugani et al., 2001). Functional MRI studies of anxiety circuits in neglected children may help the field understand the neuromechanisms of anxiety-driven aggression in neglected children.

THE SUPERIOR TEMPORAL GYRUS AND SOCIAL INTELLIGENCE

The amygdala and its projections to the superior temporal gyrus, thalamus, and to the prefrontal cortex are thought to compose 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 fMRI 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 anxiety and modulation of amygdala activity (Quirk, Armony, & LeDoux, 1997).

Individuals who have a history of neglect have difficulty with social relationships (J. G. Johnson et al., 1999). Although there are no studies on social intelligence and child neglect, maltreated children with PTSD demonstrated larger superior temporal gyrus volumes, the structures involved in social processing (De Bellis, Keshavan, Frustaci, et al., 2002). Maltreated children with PTSD had more superior temporal gyrus gray matter, a finding that may indicate a developmental deficit in the age-appropriate pruning of the superior temporal gyrus. Functional MRI studies of social intelligence are warranted in neglected children.

CHILDHOOD MALTREATMENT AND BRAIN DEVELOPMENT

Myelinated areas of the brain appear particularly susceptible to the effects of early exposure to chronic stress. It is hypothesized that a lack of experience-dependent stimulation may lead to delays in myelination in neglected children (Diamond, Krech, & Rosenzweig, 1964; Juraska & Kopcik, 1988). Given the lack of data on brain maturation and child neglect, we will review the few studies published to date in maltreated children.

Recently, MRI has been used as a novel approach to measure brain maturation in maltreated children. To date, only four studies involving maltreated children were reported. The results of these studies suggest that pediatric maltreatment-related PTSD is associated with adverse brain development. Teicher et al. (1997) provided the initial data that suggested early childhood trauma had a deleterious effect on the development of the corpus callosum. These researchers found a reduction in the middle portion of the corpus callosum in children who were hospitalized at psychiatric facilities with a documented history of trauma, which included abuse or neglect, as com-

pared to psychiatric control children. Thus, a smaller corpus callosum was seen in children affected by early adverse experience. This negative effect appeared to be more significant in males.

In a study of 44 children and adolescents with PTSD secondary to maltreatment and 61 matched controls, De Bellis, Keshavan, Clark, et al. (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 participants compared to controls. 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 8%, in PTSD participants compared to controls. Earlier onset of abuse and longer duration of abuse correlated with smaller intracranial volume. Furthermore, 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 children 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 chronic abuse may have a cumulative, harmful effect on brain development.

Another study by Carrion et al. (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. Although this study did not control for IQ or for socioeconomic factors, which also influence brain volume, findings were consistent with the work of De Bellis, Keshavan, et al. (1999).

Another study of 28 psychotropic naïve children and adolescents with maltreatment-related PTSD showed smaller intracranial, cerebral cortex, prefrontal cortex, prefrontal cortical white matter, and right temporal lobe volumes in comparison to 66 sociodemographically matched healthy controls (De Bellis, Keshavan, Shifflett, et al., 2002). Compared with controls, participants with PTSD had decreased areas of the corpus callosum and its Subregions 2, 4, 5, 6, and 7 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 trauma-causing 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. Thus, children with PTSD or subthreshold PTSD secondary to maltreatment show evidence of adverse brain development.

