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Early Adversity and Developmental Outcomes: Interaction Between Genetics, Epigenetics, and Social Experiences Across the Life Span

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Abstract

Longitudinal studies in humans demonstrate the association between prenatal and postnatal experiences of adversity and long-term changes in neurodevelopment. These studies raise the question of how experiences become incorporated at a biological level to induce persistent changes in functioning. Laboratory studies using animal models and recent analyses in human cohorts implicate epigenetic mechanisms as a possible route through which these environmental effects are achieved. In particular, there is evidence that changes in DNA methylation are associated with early life experiences with consequences for gene expression and behavior. Despite the potential stability of DNA methylation, it is apparent that this epigenetic mark can be dynamically modified through pharmacological targeting and behavioral experiences. Developmental plasticity may also be achieved through modification of the juvenile environment. Although these juvenile experiences may lead to common endpoints, there is evidence suggesting that the effects of early and later life experiences may be achieved by different molecular pathways. This review discusses evidence for the role of epigenetic mechanisms in shaping developmental trajectories in response to early life experience as well as the potential plasticity that can occur beyond the perinatal period. These studies have implications for approaches to intervention and suggest the importance of considering individual differences in genetic and epigenetic vulnerability in developing treatment strategies.

Keywords

prenatal, maternal care, juvenile enrichment, DNA methylation, intervention

The experience of adversity during early periods of development predicts later life risk of physical and psychiatric disease. Although the form of this experience can vary dramatically—ranging from exposure to toxins and nutritional restriction to abuse and neglect—the long-term consequences of these exposures are increasingly evident. Moreover, there is evidence that variations in underlying genotype may interact with these environmental events to determine risk or resilience. To understand the pathways through which plasticity in response to early life experiences is induced and persistent effects on physiological, neurobiological, and behavioral outcomes are maintained, we explored the biological substrates of environmental exposures. Consequently, there is emerging evidence that changes in gene expression both within the brain and in peripheral tissues are associated with differences in the quality of the early environment and that these developmental effects are maintained by epigenetic mechanisms that control the activity of genes involved in disease risk and behavioral variation. This review highlights recent evidence from both animal and human studies that implicates the epigenetic regulation of gene expression in sustaining the effects of early life events. The dynamic nature of these epigenetic mechanisms may have important implications when considering the possibility of intervention. There is evidence that the quality of the environment experienced beyond the perinatal period can shift developmental trajectories, and this review explores current evidence regarding the biological mechanisms that mediate the compensatory effects of these experiences and discuss the implications of this research for approaches to treatment.

Evidence for Early Environmental Influence on Human Development

The experiences of a developing organism during both the pre- and postnatal periods can have a profound effect on long-term

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physiological and behavioral functioning. In humans, longitudinal studies indicate that in utero exposure to drugs, nutrient restriction, and maternal psychosocial stress can lead to metabolic and neurobiological abnormalities associated with specific disease states. Impaired cognitive performance has been found in a follow-up of 4-year-old children prenatally exposed to cocaine (Singer et al., 2004), and other teratogens have likewise been found to affect brain development and behavior (Kyle, 2006). Data from the Dutch Famine Study suggest that caloric restriction—particularly during the second trimester—is associated with neurodevelopmental abnormalities that lead to an increased risk of schizoid personality and schizophrenia (Susser & Lin, 1992) as well as broad effects on reproduction and metabolism that lead to an increased incidence of obesity and cardiovascular disease (Roseboom, de Rooji, & Painter, 2006). Maternal stress during pregnancy has been demonstrated to lead to reduced gestational length and birth weight and long-term effects on the hypothalamic-pituitary-adrenal (HPA) response to stress and emotional reactivity leading to increased risk of affective disorders (Lazinski, Shea, & Steiner, 2008; O'Connor, Heron, & Glover, 2002). This is a particularly important clinical concern given that prevalence data suggest that more than 50% of women experience antenatal depression or anxiety associated with increased maternal HPA reactivity (Lazinski et al., 2008; A.M. Lee et al., 2007).

