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Effects of early stress on brain structure and function: Implications for understanding the relationship between child maltreatment and depression

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Abstract
Child abuse is associated with markedly elevated rates of major depression (MDD) in child, adolescent, and adult cohorts. This article reviews preclinical (e.g., animal) studies of the effects of early stress and studies of the neurobiological correlates of MDD in adults and children, and it highlights differences in the neurobiological correlates of MDD and stress at various developmental stages. The preclinical studies demonstrate that stress early in life can alter the development multiple neurotransmitter systems and promote structural and functional alterations in brain regions similar to those seen in adults with depression. Preclinical and clinical studies suggest, however, that long-term neurobiological changes associated with early stress can be modified by familial/genetic factors, the quality of the subsequent caregiving environment, and pharmacological interventions. Little is known about how developmental factors interact with experiences of early stress and these other modifying factors. Moreover, in cases of child maltreatment, the effects of early abuse are often exacerbated by failures in the child protection system and repeat out-of-home placements. Given the number of factors that impact on the long-term outcome of maltreated children, multidisciplinary research efforts are recommended to address this problem—with foci that span from neurobiology to social policy.

Child abuse is a pervasive social problem, with victims of abuse comprising a significant number of all psychiatric admissions. Each year there are almost 1,000,000 substantiated reports of child maltreatment (U.S. Department of Health and Human Services, 2001), many reported cases of actual abuse that are not verified (Kaufman & Zigler, 1996), and, as numerous studies have indicated, countless other cases which never come to the attention of authorities (Wolfner & Gelles, 1993). Rates of physical and sexual abuse among child and adolescent psychiatric outpatients and inpatients are estimated at 30 and 55%, respectively (Lanktree, Briere, & Zaidi, 1991; McClellan, McCurry, Ronnei, Adams, Eisner, & Storck, 1996). Rates of child abuse in adult psychiatric cohorts have been reported to be comparably high in several studies (Windle, Windle, Scheidt, & Miller, 1995), with rates greatest among patients with suicidality, anxiety, and substance use disorders.

Child abuse is frequently associated with long-term significant psychiatric sequelae and markedly elevated rates of major depression (MDD) in child, adolescent, and adult cohorts. The point prevalence of MDD in children and adolescents is 2 and 5–8%, respectively (Birmaher, Ryan, Williamson, Brent, & Kaufman, 1996). Among representative nonclinically referred samples of protective service cases, 18% of preadolescents and 40% of adolescents with a history of child maltreat-

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ment have been found to meet current diagnostic criteria for MDD (Famularo, Kinscherff, & Fenton, 1992; Kaufman, 1991; McLeer, Callaghan, Henry, & Wallen, 1994). In population surveys, lifetime rates of MDD in women with a history of abuse have ranged from 13 to 64%, with rates of depression significantly greater among women with a history of abuse in all prior reports (see Weiss, Longhurst, & Mazure, 1999, for a review of the literature).

As reviewed elsewhere, preclinical (e.g., animal) studies suggest that stress early in life can promote long-term changes in multiple neurotransmitter systems and brain structures implicated in the etiology of MDD in adults (Arborelius, Owens, Plotsky, & Nemeroff, 1999; Heim, Owens, Plotsky, & Nemeroff, 1997; Kaufman, Plotsky, Nemeroff, & Charney, 2000). Consequently, it is hypothesized that neurobiological changes associated with adverse early experiences can confer a vulnerability for the development of MDD.

This paper reviews functional connections among key structures and neurotransmitter systems involved in the stress response, and preclinical studies examining the long-term effects of early stress on the hypothalamic–pituitary–adrenal (HPA) axis and central corticotropin releasing hormone (CRH), monoaminergic (e.g., norepinephrine [NE], dopamine, serotonin), and gamma-aminobutyric acid/benzodiazepine (GABA/BZ) systems. Structural and functional brain changes associated with early or severe stress are also reviewed. In addition, factors that modify the impact of early stress are discussed, together with pharmacological interventions shown to prevent or reverse the neurobiological alterations associated with early stress. Similarities in the neurobiological correlates of stress and depression in *adults* are highlighted, and differences in the neurobiological correlates of depression in children, adolescents, and adults are discussed to emphasize the importance of utilizing a developmental framework in future preclinical and clinical investigations in order to better understand the neurobiological mechanisms that link child maltreatment and depression across the life cycle. In addition, as preclinical and clinical studies suggest that the provision of optimal parenting can diminish the long-term impact of early stress, the role of the child protection system in moderating the long-term outcome of maltreated children is also discussed.

Key Structures and Neurotransmitter Systems Involved in the Stress Response: Overview

The brain responds to stress in a complex and orchestrated manner, with both general and stimuli-specific components to the stress response (Lopez, Akil, & Watson, 1999). Knowledge about the structural and functional components of the stress system is still evolving. The review of the stress response included in this section is not exhaustive. It focuses on key components of the stress system and emphasizes the structures and neurotransmitter systems most extensively studied in preclinical studies examining the long-term effects of early stress. In the majority of these research studies, early stress has been operationally defined as repeat separation of the infant from its mother during the perinatal period. The reader is referred to Chrousos (1998) and Lopez and colleagues (1999) for a more detailed discussion of the central and peripheral components of the stress system.

Figure 1 depicts the functional connections among the different cortical and subcortical brain regions involved in the stress response. There is growing appreciation of the role of cortical inputs, with medial prefrontal cortex (PFC), anterior cingulate, and orbital PFC currently understood to play an important role in relaying information from primary sensory and association cortices to subcortical structures involved in the stress response (Lopez et al., 1999). Medial and orbital PFCs are reciprocally interconnected, and each have indirect connections with the hypothalamus and amygdala via inputs to the periaqueducatal gray (PAG) and parabrachial nucleus (PBN; An et al., 1998; Bernard & Bandler, 1998; Krout et al., 1998). The medial and orbital prefrontal cortices also provide direct inputs to the hypothalamus and are reciprocally connected with the amygdala (Ongur, An, & Price, 1998). These prefrontal regions appear