CHILDHOOD MALTREATMENT AND GENDER EFFECTS ON BRAIN DEVELOPMENT

Findings from a secondary analysis of sex differences in the published data of De Bellis, Keshavan, Clark, et al. (1999) and De Bellis, Keshavan, Frustaci, et al. (2002) suggest that there are similarities and differences in the brain structures of maltreated children with PTSD that are dependent on gender (De Bellis & Keshavan, 2003). For example, findings of larger prefrontal lobe cerebrospinal fluid volumes and smaller midsagittal area of the corpus callosum Subregion 7 (splenium) were seen in both boys and girls with maltreatment-related PTSD compared to their gender-matched comparison participants (De Bellis & Keshavan, 2003). This finding suggests prefrontal deficits in maltreated children with PTSD, a finding similar to the data in adult PTSD. Child participants with PTSD did not show the normal age-related increases in the area of the total corpus callosum and its Subregion 7 (splenium) compared to nonmaltreated participants, indicating deficits in age-appropriate myelination in these traumatized children. This latter white matter finding is similar to the work in nonhuman primates and extends the earlier work. An interesting finding was that this failure of the normal age-related increases in the area of the corpus callosum was more prominent in males with PTSD. Significant sex by group effects demonstrated smaller cerebral volumes and corpus callosum Regions 1 (rostrum) and 6 (isthmus) in PTSD males and greater lateral ventricular volume increases in maltreated males with PTSD than maltreated females with PTSD, suggesting sex differences of more adverse brain maturation of boys compared with girls with maltreatment-related PTSD (De Bellis & Keshavan, 2003). These sex differences persisted, despite similar ages of onset, duration, length of time since disclosure, and similar types of abuse between the male and female pediatric

PTSD participants. An interesting finding was that in a study of a large sample of adult survivors of child abuse and neglect, who were followed from childhood in a long-term prospective study of early (younger than age 11) child abuse and neglect, compared with sociodemographically matched controls, maltreated males demonstrated lower levels of a comprehensive measure of resilience as adults than maltreated females (McGloin & Widom, 2001).

The smaller hippocampal volumes seen in adult PTSD secondary to child abuse (Bremner, Randall, et al., 1997) were not seen in these cross-sectional studies of pediatric PTSD (Carrion et al., 2001; De Bellis, Keshavan, et al., 1999; De Bellis, Keshavan, Shifflett, et al. 2002) or in a longitudinal study of pediatric maltreatment-related PTSD (De Bellis, Hall, Boring, Frustaci, & Moritz, 2001); although, there was some indication that hippocampal volumes may be larger in pediatric PTSD. The hippocampus is critical to the functions of spatial memory and attention. A suggested explanation 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 postpubertal 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 or dependence, particularly in adults. This hypothesis has been supported by research on adolescent onset alcohol-use disorders where decreased hippocampal volumes were found (De Bellis, Clark, et al., 2000). Maltreated children are at higher risk for adolescent alcohol- and substance-use disorders (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 (see Gould & Gross, 2002). 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 child neglect, with a particular focus on hippocampal neurogenesis.

As described above, recent neuroimaging studies provide evidence for medial prefrontal and anterior cingulate dysfunction in adults with PTSD secondary to childhood abuse. Positron emission tomography (PET) investigations comparing women who had been sexually abused as children and had PTSD with women who have similar histories and did not have PTSD found a lower level of anterior cingulate blood flow during traumatic reminder imagery (Shin et al., 1999) and during recalled memories of sexual abuse (Bremner et al., 1999) in those with PTSD. In these studies, participants with PTSD activated the amygdala but not the medial frontal cortex, whereas participants without PTSD activated their medial frontal cortex, but did not show the same degree of amygdala activation. Consequently, neuroimaging studies in adults support the hypotheses that the medial prefrontal regions are hyporesponsive and that the amygdala is hyperresponsive in adult PTSD that is secondary to child abuse (Bremner et al., 1999; Lanius et al., 2002; Rauch et al., 1996; Rauch et al., 2000; Shin et al., 1999).

Currently, PET investigations are not feasible in developing children as PET involves the use of radiation. However, new technologies, such as magnetic resonance spectroscopy (MRS), a safe and novel approach, were used to study the in vivo neurochemistry of the medial frontal cortex in the brains of living children. The N-acetyl signal in the proton (^{1}H) spectrum consists mainly of N-acetylaspartate (NAA) and is considered to be a marker of neural integrity. Decreased NAA concentrations are associated with increased metabolism and loss of neurons (see Prichard, 1996). For example, brain NAA levels decrease in stroke victims. A preliminary investigation suggested that medically healthy maltreated children and adolescents with PTSD have lower NAA-creatine ratios in the medial prefrontal cortex compared to sociodemographically matched controls (De Bellis, Keshavan, Spencer, & Hall, 2000). These findings suggest neuronal loss in the anterior cingulate region of the medial prefrontal cortex and were not affected by the gender of our child participants. Findings of neuronal loss in the anterior cingulate of pediatric PTSD patients agree with the adult neuroimaging studies, which provide evidence for medial prefrontal and 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 pediatric PTSD and may serve as one of the mechanisms for poor cognitive function, particularly inattention, in neglected children. The integrity and neurochemistry of the anterior cingu-

late and other brain regions of interests can be measured with MRS in children. These types of studies are noninvasive and warranted.