Although rapid changes in brain development occur during the prenatal period that create a sensitive period for the damaging effects of drugs, nutritional levels, and maternal physiology, there is certainly evidence that the quality of the postnatal environment can also exert profound changes in an infant's neurodevelopment. Longitudinal studies of abuse and neglect indicate increased risk of cognitive impairment, social/emotional difficulties, and risk of mental and physical disease (Trickett & McBride-Chang, 1995). Among children exposed to abuse who manifest posttraumatic stress disorder, brain volume is positively correlated with the age at onset of abuse (i.e., early onset trauma is associated with smaller cerebellar and cerebral volumes) and negatively correlated with the duration of trauma (De Bellis et al., 1999; De Bellis & Kuchibhatla, 2006). In adulthood, the experience of childhood maltreatment is associated with increased HPA and immune system activation (Danese, Pariante, Caspi, Taylor, & Poulton, 2007; Heim et al., 2000). Follow-up studies of Romanian orphans who were subsequently adopted have reported similar findings in children raised under conditions of extreme social neglect. Length of time spent in this type of postnatal environment is associated with increased HPA activity and difficulty forming an emotional attachment to adoptive caregivers (Gunnar, Morison, Chisholm, & Schuder, 2001; O'Connor & Rutter, 2000; Rutter et al., 1999).

Neuroimaging studies have suggested decreased neural activity and altered connectivity may account for the long-term cognitive and social deficits associated with early deprivation (Chugani et al., 2001; Eluvathingal et al., 2006). The quality of mother–infant attachment and indices of parental bonding have been found to predict later life risk of psychopathology (Parker, Hadzi-Pavlovic, Greenwald, & Weissman, 1995; Sroufe, 2005). In a comparison of 4-month-old infants whose mothers displayed either high or low sensitivity to infant cues, analysis indicated decreased electroencephalography asymmetry, increased fear response, and elevated levels of observed negative affect among infants of low-sensitivity caregivers (Hane & Fox, 2006). Overall, these studies illustrate that aspects of the early environment can lead to dramatic changes in neurodevelopment and behavior leading to differential risk of physical and psychiatric disorder. The question that remains is how these experiences become incorporated at a biological level leading to long-term alterations in functioning.

Studying the Biological Basis of Environmentally Induced Effects

Although there have certainly been great advances in our ability to study physiological and neurodevelopmental abnormalities in human subjects, more in-depth analyses of the mechanisms driving these changes have come from laboratory studies in rodent models. These studies have identified several target genes that have altered transcriptional activity in response to early life experiences. In rats, prenatal exposure to cocaine has been demonstrated to increase expression of genes involved in promoting apoptosis and decreased expression of brain-derived neurotrophic factor (BDNF; Xiao & Zhang, 2008; Yan, Zheng, & Yan, 2004). BDNF plays an important role in early brain development and neuronal plasticity, suggesting that disruption of the expression of BDNF will induce adverse functional neurobiological outcomes. Prenatal caloric restriction is associated with a "thrifty phenotype" characterized by slow metabolic rate and increased susceptibility to cardiovascular disease and obesity (Gluckman, Hanson, Beedle, & Raubenheimer, 2008). Offspring born to women placed on protein-restricted diets have elevated levels of glucocorticoid receptor (GR) expression in the liver and decreased expression of 11-beta-hydroxysteroid dehydrogenase and insulin-like growth factor (Bertram, Trowern, Copin, Jackson, & Whoorwood, 2001; Gluckman et al., 2008; Muaku, Underwood, Selvais, Ketelslegers, & Maiter, 1995). Gestational stress in rodents is associated with decreased hippocampal GR and increased hypothalamic corticotrophin-releasing hormone (CRH) mRNA in offspring with consequences for heightened HPA responsivity (Kapoor, Leen, & Matthews, 2008; Welberg, Seckl, & Holmes, 2001).