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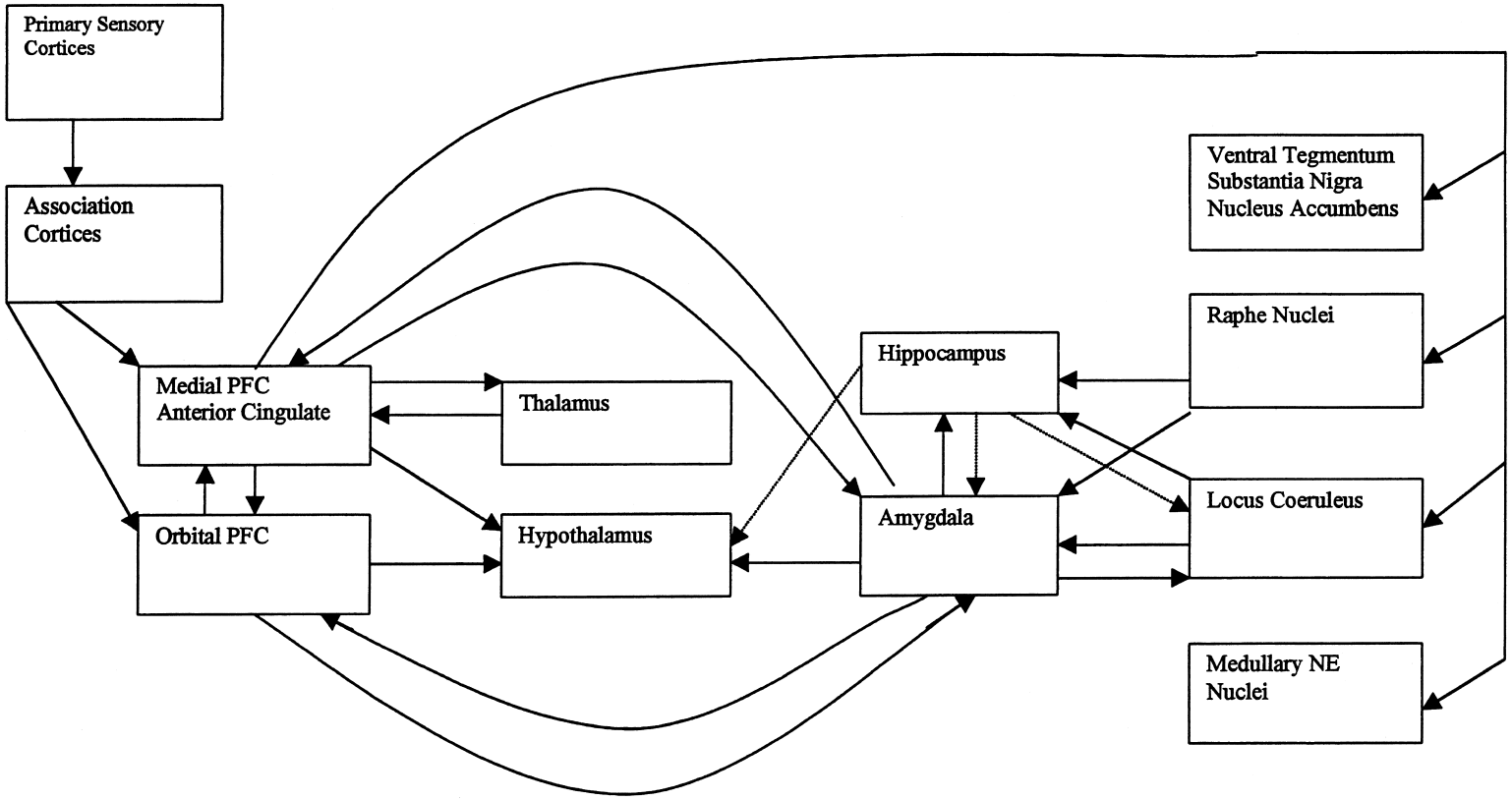


Figure 1. See caption on following page.

to be critical in restraining the acute stress response and facilitating negative feedback inhibition of the system (Herman & Cullinan, 1997). The medial PFC (mPFC) is also reciprocally connected with the mediodorsal thalamic nucleus (Groenewegen, 1988) and has extensive connections with the ventral tegmental area, substantia nigra, nucleus accumbens, raphe, locus coeruleus (LC), and brain stem autonomic nuclei (Drevets, Ongur, & Price, 1998).

Figure 2 depicts in more detail the relationships among subcortical structures involved in the stress response, and the neurotransmitter systems involved in the transmission of information between the different brain regions. CRH is the neurohormone that initiates the endocrine response to stress. Noradrenergic inputs from medullary sources to the paraventricular nucleus (PVN) of the hypothalamus promote the synthesis and release of CRH into the median eminence and hypophysial portal system (Pacak, Palkovits, Kopin, & Goldstein, 1995). CRH then binds to receptors at the anterior pituitary gland, and through a cascade of intracellular events promotes the release of adrenocorticotropin (ACTH). ACTH then promotes the synthesis and release of glucocorticoids (cortisol in primates; corticosterone in rats) from the adrenal cortex, which exert negative feedback on the pituitary, hypothalamus, and other central sites involved in the stress response (Arborelius et al., 1999).

CRH also appears to act centrally as a neurotransmitter to initiate the autonomic and behavioral changes observed in response to stress (Owens & Nemeroff, 1991; Valentino, Curtis, Page, Pavcovich, & Florin–Lechner, 1998). The LC appears to be the critical site in initiating the catecholamine response to stress (Page & Abercrombie, 1999; Valentino et al., 1998). It receives endogenous CRH inputs from the central nucleus of the amgydala (CnAmy). The amygdala is activated during stress by ascending catecholamine neurons originating in the brain stem, and by cortical association neurons involved in processing stressful stimuli (Lopez et al., 1999). CRH neurons of the CnAmy respond positively to glucocorticoids to activate the LC/NE component of the stress system.

The hippocampus, in contrast, serves to inhibit the stress response via multiple direct and indirect links with several of the brain structures activated during stress (Lopez et al., 1999). For example, CRH synthesis in the CnAmy is inhibited by GABA inputs from the hippocampus (Owens & Nemeroff, 1991). The hippocampus also inhibits the LC via direct connections and inhibits the PVN via indirect inputs through the lateral septum and bed nucleus of the stria terminalis (BNST).

The stress response is further modified by serotonin inputs from the dorsal and median raphe to the basolateral and central nucleus of the amygdala, serotonin inputs from the dorsal raphe to the PVN, and serotonin inputs

Figure 1. Key cortical and subcortical structures involved in the stress response. Medial prefrontal cortex (PFC), anterior cingulate, and orbital PFC relay information from primary sensory and association cortices to subcortical structures involved in the stress response. Medial and orbital PFC are reciprocally interconnected. The medial and orbital prefrontal cortices provide direct inputs to the hypothalamus and are reciprocally connected with the amygdala. Not shown in the diagram are indirect connections from these prefrontal structures to the hypothalamus and amygdala via inputs to the periaqueducatal gray and parabrachial nucleus. The medial PFC is also reciprocally connected with the mediodorsal thalamic nucleus and has extensive connections with the ventral tegmental area, substantia nigra, nucleus accumbent, raphe, locus caeruleus, and brain stem autonomic nuclei. These connections facilitate initiation and regulation of the endocrine response to stress that is mediated by the hypothalamic–pituitary–adrenal (HPA) axis, and the autonomic response to stress that is promoted by the locus caeruleus. Connections among brain stem nuclei, the hippocampus, amygdala, and HPA axis are detailed in Figure 2. Straight line, stipulatory; dotted line, inhibitory. *Note:* From "Effects of Early Adverse Experience on Brain Structure and Function: Clinical Implications," by J. Kaufman, P. Plotsky, C. Nemeroff, and D. Charney, 2000, *Biological Psychology, 48,* p. 779. Copyright 2000 by Elsevier. Reprinted with permission.