In summary, smaller intracranial and cerebral volumes and total midsagittal area of corpus callosum, and its posterior subregion—a lack of the normal age-related growth of myelination—and larger prefrontal cerebrospinal fluid (CSF) volumes were seen in maltreated boys and girls with PTSD compared with nonmaltreated comparison participants (De Bellis & Keshavan, 2003). However, gender effects reveal a more complex developmental picture, which showed that despite similar ages of onset of abuse, duration of abuse, length of time since abuse disclosure, similar types of abuse, and similar symptom profiles between the male and female pediatric PTSD participants, maltreated males with PTSD showed more evidence of adverse brain development than maltreated females with PTSD by demonstrating smaller overall and total midsagittal area of corpus callosum and larger lateral ventricles (De Bellis & Keshavan, 2003). It is hypothesized that this tendency for males to show evidence for more adverse brain development than females, although showing similar levels of childhood psychopathology, may be a marker for future antisocial behavior. Because child neglect is associated with adolescent and adult antisocial behavior, this is another area of psychobiological study that warrants exploration.

In pediatric studies, it should be noted that genetics, hormones, growth factors, nutrients, and an enriched environment also influence brain development. Additionally, ecological and family factors may likely influence psychobiological development and brain maturation. These factors need to be measured in studies of biological stress system responses and in childhood brain development.

ENVIRONMENTAL AND EMOTIONAL FACTORS IN NEGLECT RESEARCH

In child neglect, the child's needs are typically not met in a number of domains, thus making it hard to elucidate the effects of specific forms of neglectful behavior. For researchers interested in the psychobiology of neglect, environmental and emotional factors are important factors that influence brain development. These factors encompass many variables, including parenting, parental mental health, family psychosocial adversity, the child's home and family environment, nutrition, the presence of family or community violence, and a child's educational opportunities.

PARENTING, PARENTAL HISTORY OF MALTREATMENT, MENTAL HEALTH, AND PARENTAL HISTORY OF SUBSTANCE ABUSE IN NEGLECT

Parental behaviors can be seen as constituted by various domains (e.g., attachment, play, teaching, protection, physiological regulation, emotional regulation), which meet different needs of the child (Emde, 1989). Parental care affects many physiological variables in developing animals (Hofer, 1996). 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 (see Caldji et al., 2001). 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 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).

It is known that parental history of maltreatment contributes to the intergenerational transmission of abuse and neglect. Parental mental health, including substance-use disorders, are important and often unrecognized parental factors that contribute to child maltreatment and may influence brain development either directly through the transmission of familial or genetic vulnerability or indirectly through interference with appropriate parenting. Children whose parents suffer from mental illness, particularly depression with other comorbid psychiatric disorders, are more likely to be identified as maltreated (De Bellis, Broussard, et al., 2001). A history of parental trauma exposure and increased maternal depression mediates the risk of child maltreatment (Banyard, Williams, & Siegel, 2003).

Studies of familial or genetic vulnerability to mental illness are in their infancy. A direct pathway from the inherence of genes to mental illness with no interactions between familial or genetic and environment risk factors is unlikely (Stoltenbery & Burmeister, 2000). Recently, Foley et al. (2004) reported that a functional polymorphism in the gene encoding the neurotransmitter-metabolizing enzyme monoamine oxidase A (MAOA) increased the risk for conduct disorder only in the presence of childhood adversity (parental neglect, inconsistent discipline, and interparental violence). The MAOA gene is x-linked and

codes for an enzyme that oxidizes monoamine neurotransmitters (5-HT, NE and DA). Low MAOA activity is associated with low central serotonin and catecholamine activity and, thus, low concentrations of these neurotransmitters, a finding commonly seen in individuals with depressive and impulsive behaviors (De Bellis, Geracioti, Altemus, & Kling, 1993). The study by Foley et al. replicated another landmark study of Caspi et al. (2002), who demonstrated that low MAOA activity increased the risk for antisocial behavior only in the presence of maltreatment (defined as maternal rejection, repeated loss of a primary caregiver, harsh discipline, physical abuse, or sexual abuse). Thus, maltreated children with a genotype conferring high levels of MAOA expression were less likely to develop antisocial problems. Psychobiological studies need to include a comprehensive examination of familial or genetic vulnerability to mental illness.