The quality of the postnatal environment has likewise been demonstrated to be associated with long-term changes in gene expression. In rodent models, maternal separation—involving prolonged periods of isolation of pups from mothers—results in increased HPA response to stress and impaired cognitive ability associated with decreased hippocampal GR mRNA, increased hypothalamic CRH mRNA, and decreased BDNF (Lippmann, Bress, Nemeroff, Plotsky, & Monteggia, 2007). Natural variations in maternal care in rodents can, as in studies of human mother–infant interactions, be characterized and associated with changes in offspring brain and behavior. Individual differences in HPA response to stress, cognition, and

social behavior are associated with variations in the frequency of postpartum maternal licking/grooming (LG) of pups (Champagne, Francis, Mar, & Meaney, 2003; Meaney, 2001). Decreased hippocampal GR, elevated hypothalamic CRH mRNA, and decreased hippocampal BDNF mRNA are associated with low levels of maternal LG (Francis, Diorio, Liu, & Meaney, 1999; Liu, Diorio, Day, Francis, & Meaney, 2000; Liu et al., 1997). It is important to note that cross-fostering studies have demonstrated that these maternal effects are related to the level of postpartum care received rather than genetic or prenatal factors (Champagne, Francis, et al., 2003; Francis, Diorio, Plotsky, & Meaney, 2002).

Epigenetic Regulation of Gene Expression in Response to Early Experiences

Although there is certainly a broad range of potential routes through which early life experiences may mediate long-term effects on development, the changes in gene expression that have been highlighted in the previous section raise a critical question: "What mechanisms are involved in regulating the sustained changes in gene expression that are induced by these experiences?" Events occurring during prenatal and postnatal development have effects that persist beyond the period of exposure. These findings suggest the presence of molecular mechanisms that can respond dynamically to environmental cues but that can also maintain stable differences in gene expression. Levels of gene expression are primarily determined by the accessibility of the gene promoter to transcription factors and RNA polymerase. Within the cell nucleus, DNA is typically stored as densely packed heterochromatin, which has limited transcriptional activity. Thus, the process of gene expression requires the induction of a shift in chromatin structure, which permits access of the promotor region to enzymes and proteins that initiate transcription (Turner, 2001). There are several factors that influence the structure—but not the sequence—of DNA to regulate the level of gene expression and are thus referred to as *epigenetic*, meaning "over or above" genetic. In particular, two epigenetic mechanisms have been studied in the context of environmentally induced changes in transcriptional activity: histone modification and DNA methylation. Within the cell nucleus, DNA is wrapped tightly around a core of histone proteins. One of the structural components of these histones is the "histone tail," which extends outside the nucleosome core and physically wraps around DNA. Posttranslational chemical modifications to the histone tails—such as acetylation, methylation, and phosphorylation—can occur, which change the dynamics between DNA and these proteins (Turner, 2001). For example, acetylation leads to a shift in the structure of the nucleosome such that DNA is more accessible. In addition, the DNA itself can be modified to alter transcription. DNA methylation is a chemical modification to cytosines within the DNA sequence, which can result in gene silencing (Razin, 1998; Strathdee & Brown, 2002). The addition of a methyl group to the DNA sequence acts as a physical barrier to transcription factors and attracts enzymes and proteins that further promote reductions in the transcriptional activity of a gene. There are specific regions within a sequence of DNA that can become methylated, which are referred to as *CpG sequences*. These sequences can be found primarily within the promotor region of a gene and thus are well situated to control the level of expression of a gene. DNA methylation also plays an important role in cellular differentiation: providing a mechanism through which a unique pattern of gene activity can be created in different cell types. Patterns of DNA methylation are stable and heritable and thus provide an epigenetic route to long-term differential gene expression.