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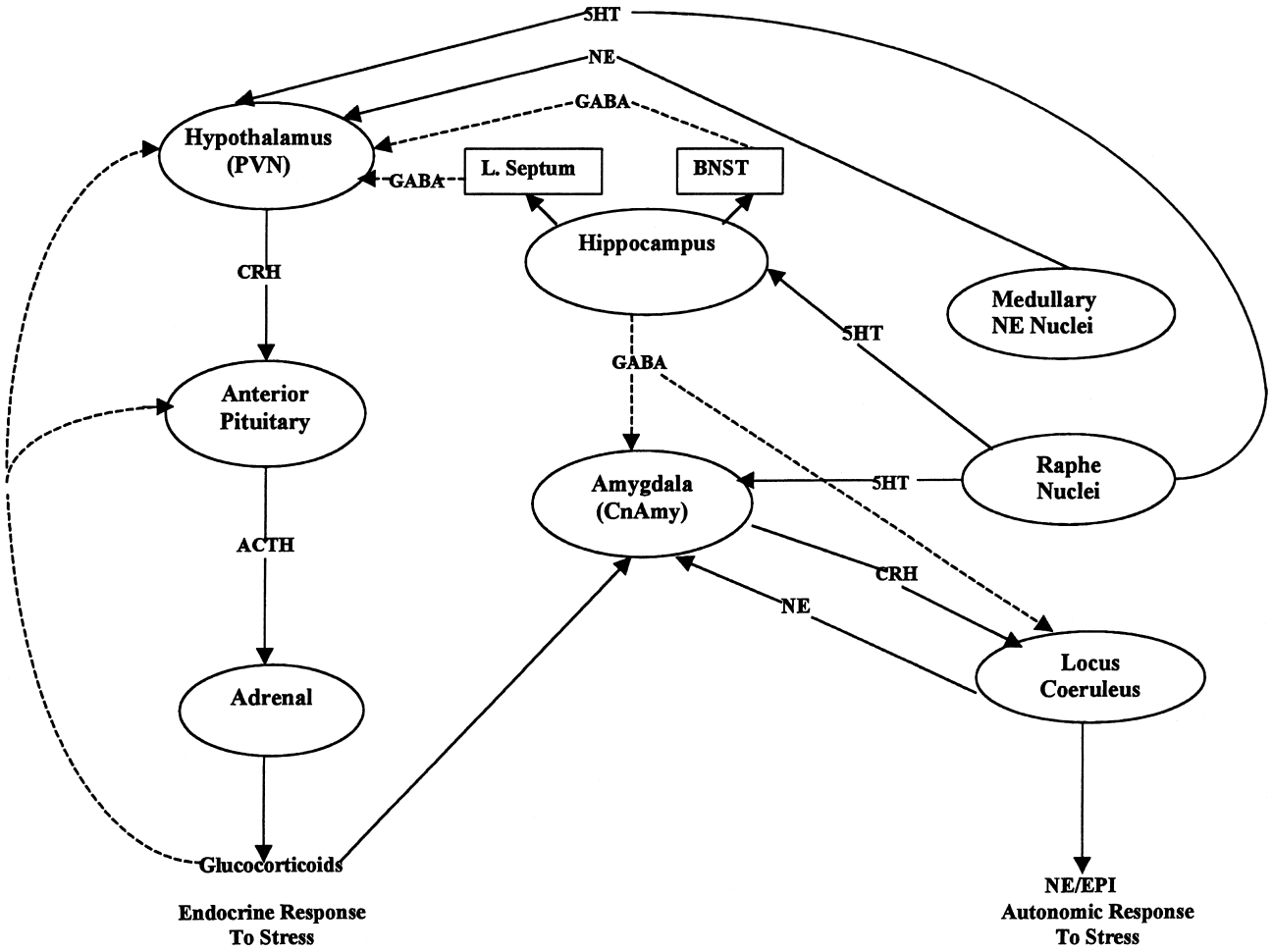


Figure 2. See caption on following page.

form the median raphe to the hippocampus (Lopez et al., 1999). These latter 5HT neurons terminate on inhibitory GABA neurons.

Both the paraventricular CRH and LC NE systems innervate and activate the mesocortical and mesolimbic components of the dopaminergic (DA) system (Chrousos, 1998). The mesocortical system includes DA neurons of the ventral tegmentum that send projections to the prefrontal cortex, and the mesolimbic system consists of DA neurons from the same region that innervate the nucleus accumbens. The mesocortical system is involved in anticipatory and cognitive functions and exerts a suppressive effect on the stress system, and the mesolimbic system is involved in processing motivation and reward aspects of experience. Portions of the PFC appear to be critical in restraining the acute stress response and facilitating negative feedback inhibition of the system (Herman & Cullinan, 1997), with inhibition from this region also mediated by GABAergic connections.

Neurobiological Effects of Early Stress: Preclinical Studies

As reviewed elsewhere (Kaufman et al., 2000), there has been extensive preclinical research conducted examining the neurobiological effects of early maternal separation. These experiences are associated with increased CRH and NE drive in adulthood (Ladd, Owens, & Nemeroff, 1996; Plotsky & Meaney, 1993). Rat pups separated from their mothers 6 hr per day during the first 3 weeks of life have been found to have increased basal and stress induced adrenocorticotropic hormone (ACTH) concentrations and decreased CRH binding in the anterior pituitary. Maternal deprivation has also been associated with increased CRH mRNA expression in the hypothalamic PVN and increased CRH concentration in the median eminence. Separation has also been associated with increased CRH mRNA expression in the CnAmy and BNST, increased CRH content in the parabrachial nucleus, a region which adjoins the LC, increased CRH binding in the LC, and increased NE concentration in the PVN (Liu, Caldji, Sharma, Plotsky, & Meaney, 2000; Menzaghi, Heinrichs, Pich, Weiss, & Koob, 1993; Plotsky & Meaney, 1993).

The increase in CRH and NE drive in maternally deprived rats is also associated with a decrease in tone of the inhibitory GABA/BZ system (Caldji, Francis, Sharma, Plotsky, & Meaney, 2000; Francis, Diorio, Liu, & Meaney, 1999). Specifically, rats subjected to repeat separations from their mothers during the first 3 weeks of life have been found in adulthood to have reduced $GABA_A$ receptor

Figure 2. Key subcortical structures and neurotransmitter systems involved in the stress response. The release of the neurohormone CRH from the PVN of the hypothalamus initiates the endocrine response to stress. CRH then promotes the release of ACTH from the pituitary, which initiates the release of glucocorticoid from the adrenal. Glucocorticoids provide negative feedback at the pituitary and PVN, among other sites. The release of CRH from the PVN is modified by multiple neurotransmitters, but NE inputs from medullary nuclei provide the primary stimulus for CRH synthesis and release. CRH also acts as a neurotransmitter to initiates the autonomic response to stress. The autonomic component of the stress response is initiated by CRH inputs from the CnAmy to the LC. Glucocorticoids provide positive stimulation to the CnAmy, promoting the synthesis and release of CRH. The hippocampus serves to inhibit the stress response via multiple direct and indirect GABAergic inputs to the PVN, amygdala, and LC. The stress response is further modified by 5HT inputs from the raphe nuclei to the PVN, hippocampus, and amygdala. GABAergic interneurons located at each of the structures likely further modify stress reactivity, as do connections from multiple other brain regions including the PFC, thalamus, association cortex, and mesocortical and mesolimbic structures. NE, norepinephrine; CRH, corticotropin releasing hormone; PVN, paraventricular nucleus; CnAmy, central nucleus of the amygdala; GABA, gamma-aminobutyric acid; 5-HT, serotonin; EPI, epinephrine; PFC, prefrontal cortex; L. Septum, lateral septum; BNST, bed nucleus stria terminalis. Solid lines, stipulatory inputs; dotted lines, inhibitory inputs. *Note:* From "Effects of Early Adverse Experience on Brain Structure and Function: Clinical Implications," by J. Kaufman, P. Plotsky, C. Nemeroff, and D. Charney, 2000, *Biological Psychology, 48,* p. 780. Copyright 2000 by Elsevier. Reprinted with permission.