It is also likely that the presence of an addiction in a parent interferes with nurturing. Studies of children of parents who have a history of substance-use disorders (defined as abuse or dependence) show that these children are more likely to be identified as maltreated than sociodemographically matched control children (Chasnoff & Lowder, 1999). In retrospective and prospective studies, parental substance-use disorder is strongly associated with child abuse and neglect (Chaffin, Kelleher, & Hollenberg, 1996; Kelleher, Chaffin, Hollenberg, & Fischer, 1994; Murphy et al., 1991). There are no published studies examining the incidence of prenatal substance exposure in child maltreatment samples. This is an important oversight because prenatal exposure to alcohol or drugs, including tobacco, is associated with attentional problems and may have independent adverse effects on the biological stress systems and brain maturation of the developing fetus (Chasnoff, Anson, & Iaukea, 1998; Chasnoff, Griffith, Freier, & Murray, 1992; Eyler, Behnke, Conlon, Woods, & Wobie, 1998; Ornoy, Michailevskaya, Lukashov, Bar-Hamburger, & Harel, 1994). Prospective studies of children who were prenatally exposed to illicit drugs typically have not directly measured the presence of the various subtypes of child neglect and abuse in their sample. Thus, psychobiological studies of neglect need to include not only a comprehensive examination of a neglected child's familial or genetic vulnerability to substance-use disorders but also measures of prenatal substance exposure as part of their design.

FAMILY PSYCHOSOCIAL ADVERSITY

There is a clear relation between parental poverty, an ecological stressor, and neglect (Garbarino, 1982; Garbarino & Collins, 1999; Pelton, 1981; Russell & Trainor, 1984). Individuals from more advantaged backgrounds have better physical and mental health than do individuals from lower socioeconomic status (SES; Adler et al., 1994). Differential exposure to stress influences biological stress systems (McEwen, 1998). Thus, the experience of greater stress is one possible pathway for the relationship between SES, parental factors, and child mental health (Anderson & Armstead, 1995). Rosenblum and Andrews (1994) have developed a primate model of 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 in which 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 less social competence, and more anxious behaviors than infants of mothers with low foraging demands (Rosenblum & Andrews, 1994). Furthermore, infants 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). Also, CSF concentrations of 5-HT, DA, and NE metabolites were elevated in these monkeys (Coplan et al., 1998). As previously discussed, sexually abused girls have elevated urinary excretion of dopamine metabolites (De Bellis et al., 1994), whereas maltreated children with PTSD had elevated excretion of catecholamines (DA and NE) and cortisol (De Bellis, Baum, et al., 1999). An interesting finding was that elevations in cerebrospinal fluid concentrations of CRF are seen in adults with PTSD (Baker et al., 1999; Bremner, Licinio, et al., 1997). In the one study published to date, children who grew up in low SES households had significantly higher salivary cortisol levels than children who grew up in more advantaged environments (Lupien, King, Meaney, & McEwen, 2001). The effects of SES emerged as early as age 6, with the largest SES differences appearing about the age of 10 years. In our study of maltreated children with PTSD, SES and PTSD status were significant factors in determining smaller cerebral volume and lower IQ (De Bellis, Keshavan, et al., 1999). However, in a replication study that controlled for SES, smaller cerebral volumes were seen in maltreated children with PTSD compared to sociodemographically matched controls (De Bellis, Keshavan, Shifflett, et al., 2002). Most poor parents are not neglectful. There is a transaction between ecological variables "external" to the parent

and "internal" parental factors that results in neglect (Crittenden, 1999). Parental factors may interact with ecological variables to protect against or increase the likelihood of neglect. Consequently, the psychobiological influence of ecological factors, important variables in child neglect research, is understudied in humans.