Studies examining the influence of prenatal exposures on DNA methylation and gene expression in rodents suggest that epigenetic mechanisms are particularly susceptible to environmental regulation during this period. When maternal dietary restriction during pregnancy reduces choline consumption, there are altered patterns of methylation and gene expression in offspring tissue, including effects on insulin-like growth factor 2 and GR (Kovacheva et al., 2007; Lillycrop et al., 2007). Augmenting the amount of methyl donors in the gestational maternal diet also has been found to alter aspects of offspring phenotype associated with methylation status of the Agouti- and Axin-fused gene promoters (Waterland, 2006; Waterland et al., 2006; Wolff, Kodell, Moore, & Cooney, 1998). Prenatal exposure to endocrine disruptors can lead to altered patterns of methylation within the male germline that persist across multiple generations (Anway, Cupp, Uzumcu, & Skinner, 2005). Moreover, supplementing the maternal diet with methyl donors can reverse the damage caused by early exposure to endrocrine disruptors (Dolinoy, Huang, & Jirtle, 2007). Toxins such as methylmercury have been found to lead to hypermethylation of the BDNF gene in the hippocampus of offspring exposed in utero (Onishchenko, Karpova, Sabri, Castren, & Ceccatelli, 2008) and exposure to chronic variable stress during the first trimester is associated with hypermethylation of the GR promotor and increased HPA reactivity as measured by stress-induced corticosterone levels (Mueller & Bale, 2008). These stress-induced epigenetic modifications alter placental gene expression that may lead to the increased susceptibility of males to prenatal insults. Thus, genes such as GR and BDNF appear to be the target of epigenetic modification during prenatal development in response to a variety of chemical, nutritional, and physiological insults.

During the postnatal period of development, there is evidence that the quality of mother–infant interactions is associated with changes in offspring DNA methylation. The postnatal experience of increased levels of maternal LG is correlated with decreased methylation of the GR promotor region in hippocampal tissue corresponding to increased GR expression and an attenuated stress response (Weaver et al., 2004). Cross-fostering studies indicate that these epigenetic modifications occur in response to the postnatal rearing environment and are sustained into adulthood (Weaver et al., 2004). Similar changes to DNA methylation have been found within the estrogen receptor α promotor region in female offspring as a function of maternal care. Elevated expression of estrogen receptor α in the medial preoptic area of the hypothalamus is

associated with exposure to high levels of maternal LG, whereas low levels of LG lead to decreased estrogen receptor α expression (Champagne, Weaver, Diorio, Sharma, & Meaney, 2003). Analysis of the estrogen receptor α promotor region indicates that offspring who have received high levels of maternal care have decreased DNA methylation (Champagne et al., 2006). Moreover, these maternally induced epigenetic effects on estrogen receptor α have implications for the transmission of maternal LG across generations. In mammals, neuroendocrine regulation of maternal care is dependent on estrogen–oxytocin interactions (Keverne, 1988; McCarthy, 1995) involving hypothalamic estrogen receptors (Young, Wang, Donaldson, & Rissman, 1998). Thus, exposure to low levels of maternal LG in infancy is associated with increased DNA methylation and decreased expression of a gene that regulates offspring maternal care. Consequently, there can be a transgenerational effect of maternal care on offspring development associated with the epigenetic regulation of estrogen receptor α (Champagne, 2008). Accordingly, under stable environmental conditions, there is a very high correlation among mother, offspring, and grand-offspring maternal LG (Champagne & Meaney, 2007). Similar transgenerational effects are observed in rats in response to postnatal exposure to abusive caregiving, with methylation levels within the BDNF promotor being particularly susceptible to this adverse early life experience (Roth, Lubin, Funk, & Sweatt, 2009).