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binding in the CnAmy, basolateral nuclei of the amygdala (BnAmy), and the frontal cortex. They have also been found to have reduced central benzodiazapine binding in the CnAmy, BnAmy, LC, and nucleus of the solitary tract (NTS). These effects were associated with decreased expression of mRNA for the γ_2 subunit that encodes for the benzodiazapine site of the $GABA_A$ receptor. In addition, adult rats separated from their mothers during the first 3 weeks of life also had increased mRNA expression for the $\forall_2$ and $\forall_3$ subunits, and decreased expression of the $\forall_1$ subunit mRNA (Caldji et al., 2000). This profile is associated with decreased GABA binding (Wilson, 1996). It is likely that the dampened GABAergic tone in rats subjected to these stress paradigms contributes to the enhanced CRH expression in the amygdala and the increased stress induced activation of the noradrenergic systems (Francis, Diorio, et al., 1999).

In a set of related experiments (Braun, Lange, Metzger, & Poeggel, 2000; Poeggel, Lange, Hase, Metzger, Gulyaeva, & Braun, 1999), Braun and colleagues examined the impact of early maternal separation and social isolation on the development of efferents to the mPFC. Specifically, Octodon Degus rodents were separated from their mothers three times a day for 1 hr from Postnatal Day 1 to Postnatal Day 21. After weaning, the deprived animals were reared in isolation in single cages until Postnatal Day 45 when they were sacrificed and monoamine fiber innervation to the mPFC was examined using immunocytochemical detection of tyrosine hydroxylase (TH) and serotonin (5-HT). As reviewed previously, the mPFC is reciprocally connected with the mediodorsal thalamic nucleus (Groenewegen, 1988) and is believed to be involved in mediating ACTH and corticosterone response to stress, controlling the negative feedback effects of glucocorticoids on stress related HPA axis activity, and processing affective and cognitive components of mother–child interactions (Braun & Scheich, 1997; Drevets et al., 1998). This region also has extensive connections with the amygdala, lateral hypothalamus, nucleus accumbens, ventral tegmental area, substantia nigra, raphe, LC, PAG, and brain stem autonomic nuclei (Drevets et al., 1998).

When compared to rodents reared under undisturbed conditions, maternally deprived and socially isolated rats had significantly reduced TH-positive fiber innervation in the precentral medial, anterior cingulate, and prelimbic cortex subdivisions of the mPFC, and increased 5-HT-positive fiber densities in the infralimbic cortex (nomenclature according to Groenewegen, 1988). The number of TH-positive somata in the ventral tegmental area and in the substantia nigra did not differ between the groups, suggesting that the reduced fiber densities were likely due to suppressed axonal sprouting and aborization. Maternally deprived and socially isolated animals, in addition to having altered DA/5-HT balance in the mPFC, were also found to have a significant decrease of nicotinamide adenine dinucleotide phosphate (NADPH)–diphorase-reactive neurons in the anterior cingulate cortex and the core region of the nucleus accumbens, and a trend for reduced NADPH–diphorase-reactive neurons in the infralimbic, precentral medial, and prelimbic prefrontal areas. Since some NADPH containing neurons have been found to be GABAergic (Poeggel et al., 1999), the reduced NADPH–diphorase neurons may represent a loss of inhibitory interneurons in this cortical region which plays a critical role in integrating affective and cognitive information processing.

In an attempt to more closely parallel the experience of neglectful parenting and exposure to stressful environments in young human infants, Coplan, Andrews, Rosenblum, Owens, Friedman, Gorman, and Nemeroff (1996) subjected macaque infant–mother dyads to variable foraging demands. Primates in the low foraging demand condition had easy access to food, primates in the high foraging demand condition had to work hard to find food, but foraging demands and food supply were predictable, and primates in the variable foraging demand condition experienced changing and unpredictable access to food. In adulthood, consistent with the maternal deprivation rodent studies discussed above, monkeys reared in the variable foraging condition had higher cerebrospinal fluid (CSF) CRH concentration

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than monkeys reared under the two other more predictable and less stressful experimental conditions (Coplan et al., 1996). The variable foraging condition was also associated with overactivity of the NE system, with these animals as adults showing enhanced behavioral response to yohimbine, an $\forall_2$ adrenergic antagonist (Rosenblum, Coplan, Friedman, Bassoff, Gorman, & Andrews, 1994).

In contrast to the negative effects of early stress, rats provided positive stimulation via 15 min of handling per day during the first 3 weeks of life have been found to have reduced stress reactivity in adulthood when compared to nonhandled or maternally separated rats (Plotsky & Meaney, 1993). Specifically, in adulthood, rats handled in the first 3 weeks of life show decreased fearfulness in novel environments. The neurobiological alterations associated with early handling are essentially the opposite of those reported in maternally separated rats. Handled rats show reduced ACTH and corticosterone response to exogenous stressors, with quicker return of corticosterone to baseline levels. They show enhanced negative feedback of circulating glucocorticoids and increased glucocorticoid receptor mRNA expression and glucocorticoid receptor number in the hippocampus and the frontal cortex, sites involved in the inhibitory control of CRH synthesis in PVN neurons. Accordingly, handled rats have reduced CRH mRNA levels in the PVN and reduced basal CRH concentration in the median eminence. Handled rats also have reduced CRH mRNA concentrations in the CnAmy and lower CRH content in the LC (Plotsky & Meaney, 1993). They also have attenuated CRH-induced activation of the LC and smaller resulting increases in extracellular NE levels in the PVN after acute restraint stress (Liu et al., 2000). Handled rats have increased $GABA_A$ receptor levels in noradrenergic cell body regions of the LC and NTS, as well as increased central benzodiazepine receptor levels in the CnAmy, LC, and NTS (Francis, Caldji, Champagne, Plotsky, & Meaney, 1999). In addition, handled rats have attenuated age-related cell loss in the hippocampus and improved performance on hippocampal mediated cognitive tasks (Meaney, Aitken, Bhatnagar, & Sapolsky, 1991; Meaney, Bhatnagar, Diorio, Larocque, Francis, O'Donnell, Shanks, Sharma, Smythe, & Viau, 1993).