THE HOME AND FAMILY ENVIRONMENT

Neglect exists as a broader aspect of parental dysfunction that includes social isolation and family violence (Polansky, Gaudin, & Kilpatrick, 1992). As described above, cortisol is elevated in distressed children. However, social support attenuates heart rate and cortisol levels during stress (Thorsteinsson, James, & Gregg, 1998). Quality of childcare is associated with a buffering of LHPA axis to stress (Gunnar, 1998). This buffering may lead to fewer psychobiological changes and, hence, fewer psychosocial impairments.

There is little formal research on the prevalence of domestic violence in CPS-defined neglected children. In a sample of 2,544 at-risk mothers with firstborn children, domestic violence occurred in 40% of the 155 cases of confirmed neglect (McGuigan & Pratt, 2001). Domestic violence preceded child neglect in 80% of these cases. An analysis of a centralized U.S. Army database revealed that an identified episode of spouse abuse was associated with an increased risk of subsequent child abuse (Rumm, Cummings, Krauss, Bell, & Rivara, 2000). In the United States, 42 states and the District of Columbia recently recognized that children who witness domestic violence are in need of protection from this type of emotional abuse (U.S. Department of Health and Human Services, 2004). In clinically referred samples, the reported incidence rates of PTSD, resulting from witnessing domestic violence, ranges from 50% to 100% (for domestic homicide; Pynoos & Nader, 1989). Consequently, neglected children are likely to witness interpersonal traumas and experience PTSD from exposure to extreme domestic violence. A prospective study demonstrated that witnessing partner violence during the preschool years was strongly associated with boys externalizing problems and girls internalizing problems during adolescence (Yates, Dodds, Sroufe, & Egeland, 2003). Koenen, Moffitt, Caspi, Taylor, and Purcell (2003) focused specifically on the relationship between domestic violence and cognitive or intellectual ability as measured by IQ. This large-scale twin study, which used 1,116 monozygotic and dizygotic 5-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, that were 8 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. This environmental effect was speculated to be specific to domestic violence as it persisted even after controlling for maltreatment, which was the larger source of extreme childhood stress. Consequently, psychobiological studies need to include a comprehensive examination of family factors, such as social support, family violence, and variables of cognitive and emotional stimulation. Additionally, it is known that neglected children have poorer academic achievement compared to sociodemographically matched control children (Perez & Widom, 1994). There is little data on the consequences of neglect on more specific cognitive functions than IQ and academic achievement. To identify the specific mechanisms of these cognitive deficits in neglected children for intervention, measures of cooccurring family violence need to be included in the design of psychobiological studies in this area.

GROWTH AND NUTRITION

Poor nutrition and child neglect can coexist. Both are likely the result of parental and ecological factors. In humans, linear growth and final adult stature depend on genetic constitution, nutrition, hormones, the presence or absence of systemic diseases, and a nurturing psychosocial environment (E. O. Johnson, Kamilaris, et al., 1992). Inadequate nutrition and undernutrition are potential confounding factors when one undertakes psychobiological research in neglected children. Although it is beyond the scope of this review, psychobiological studies of neglect need to include a comprehensive assessment of a child participant's birth weight, birth head circumference, diet, and physical growth.

SUMMARY AND FUTURE DIRECTIONS

It is evident that neglected children have adverse outcomes. However, neglected children may suffer

from various subtypes of neglect and many other adversities, which may contribute to adverse brain development and compromised neuropsychological and psychosocial outcomes. It is still not clear if some of the biological differences seen in abused and neglected children are adaptive or maladaptive. In this article, we comprehensively outlined psychobiological areas for investigation. Novel noninvasive neuroimaging methods, such as anatomical MRI, MRS, fMRI, and DTI, will allow for pioneering studies in developmental traumatology. There are only a few published studies of children using MRI. These investigations have mainly focused on "super" healthy children and children with developmental and neurological disorders, head injury, and mental illness. Thus, the study of childhood brain development using these MRI methods is only in its infancy. A comprehensive examination of clinical variables, which can also influence brain development, will allow the field to examine the neurobiological consequences of child neglect. Combining evidence-based interventions with comprehensive baseline psychobiological assessment and longitudinal follow-up is a promising strategy to further our understanding of the psychobiology of neglect and help the field identify the best predictors for the permanence and therapeutic reversibility of the many adverse effects associated with child neglect.

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