Studying Epigenetic Influences on Human Development

Although these animal studies are promising in providing a novel approach to our understanding of the biological basis of prenatal and postnatal effects, it is important to consider the relevance of these mechanisms to neurodevelopment in humans. One approach to studying environmentally induced epigenetic effects in humans is to compare monozygotic twins. Comparison of the gene expression of 3-year-old and 50-year-old monozygotic twins indicates a fourfold discordance among older twins that is associated with increasing differences in DNA methylation and histone acetylation of genes in peripheral blood lymphocyte and other nonneural tissues (Fraga et al., 2005). Further, Petronis et al. (2003) found differential methylation in the promotor region of the dopamine D2 receptor gene in lymphocytes of monozygotic twins discordant for schizophrenia. Methylation mapping of buccal cell samples from 5-year-old monozygotic twins indicates variation in the degree of discordance in methylation status of the promoter region of the catechol-O-methyltransferase gene. Some monozygotic twin pairs showed a high degree of discordance, whereas others were very similar in their epigenetic status (Mill et al., 2006). Although most previous work has focused on how different genetic polymorphisms of genes such as catechol-O-methyltransferase and dopamine D2 receptor may be associated with psychopathology (Kukreti et al., 2006; Shifman et al., 2004), these recent epigenetic studies suggest that the accumulation of epigenetic variation in gene promoters through environmental or stochastic means may account for changes in brain development and risk of mental illness; however, it is yet unknown what particular experiences may drive this variation or the nature of the effect of this variation on neurodevelopment and behavior.

Recent evidence for the epigenetic influence of antenatal mood comes from a study by Oberlander et al. (2008), who explored methylation within the GR promotor in fetal-cord blood samples. Elevated neonatal GR promotor methylation levels were found in infants born to mothers with elevated ratings of depression (using the Hamilton Depression Scale) during the third trimester (Oberlander et al., 2008). Moreover, the methylation of the neonatal GR promotor predicted increased salivary cortisol levels of infants at 3 months of age. These effects were found to be independent of exposure to SSRIs during pregnancy. These data are consistent with rodent data suggesting that perinatal environmental conditions can result in long-term silencing of the GR promotor through DNA methylation and that this epigenetic modification results in changes to HPA responsivity that persists into adulthood (Liu et al., 1997; Weaver et al., 2004). However, it is yet unclear what mechanisms are involved in establishing the link between antenatal mood and changes in DNA methylation and how patterns of methylation within cord blood samples corresponds to methylation patterns in the brain. Although there is in vitro evidence that glucocorticoid-mediated inhibition of inflammation may involve increased DNA methylation (Kagoshima et al., 2001), the effect of glucocorticoids on chromatin remodeling has not been explored in the context of the neurobiology of stress responsivity.

The stability of the covalent chemical bond involved in DNA methylation also permits analysis of this epigenetic modification in postmortem tissue. Analysis of cortical tissue samples from bipolar and schizophrenic patients indicates a general hypermethylation compared with individuals having no history of mental illness (Veldic, Guidotti, Maloku, Davis, & Costa, 2005). In particular, this hypermethylation is within the reelin gene promoter leading to a downregulation of reelin gene expression in various cortical regions (Abdolmaleky et al., 2005; Grayson et al., 2005). Reelin is critical for the process of neuronal migration during early brain development, and disruptions to this gene have been linked to altered cortical layering and schizophrenia-like phenotypes in rodent models (Brigman, Padukiewicz, Sutherland, & Rothblat, 2006; Tueting, Doueiri, Guidotti, Davis, & Costa, 2006). In contrast, hypomethylation of the catechol-O-methyltransferase gene in the frontal lobe has been found in the postmortem brain tissue from schizophrenia patients (Abdolmaleky et al., 2006). Exposure to abuse in infancy has recently been demonstrated to be associated with altered levels of DNA methylation in the hippocampal tissue (McGowan et al., 2009). Suicide victims with a history of childhood abuse were found to have decreased GR expression and elevated GR promotor methylation associated with disruptions of the early environment. Analysis of DNA methylation of ribosomal genes has likewise been reported in hippocampal tissue of suicide victims with a history of abuse and neglect, with a finding of

hypermethylation of ribosomal RNA associated with decreased ribosomal RNA expression among suicide victims (McGowan et al., 2008). This effect was found to be region specific, because hypermethylation was not detected in the cerebellum and was also not simply representative of genomewide hypermethylation. The issue of site- and gene-specific epigenetic modification is incredibly important from both a mechanistic and methodological perspective. Although peripheral tissue samples from subjects may provide some useful insight into the role of DNA methylation in shaping phenotypic diversity, the investigation of environmentally induced effects on neurodevelopment may ultimately require epigenetic analysis of tissue from specific brain regions.