The maternal deprivation and postnatal handling animal studies highlight the importance of early experience on the development of the brain and multiple neurotransmitter systems. The stress effects on hippocampus development are likely mediated by a minimum of three forms of structural plasticity: neuronal atrophy, neurotoxicity, and neurogenesis. Neuronal atrophy in the CA3 region of the hippocampus can be caused by 3 weeks of exposure to stress or administration of exogenous glucocorticoids at stress levels (Sapolsky, 1996; Woolley, Gould, & McEwen, 1990). At this level, glucocorticoids produce a reversible decrease in number of apical dendritic branch points and length of apical dendrites of sufficient magnitude to impair hippocampal dependent cognitive processes (Watanabe, Gould, & McEwen, 1992). More sustained glucocorticoid exposure can lead to neurotoxicity—actual permanent loss of hippocampal neurons. Rats exposed to high concentrations of glucocorticoids for approximately 12 hr/day for 3 months experience a 20% loss of neurons specific to the CA3 region of the hippocampus (Sapolsky, Krey, & McEwen, 1985). Evidence of stress induced neurotoxicity of cells in this region has been reported in nonhuman primates as well (Uno, Eisele, Sakai, Shelton, Baker, DeJesus, & Holden, 1994) and is suggested in adult humans by magnetic resonance imaging (MRI) studies reporting reduced hippocampal volume in stress related disorders (e.g., Bremner, Narayan, Anderson, Staib, Miller, & Charney, 2000; Bremner, Randall, Scott, Bronen, Seibyl, Southwick, Delaney, McCarthy, Charney, & Innis, 1995; Bremner, Randall, Vermetten, Staib, Bronen, Mazure, Capelli, McCarthy, Innis, & Charney, 1997). Assessments of hippocampal volume may also be affected by decreases in neurogenesis (Gould & Cameron, 1996). The granule cells in the dentate gyrus of the hippocampus continue to proliferate into adulthood, and neurogenesis in this region is markedly reduced by stress.

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Factors that Modify the Impact of Early Stress: Preclinical Studies

The animal studies reviewed in the prior section demonstrate that early life experiences can have profound effects on brain structure and function. There is emerging preclinical data to suggest, however, that the subsequent caregiving environment can modify the adverse effects of early stress. To determine if the neurobiological changes associated with early handling could be altered by subsequent caregiving experiences, rat pups exposed to early handling or maternal separation experiences were cross-fostered with dams whose children were assigned the same or opposite condition (Gonzalez, Ladd, Huot, Owens, & Plotsky, 1999). In the initial set of experiments, handled pups were either cross-fostered to other dams assigned to the handled condition or to dams assigned to the maternal separation condition. Similar cross-fostering was performed on pups exposed to the maternal separation condition. When tested as adults, the handled pups cross-fostered to dams assigned to the maternal separation condition reacted to novel stressors like rats subjected to maternal separation during the neonatal period. Conversely, maternally separated pups reared by dams assigned to the handling condition looked more like handled animals. The parenting of mothers in the maternally separated group is disturbed (e.g., lower rates of licking and grooming behaviors) and appears to contribute significantly in determining the long-term impact of early separation experiences.

In a second set of experiments (Gonzalez et al., 1999), dams assigned the maternal separation conditions were provided with an age-matched foster litter during the period when their own pups were away. This simple manipulation seemed to normalize maternal behavior by the dams, and the adult offspring that had been assigned to the maternal separation condition appeared like handled animals rather than like maternally separated animals. These findings are consistent with the results of studies examining the effects of prenatal stress. In these studies "adoption" with "optimal parenting" has also been found to reverse the HPA axis alterations typically observed in these experiments (Barbazanges, Vallee, Mayo, Day, Simon, Le Moal, & Maccari, 1996; Maccari, Piazza, Kabbaj, Barbazanges, Simon, & Le Moal, 1995). These results are consistent with emerging data demonstrating the powerful role of different components of mother–infant interaction (e.g., tactile stimulation) in regulating physiological systems involved in the stress response (Caldji, Tannenbaum, Sharma, Francis, Plotky, & Meaney, 1998; Kuhn & Schanberg, 1998).

These preclinical studies suggest that the effects of early experiences can be modified by subsequent rearing experiences. As the influence of genetic factors or strain effects has been well established in preclinical studies of stress reactivity (Dhabhar, McEwen, & Spencer, 1997), the cross-fostering studies raise questions as to whether or not manipulations in parenting can overcome genetic or breed differences in stress reactivity. To address this question, Meaney and colleagues subjected BALB/cByJ and C57BL/6ByJ mice to early handling experiences and randomly assigned them to BALB/cByJ or C57BL/6ByJ mothers for subsequent rearing (Anisman, Zaharia, Meaney, & Merali, 1998; Zaharia, Kulczycki, Shanks, Meaney, & Anisman, 1996). BALB/cByJ mice are inherently high reactors and have elevated corticosterone and brain catecholamine responses to acute stressors. In addition, mice of this strain exhibit impaired performance on a Morris water maze that is exacerbated by footshock application. Early handling of BALB/cByJ mice reduced the learning impairments seen when mice were tested in the Morris water maze as adults, and prevented stress-induced elevations of corticosterone and disturbances with task performance. Likewise, cross-fostering BALB/cByJ mice with C57BL/6ByJ dams prevented corticosterone hyperactivity and performance deficits. However, cross-fostering and handling did not alter stress-induced changes in NE concentration in the hypothalamus, LC, hippocampus, or PFC. Early handling and cross-fostering of the more resilient C57BL/6ByJ mice had no impact on maze performance,

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corticosterone stress reactivity, or brain NE. A similar set of findings was reported by investigators studying two different high- and low-reactive rat species (Steimer, Escorihuela, Fernandez–Teruel, & Driscoll, 1998). Effects of handling and cross-fostering were only observed in the high-reactive rats, and these experimental manipulations affected only stress-induced corticosterone levels, not central NE measures.

These studies highlight the need for a better understanding of gene and environmental interactions in determining an individual's stress reactivity. They suggest that species with more intrinsic reactivity are more responsive to the effects of environmental manipulations than species that are less intrinsically reactive, and that environmental manipulations have greater impact on some (e.g., HPA axis) more than other (e.g., central NE) neurobiological systems. The clinical and research implications of these findings are far reaching. They imply that there are multiple pathways to the development of stress related psychopathology and that phenotypes with similar neurobiology may have distinct etiologies. The Human Genome Project and evolving methodologies such as gene chips, which permit the simultaneous analysis of thousands of genes, will help to identify the relevant genes that confer risk in future preclinical studies examining gene and environment interactions (Watson & Akil, 1999).

Neurobiological Effects of Early Stress: Pharmacological Prevention and Treatment

The long-term stress-related changes in brain structure observed in the animal studies reviewed above can be altered by multiple different pharmacological interventions. Emerging preclinical data suggests that in addition to glucocorticoids, serotonin and excitatory amino acids (EAA) are involved in the mechanisms that promote neuronal atrophy, neurotoxicity, and neurogenesis (Gould, 1999; McEwen, Conrad, Kuroda, Frankfurt, Magarinos, & McKittrick, 1997; Sapolsky, 1996). Consistent with these findings, several classes of medications have been found to prevent dendritic atrophy caused by stress in animals, including serotonin reuptake enhancers (e.g., tianeptine), benzodiazepine agonists (e.g., adinazolam), the antiseizure drug phenytoin (which reduces EAA release), and adrenal steroid inhibitors (Magarinos, Deslandes, & McEwen, 1999; McEwen et al., 1997; Sapolsky, 1996). Tianeptine, in addition to preventing reduction in number of apical dendritic branch points and length of apical dendrites, also reverses already established hippocampal atrophy (Magarinos et al., 1999). Surprisingly, given the clinical effectiveness of selective serotonin reuptake inhibitors (SSRI) in treating depression, fluoxetine and fluvoxamine do not block dendritic atrophy caused by repeated restraint stress (Magarinos et al., 1999). These agents do, however, reverse the HPA axis alterations observed in adult rodents subject to repeat maternal separation during the neonatal period (Plotsky, personal communication, November 1999). In addition, in adult primates subject to maternal deprivation in infancy, electroconvulsive therapy (ECT) and chronic tricyclic antidepressant (e.g., imipramine) treatments have also been found to reverse HPA axis overactivation following acute stress (Suomi, 1991).