Beyond the Perinatal Period: Plasticity Across the Life Span

Although there are certainly persistent effects of early life experiences, this may not imply that developmental trajectories are insensitive to later life environmental conditions. In the case of DNA methylation, there is evidence that pharmacological manipulation of the epigenome can reverse the effects differential postnatal maternal care. Intracerebroventricular infusion studies indicate that adult offspring who had received low levels of maternal LG in infancy who are then given a 2-week treatment with trichostatin A, a drug that promotes histone acetylation and reduced methylation, can be observed to have decreased hippocampal GR methylation, increased GR mRNA, and decreased response to stress (Weaver et al., 2004). In contrast, adult offspring who had received high levels of maternal LG in infancy can be given a 2-week treatment with methionine, which results in increased availability of methyl groups, and they were observed to have increased hippocampal GR methylation, decreased GR expression and a heightened behavioral response to stress (Weaver et al., 2005). Moreover, the plasticity of these epigenetic mechanisms is not limited to intense pharmacological manipulation. Despite the potential of DNA methylation to exhibit a high degree of stability across the life span, there is recent evidence that dynamic changes in DNA methylation in the adult brain occur in response to specific experiences and that these modifications are an essential part of the process of learning and memory. Researchers have found that in rodents, fear conditioning induces rapid changes in DNA methylation of reelin and BDNF promotor regions with consequent changes in gene expression (Lubin, Roth, & Sweatt, 2008; Miller & Sweatt, 2007). In addition, pharmacological inhibition of the methylation process leads to impairments in memory formation. Thus, the epigenome may be a critical target when considering the incorporation at a biological level of experiences during early development and in later life.

Interaction Between Genetic/Epigenetic Vulnerability and the Juvenile Environment

Perhaps one of the most useful experimental paradigms for exploring the role of later life experiences in shaping development is manipulation of the social and physical environment of juvenile rodents. While standard laboratory housing typically consists of same-gender, same-age animals pair-housed in cages from the time of weaning, juvenile enrichment usually includes housing in larger cages with multiple animals and the addition of running wheels, toys, and other sensory stimuli that increase the complexity of the environment. Rodents housed in enriched environments throughout the juvenile period demonstrate numerous developmental changes, including increased neurogenesis and dendritic branching (Greenough, Volkmar, & Juraska, 1973; Kempermann, Kuhn, & Gage, 1997), improved performance on cognitive measures (E.H. Lee, Hsu, Ma, Lee, & Chao, 2003), and an attenuated HPA and behavioral response to stress (Belz, Kennell, Czambel, Rubin, & Rhodes, 2003). Expression of growth factors such as BDNF and nerve growth factor are elevated within the hippocampus of enriched animals (Pham et al., 1999). The plasticity in transcriptional activity observed in response to these conditions certainly suggests the involvement of epigenetic pathways, and recent evidence suggests that environmental enrichment can induce increased histone acetylation in the hippocampus and cortex (Fischer, Sananbenesi, Wang, Dobbin, & Tsai, 2007).

The plasticity than can occur during the juvenile period in response to environmental enrichment has further been demonstrated in studies in which researchers have examined the amelioration of neurobiological and behavioral impairments that is possible through use of this paradigm. In a classic demonstration of a gene–environment interaction, enriched environments were used to eliminate group differences in cognitive performance among "maze-dull" and "maze-bright" rats (Cooper & Zubek, 1958). Despite genetically derived differences in maze-learning ability, these environmental conditions provided a powerful influence on behavior. More recent studies have implemented these environmental manipulations to delay onset of symptomatology in genetic mouse models of Huntington's disease (van Dellen, Blakemore, Deacon, York, & Hannan, 2000), Alzheimer's disease (Jankowsky et al., 2005) and Fragile X syndrome (Restivo et al., 2005), and to promote recovery following stroke (Buchhold et al., 2007) or CNS damage (Kim, Dai, McAtee, & Bregman, 2008). In addition, Morley-Fletcher, Rea, Maccari, and Laviola (2003) found that postweaning enrichment reduces the HPA reactivity and enhances social behavior of prenatally stressed offspring. Although offspring who have been deprived of maternal contact for prolonged periods during postnatal development typically show heightened neuroendocrine and emotional reactivity, this deficit can be reversed through environmental enrichment (Francis, Diorio, Plotsky, & Meaney, 2002). Cognitive deficits in maze learning among offspring who received low levels of maternal LG during the postnatal period can also be reversed using postweaning social enrichment (Bredy, Humpartzoomian, Cain, & Meaney, 2003; Bredy, Zhang, Grant, Diorio, & Meaney, 2004). Although female offspring who receive low levels of maternal LG would, under standard housing conditions, display low levels of maternal LG and

decreased hypothalamic oxytocin receptor levels, this trajectory is significantly altered when they are provided with social and physical juvenile enrichment (Champagne & Meaney, 2007). Moreover, these environmental effects can be transmitted across generations. For example, offspring exposed to low levels of maternal LG who are then placed in enriched environments display elevated levels of maternal LG, and this increased frequency of maternal care is likewise observed among their own female offspring. This inheritance of phenotype is likely mediated by the behavioral transmission of postpartum maternal care, although there is recent evidence suggesting that the effects of enrichment on experience-dependent plasticity may also be transmitted via prenatal or germline mechanisms (Arai, Li, Hartley, & Feig, 2009).

These studies highlight two important issues in considering developmental plasticity across the life span: (a) the selective effects of later environments dependent on underlying genetic/epigenetic vulnerability and (b) the common versus unique pathways through which early and later environments exert their effects. Although juvenile environments can exert very profound effects on development, these effects are certainly more consistent in vulnerable populations. For example, the huntingtin protein plays an important role in the upregulation of cortical BDNF, whereas among Huntington's disease patients the mutated huntingtin protein is not effective in increasing BDNF transcription (Zuccato et al., 2005). Environmental enrichment, which has been demonstrated to increase BDNF expression, would thus be predicted to exert more pronounced phenotypic changes in this BDNF-compromised group. In the study of environmental effects on maze-learning ability, it is the maze-dull rats that benefit in response to enrichment, whereas maze-bright rats show no enhanced performance in response to these conditions (Cooper & Zubek, 1958). Likewise, rodent offspring who have received high levels of maternal care in infancy show no neuroendocrine or behavioral changes in response to the enrichment of the juvenile environment (Bredy et al., 2003; Champagne & Meaney, 2007). However, this is not to suggest that these individuals have reduced plasticity. Offspring who have received high levels of care in infancy are susceptible to juvenile social isolation and adult stress, and they exhibit significant reductions in social and exploratory behavior in response to these later life experiences (Champagne & Meaney, 2006, 2007). Overall, it is clear that to understand the effects of environmental conditions in later life, there must be a thorough analysis of the developmental trajectories predicted by genetic and epigenetic risk factors.

The variation in phenotype that is achieved through the influence of the juvenile environment does not necessarily involve the same neural mechanisms that mediate the effects of early environments; however, there may certainly be common endpoints. In the case of mouse models of Huntington's disease, the increase in BDNF in response to environmental enrichment is not achieved through reversal of the mutation in the huntingtin gene but rather through other regulatory pathways that lead to transcriptional upregulation of BDNF (Spires et al., 2004). Social enrichment was not found to affect the elevated levels of hypothalamic CRF and decreased levels of hippocampal GR mRNA found in maternally separated male subjects (Francis et al., 2002). Hippocampal N-methyl-D-aspartate receptor binding in the offspring of low-LG mothers was also not altered by these postweaning manipulations (Bredy et al., 2003; Bredy et al., 2004). Although enrichment results in an increase in oxytocin receptor density in the hypothalamus of female subjects (Champagne & Meaney, 2007), it is not yet known whether these effects are achieved through differential methylation of estrogen receptor α. Although plasticity in later life certainly exits, the mechanisms that mediate the long-term effects of these experiences may differ from those that operate at earlier developmental timepoints, suggesting that compensation—rather than reversibility—may be an effective strategy for intervention.