Similarities in the Neurobiological Correlates of Stress and Depression in Adults

The preclinical studies of the effects of stress provide a valuable heuristic for thinking about the pathophysiology of depression in adults and organizing findings of the neurobiological correlates of MDD in adults. Many of the biological alterations associated with early stress in preclinical studies have been reported in *adults* with depression and other stress-related disorders. For example, adults with depression have been reported to have multiple alterations of the HPA axis, including increased basal cortisol secretion (Schildkraut, Green, & Mooney, 1989), reduced negative feedback as evidenced by dexamethasone non-suppression (American Psychiatric Association Task Force on Laboratory Tests in Psychiatry,

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1987; Carroll, 1982), and blunted ACTH secretion in response to administration of endogenous CRH (Gold, Calabrese, Kling, Avgerinos, Khan, Gallucci, Tomai, & Chrousos, 1986; Holsboer, Gerken, Stalla, & Muller, 1987; Plotsky, Owens, & Nemeroff, 1998). They have also been found to have increased central CRH drive, as evidenced by reports of elevated concentrations of CSF CRH (Nemeroff, Bissette, Akil, & Fink, 1991; Nemeroff, Widerlov, Bissette, Walleus, Karlsson, Eklund, Kilts, Loosen, & Vale, 1984) and reduced CRH receptor binding site number in the frontal cortex of suicide victims (Nemeroff, Owens, Bissette, Andorn, & Stanley, 1988). Depressed adults also have been found to have higher CSF NE concentration (Wong, Kling, Munson, Listwak, Licinio, Prolo, Karp, McCutcheon, Geracioti, De Bellis, Rice, Goldstein, Veldhuis, Chrousos, Oldfield, McCann, & Gold, 2000) and decreased cortical GABA measured in vivo using proton magnetic resonance spectroscopy (Sanacora, Mason, Rothman, Behar, Hyder, Petroff, Berman, Charney, & Krystal, 1999). Altered DA/5-HT balance has also been reported in adults with depression (Reddy et al., 1992), with fluoxetine treatment associated with increases in CSF DA/5-HT metabolite concentration ratios (De Bellis, Gold, Geracioti, Listwak, & Kling, 1993). (See Arborelius et al., 1999, and Charney et al., 1998, for a discussion of the similarities in the neurobiological correlates of stress reported in preclinical studies and clinical studies of patients with posttraumatic stress disorder [PTSD].)

Studies of adults with depression have also reported structural and functional alterations in the mPFC. Specifically, adults with depression have been found to have reduced gray matter volume in the subgenual PFC (Drevets, Price, Simpson, Todd, Reich, Vannier, & Raichle, 1997), and decreased blood flow and glucose metabolism in this region as well (Drevets, Videen, Price, Preskorn, Carmichael, & Raichle, 1992). In addition, preliminary histopathological data from the subgenual PFC suggests that depressed patients have a decrease in glia number in this region without a corresponding loss of neurons (Drevets et al., 1998). Reduced glucose metabolism in the ventromedial PFC (Buchsbaum, Wu, Siegel, Hackett, Trenary, Abel, & Reynolds, 1997) and decreased blood flow in the dorsal anterior cingulate has also been reported in depressed patients (Mayberg, Brannan, Mahurin, Jerabek, Brickman, Tekell, Silva, McGinnis, Glass, Martin, & Fox, 1997). These two regions are contained in the mPFC and overlap with the subgenual PFC.

Structural changes in the hippocampus have also been reported in adults with depression. While hippocampal volume reductions were not observed in early studies of adults with depression (Axelson, Doraiswamy, McDonald, Boyko, Tupler, Patterson, Nemeroff, Ellinwood, & Krishnan, 1993; Hauser, Altshuler, Berrettini, Dauphinais, Gelernter, & Post, 1989), three more recent studies using improved methodology all reported asymmetric hippocampal volume reductions in association with adult depression (Bremner et al., 2000; Shah, Ebmeier, Glabus, & Goodwin, 1998; Sheline, Wang, Gado, Csernansky, & Vannier, 1996). In two studies degree of hippocampal atrophy correlated with total duration of illness (Bremner et al., 2000; Sheline et al., 1996), raising questions as to whether these changes represent primary disturbances associated either with the onset of disorder or with secondary brain changes related to recurrence and extended glucocorticoid exposure. Hippocampal volume reductions have also been reported in adults with PTSD (Bremner et al., 1995, 1997; Gurvits, Shenton, Hokama, Ohta, Lasko, Gilbertson, Orr, Kikinis, Jolesz, McCarley, & Pitman, 1996; Stein, Koverola, Hanna, Torchia, & McClarty, 1997). Adults with depression have also been found to have reduced volume of core amygdala nuclei (Sheline, Gado, & Price, 1998), with abnormalities in resting blood flow and glucose metabolism also reported in this area (Drevets, 1999).

The pattern of findings reported in adults with depression are very similar to the neurobiological changes associated with experiences of early stress, with changes in key cortical and subcortical structures involved in the stress response consistently reported in adults with depression.

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Neurobiological Correlates of Stress and Depression in Children and Adolescents

While the preclinical studies examining the neurobiological effects of early stress provide a powerful heuristic for thinking about the pathophysiology of MDD in adults, the application of this literature for understanding the neurobiology of early onset affective disorders is more limited. Depressed children and adolescents fail show evidence of hypercortisolemia as is frequently reported in adults (Kaufman & Ryan, 1999; Ryan & Dahl, 1993). To the extent that dysregulation of basal cortisol is found in depressed subjects in this age range, it appears more subtle and is manifest as alterations in the normal diurnal pattern of cortisol secretion. Rather than have increased 24-hr cortisol secretion, depressed youngsters are more likely to only have elevated cortisol output close to the period of sleep onset, a time when the HPA axis is normally quiescent. This pattern of findings usually does not manifest itself until adolescence in nontraumatized depressed youth but has been reported in several studies of maltreated preadolescent children with depressive symptomatology (Hart, Gunner, & Cicchetti, 1996; Kaufman, 1991; Putnam, Trickett, Helmars, Dorn, & Everett, 1991). In the majority of published studies of maltreated children, the samples have included children with experiences of physical abuse, sexual abuse, neglect, or a history of witnessing domestic violence.

In addition to a lack of robust findings in basal cortisol secretion, nontraumatized depressed children and adolescents do not have blunted ACTH response to CRH infusion as is reported in adults (Birmaher, Dahl, Perel, Williamson, Nelson, Stull, Kaufman, Waterman, Rao, Nguyen, Puig–Antich, & Ryan, 1996; Dorn, Burgess, Susman, van Eye, De Bellis, Gold, & Chrousos, 1996). Among depressed children with a history of maltreatment, contradictory findings have been reported in CRH studies. One study reported maltreated children to have blunted ACTH after CRH infusion (De Bellis, Chrousos, Dorn, Putnam, & Gold, 1994), and another study reported the children to have markedly elevated ACTH secretion after CRH infusion (Kaufman, Birmaher, Perel, Dahl, Moreci, Nelson, Wells, & Ryan, 1997). In the latter study, abnormalities in the HPA axis response to CRH were limited to those maltreated children living in conditions of ongoing chronic adversity (e.g., emotional maltreatment, domestic violence). Depressed children with a history of early maltreatment who were living in currently stable and positive environments showed no evidence of HPA axis dysregulation (Kaufman et al., 1997).

No studies with child and adolescent depressed cohorts have examined hippocampal volume. The one study that examined hippocampal volume in children and adolescents with PTSD ($N = 43$), about half of whom met criteria for comorbid MDD, failed to find evidence of hippocampal atrophy (De Bellis, Keshavan, Clark, Casey, Giedd, Boring, Frustaci, & Ryan, 1999). This finding is not surprising as most of the children and adolescents in the study had not experienced more than one episode of depression and hippocampal atrophy was found to be correlated with total lifetime duration of illness in the prior cited adult studies (Bremner et al., 2000; Sheline et al., 1996). Developmental factors may also account for the discrepant findings in child and adult studies, however, as preclinical studies report age-dependent changes in sensitivity to *N*-methyl-D-aspartate (NMDA) receptor blockade neurotoxicity in corticolimbic regions, with cell death minimal or absent in childhood and reaching peak in early adulthood (Farber, Wozniak, Price, Labruyere, Huss, St. Peter, & Olney, 1995).

Instead of hippocampal atrophy, the children and adolescents with PTSD were found to have smaller intracranial and cerebral volumes than matched controls, increased right, left, and total lateral ventricle volume; and decreased volume of the medial and posterior portions of the corpus callosum (CC; De Bellis et al., 1999). The medial and caudal portions of the midbody of the CC contains interhemispheric projections from the auditory cortices, posterior cingulate, retrospenial cortex, insula, and somatosensory and visual cortices to a lesser extent. It also includes connections from the inferior parietal lobe to the

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contralateral inferior parietal lobe, superior temporal sulcus, cingulate, and parahippocampal gyrus (Pandya & Seltzer, 1986). Several of the regions with interhemispheric projections through the medial and caudal portions of the midbody of the CC are involved in the processing of emotional stimuli and various memory functions—core disturbances frequently observed in children with a history of early trauma.

To the best of our knowledge, there is only one published structural MRI study in prepubescent nonhuman primates subjected to early stress (Sanchez, Hearn, Do, Rilling, & Herndon, 1998). Most preclinical studies of early stress have examined the long-term impact of these experiences on brain development in *adult* animals. Interestingly, the study with the young primates also failed to find evidence of hippocampal atrophy. Instead, consistent with the work of De Bellis and colleagues (1999), the investigators reported reductions in the medial and caudal portions of the midbody of the CC in the juvenile, nonhuman primates subjected to early stress. In a recent abstract, psychiatric inpatients with a history of maltreatment were likewise reported to have significant reduction in the volume of the medial and caudal portions of the CC when compared to psychiatric and healthy controls without a history of early child maltreatment (Teicher, Anderson, Dumont, Ito, Glod, Vaituzis, & Giedd, 2000).

The utilization of a developmental framework in future preclinical and clinical studies will help to enhance our understanding of the neurobiological mechanisms that link child maltreatment with depression across the life cycle. There are currently few preclinical studies examining possible developmental differences in the long-term impact of early stress on prepubertal, postpubertal, and mature animals. Data examining developmental changes in the acute effects of stress in rodents and nonhuman primates of different ages suggests this is an important focus of future research, as the neurobiological changes associated with the acute-stress response change with age (Pihoker et al., 1993; Suomi, 1991; Vazquez, 1998). As significant differences have been reported in the neurobiological correlates of depression across the life cycle (Kaufman, Martin, King, & Charney, 2001), more developmental preclinical and clinical research is greatly needed in these areas.

Clinical Implications

This section focuses primarily on the clinical implications of the stress research for depressed children and adolescents with a history of child maltreatment, including experiences of physical abuse, sexual abuse, neglect, or witnessing domestic violence. In the section on factors that modify the impact of early stress, genetic factors were noted. There is emerging evidence that familial–genetic factors also influence the likelihood of maltreated children developing depressive disorders. In one study, mothers of abused children who met criteria for MDD were found to have significantly more current depressive symptomatology than mothers of abused children who did not meet criteria for MDD (Kaufman, 1991). In another study, the rate of MDD in the first-degree relatives of a cohort of depressed abused children was markedly elevated, with 64% of the first-degree relatives of the depressed abused children reporting a lifetime history of MDD (Kaufman, Birmaher, Brent, Dahl, Bridge, & Ryan, 1998). These findings are consistent with the results of a recent large population-based twin study which suggested that individuals at high genetic risk for affective disorders are more vulnerable to develop depression following stressful life events than individuals at low genetic risk (Kendler et al., 1995). More research is needed, however, to understand the manner in which inherent vulnerability factors interact with experiences of abuse and other psychosocial stressors to infer a vulnerability to develop depression (Kaufman, Birmaher, Perel, Dahl, Stull, Brent, Trubnick, al-Shabbout, & Ryan, 1998). As child abuse is associated with an increased risk for a range of disorders (e.g., PTSD, alcohol abuse, antisocial personality), a better understanding of the relevant genetic and environmental risk factors will help to explain differences in the clinical outcome of individuals with a history of early child abuse.

The high familial nature of mood disor-

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ders, even among children with a history of trauma, highlights the importance of evaluating parents when working with depressed maltreated children. In a recent clinical trial examining the efficacy of cognitive behavioral therapy in the treatment of adolescent depression (Brent et al., 1998), the intervention was found to be less effective in adolescents with a currently depressed parent. Family discord also decreased the efficacy of treatment. As depression in adults is associated with marital discord and problems in parenting (Downey & Coyne, 1990), identification of parental depression and referral for treatment can be an essential "intervention" in the treatment of the child.

The section on factors that modify the impact of early stress also discussed the importance of the subsequent caregiving environment in modifying the deleterious effects of early stress. The availability of positive supports also appears to mediate some neurobiological alterations associated with early abuse, with HPA axis alterations most prominent among abused children with a history of multiple out-of-home placements, negative relationships with their primary caregivers, and few available social supports (Kaufman, 1991; Kaufman et al., 1997). In addition, the availability of a supportive parent or alternate guardian has been demonstrated to be one of the most important factors that distinguishes abused children with good developmental outcomes from those with more deleterious outcomes (Beeghly & Cicchetti, 1994; Cicchetti & Toth, 1995; Kaufman & Henrich, 2000; Pynoos, Steinberg, & Wraith, 1995).

Facilitating the formation of permanent and secure positive relations is essential in promoting adaptive outcomes for children with a history of early child abuse, and is an important focus for intervention with this clinical population (Kaufman & Henrich, 2000; Larrieu & Zeanah, 1998). Unfortunately, the development of positive and secure attachments is compromised for many maltreated children by failures in the child protection system. While the quality of child protection services departments varies from state to state, nationwide it is estimated that investigation is the only "service" provided in response to reports of child maltreatment in 40% of substantiated cases of child abuse and neglect (McCurdy & Daro, 1992). In these cases, no interventions are provided to reduce the risk of future maltreatment or alleviate the effects of past abuse. In addition, while studies suggest approximately three fourths of school-aged children receiving protective services have clinically significant emotional and behavioral problems (Kaufman, Cooke, Arny, Jones, & Pittinsky, 1994; Trupin et al., 1993), in some states less than 5% of protective service cases ever receive psychiatric treatment (Trupin et al., 1993). When they do receive care, the treatment is often poorly integrated with the protective service interventions and complicated by multiple changes in out-of-home placements (Kaufman & Zigler, 1996).

There are slightly over a half million children in foster care in this country (CDF, 1998). Children less than 5 years of age comprise more than one third of all children in out-of-home care (ACF, 1996). While the average length of stay in foster care is estimated at 2 years (ACF, 1996), the range of time in care varies widely for children. In some states, up to one third of all children who enter out-of-home care spend the majority of their lives in "foster-care drift"—moving from one home to the next without ever obtaining a permanent home (Kaufman & Zigler, 1996). In the state of Connecticut, the average child who enters care experiences between four and five placements, with placement resulting in separation from siblings in approximately 70% of all cases (Blau, personal communication, November 1999). Repeat changes in out-of-home placements and separations from siblings serve to further traumatize the children.

In addition, the road from initial placement to adoption, when clinically indicated, can be quite drawn out (Kaufman & Zigler, 1996). For example, in some states it is estimated to take 3–4 years from placement to the filing of a Termination of Parental Rights petition, 1–2 years from the filing of the petition until the date of the court hearing to determine the termination ruling, and an additional 2–5 years to process appeals (Cahn & Johnson, 1993). During this prolonged period of placement uncertainty, it is often difficult for children to form stable and secure attachments with current or future intended caregivers. In

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addition, depressive symptoms are exacerbated frequently by recurring court hearings and delays in determining permanency.

The Adoption and Safe Families Act (P.L. 105-89) passed in November 1997 was designed to facilitate permanency planning efforts on behalf of maltreated children. Permanency planning entails the identification of a caring and stable placement for abused and neglected children. The result of permanency planning efforts may be the strengthening of birth parents and their capacity to care for their children, long-term placement with kin, or adoption with nonrelative caregivers. The Adoption and Safe Families Act (P.L. 105-89) mandates permanency be achieved within 15 months of placement in out-of-home care but provides caveats to delay the termination of parental rights and permanency decisions. The legislation also provides few resources for services for maltreated children, birth parents, and foster parents, and gives states considerable leeway in the execution of the federal mandate. While some states have passed model legislation and implemented comprehensive intervention service programs, the effectiveness of caseworkers in other states is impeded by caseloads that exceed 100 children per worker (Kaufman & Zigler, 1996). Moreover, there is little to no data to utilize in the development of best-practice guidelines for protective service workers trying to promote permanency for maltreated children and for reducing the risk of long-term psychiatric sequelae (Kaufman & Henrich, 2000; Kaufman & Zigler, 1996).

For clinicians working with depressed abused children, it is important to work in active collaboration with child protective services and to advocate for children when the system is not adequately meeting their needs. The role of the clinician in working with abused children is to complete assessments of child psychopathology and family functioning, conduct therapeutic interventions to address key problem areas, facilitate referrals for additional services as necessary, keep workers appraised of therapeutic progress and report changes in risk and new incidents of abuse, evaluate child attachments over time, and make recommendations for treatment and permanency determinations in juvenile court as necessary (Kaufman & Henrich, 2000). The importance of multimodal interventions when working with this clinical population cannot be over emphasized.

Unfortunately there is very little data to guide the utilization of adjunctive pharmacological interventions in the treatment of depressed abused children. There have been surprisingly few studies on the psychopharmacological treatment of early onset MDD, and, as alluded to previously, the available research again highlights the importance of understanding differences in neurobiological correlates and treatment response of depressed patients of different ages.

While SSRI medications preliminarily appear effective in the treatment of depressed children and adolescents (Emslie, Rush, Weinberg, Kowatch, Hughes, Carmody, & Rintelmann, 1997; Keller et al., in press), unlike in adults, tricyclic antidepressants (TCAs) are not effective in the treatment of depression in this age cohort. Conclusions from early TCA studies were limited due to small sample size (Martin, Kaufman, & Charney, 2000); however, a recent multisite double-blind, placebo-controlled trial of 275 depressed outpatients 12–19 years of age randomized to paroxetine, imipramine, or placebo provides conclusive evidence regarding the inefficacy of TCA medications in this age cohort (Keller et al., in press). Patients randomized to imipramine received ratings comparable to patients receiving placebo on all of the clinical outcome measures. In contrast, paroxetine proved superior to placebo on measures of affect, global improvement, and remission of depressive symptoms. The findings of this study are consistent with the results of another study in which the SSRI fluoxetine was found to be effective in the treatment of depression in both children and adolescents (Emslie et al., 1997).

Children with active protective service involvement or comorbid PTSD were excluded from both SSRI clinical trials cited above (N. Ryan, personal communication, November 1999). Therefore, there is no data to guide the pharmacological treatment of depressed abused children. As depressed abused children have been found to have different familial and neurobiological correlates than depressed children without a history of trauma (Kaufman et

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al., 1997; Kaufman, Birmaher, Brent, et al., 1998; Kaufman, Birmaher, Perel, et al., 1998), independent investigations of the effectiveness of SSRI medications in this cohort are sorely needed. In our clinical experience, the efficacy of SSRI medications in depressed abused children is influenced by the comorbid diagnostic profile of the child. In open treatment trials, SSRIs appear effective in children with depression and comorbid PTSD but ineffective for children with comorbid attention-deficit hyperactivity disorder (ADHD). Among sexually abused school-aged psychiatric referrals (McLeer et al., 1994), and representative samples of nonreferred protective service cases (Famularo et al., 1992), rates of ADHD are estimated at slightly greater than 40%. Comparable rates of PTSD have also been reported in these samples (Famularo et al., 1992; McLeer et al., 1994). In our experience, for children with depression and ADHD the utilization of standard ADHD pharmacological treatments (e.g., psychostimulants) is essential. Without them, the child cannot make use of psychotherapeutic interventions addressing abuse issues, and disruptive behaviors tend to promote placement failures. The clinical effectiveness of all pharmacological and psychotherapeutic interventions is compromised in the absence of placement stability.

Conclusion

The problem of child maltreatment is enormous, in terms of its costs to the individual and its cost to society. Despite decades of preclinical research documenting the effects of early stress on the HPA axis, and more recent research demonstrating the impact of stress on brain development, there has been surprisingly little developmentally focused research on the neurobiological sequelae of child abuse. As systems failures and repeat out-of-home placements often complicate the treatment of maltreated children with depression, mutlidisciplinary research and treatment efforts are required to address this problem—with foci that span from neurobiology to social policy.

The neurobiological alterations associated with early stress identified in preclinical studies have important implications for understanding the pathophysiology and treatment of MDD. The studies provide a valuable heuristic for generating hypotheses regarding neurohormonal mechanism, cortical structures, and neural circuits involved in the etiology of depression, and they suggest novel pharmacological interventions that may warrant experimental investigation in clinical samples. Unfortunately, there is a paucity of preclinical studies examining the impact of early stress on prepubescent and postpubescent animals, and little work on the neurobiology of child and adolescent affective disorders. The utilization of a developmental framework in future preclinical and clinical studies will enhance our understanding of maturational changes in the long-term effects of early stress and help to identify the neurobiological mechanisms that link child maltreatment with depression across the life cycle.

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