Implications for Plasticity and Behavioral Intervention

Although laboratory studies provide strong evidence for the potential to shift developmental trajectories through later life experience, the question of how to apply these findings to the context of human intervention and treatment remains. However, data from adoption studies suggest that cognitive deficits, impairments in emotional regulation, and HPA sensitivity in response to early life adversity can be ameliorated, to varying degrees, through significant environmental manipulation. Preschool children who have experienced maternal environments characterized by maltreatment are at a high risk of experiencing emotional problems and disruptions of the HPA axis. However, if these children are placed in foster care environments in which positive parenting strategies are being used, there are significant improvements on measures of behavioral adjustment, decreases in salivary cortisol, and reestablishment of normal diurnal rhythms of cortisol release (Fisher, Gunnar, Chamberlain, & Reid, 2000; Fisher, Stoolmiller, Gunnar, & Burraston, 2007). In randomized clinical trials, cortisol levels among foster children were found to decrease in response to a relational-based intervention that is focused on attachment compared with those among foster children receiving an intervention intended to enhance cognitive skills (Dozier, Peloso, Lewis, Laurenceau, & Levine, 2008). Analysis of developmental catch-up in postinstitutionalized adoptees indicates that removal from socially impoverished environments is associated with increases in secure attachment to the adoptive caregiver and increases in cognitive functioning (van IJzendoorn & Juffer, 2006; van Londen, Juffer, & van IJzendoorn, 2007). Although recovery is often found to be limited, particularly among those individuals with prolonged exposure to institutionalized settings, there is still significant evidence for improved functioning among adoptees.

An important consideration in the design and implementation of intervention programs in these high-risk populations may be an understanding of the underlying genetic/epigenetic vulnerabilities of these individuals. As illustrated in laboratory studies of rodents, the nature of the response to later life

environments may depend on underlying biological risk factors such as site-specific changes in gene expression, which may be mediated by genetic mutation/variation or stable epigenetic regulation. On the basis of our increasing knowledge of the stable yet dynamic mechanisms through which early life adversity becomes incorporated at a molecular level, it may be possible to approach the process of intervention from an epigenetic perspective. The application of this perspective to human therapeutic intervention may provide an opportunity to design more effective strategies to promote recovery following early life adversity.

Summary and Future Directions

Converging evidence from studies of human subjects and animal models suggests that experiences across the life span can exert persistent changes in gene expression and behavior (Fig. 1). Exploration of the role of epigenetic mechanisms in sustaining environmentally induced modifications in transcriptional activity suggests that DNA methylation may serve as a cellular memory of these experiences. The dynamic yet stable nature of these heritable epigenetic marks implies the potential for phenotypic plasticity in response to environmental cues. Behavioral paradigms that incorporate a broad range of environmental conditions in later life illustrate that this plasticity is indeed possible but may involve unique mechanisms or alternative pathways at different periods in development. The potential to shift developmental trajectories that has been established in laboratory studies may have important implications for the strategies used to intervene to prevent the developmental consequences of early life adversity.

Our understanding of the nature of epigenetic responses to environmental exposures, particularly aspects of the social environment, is developing rapidly yet is still very much in its infancy. To better appreciate the role of these molecular changes in shaping human development, we will first need to explore the relation between peripheral environmentally induced epigenetic modifications and those changes occurring in the brain in order to determine whether biomarkers available from human cohort studies will be useful in predicting neurobiological epigenetic outcomes. The application of these measures to longitudinal studies, in which detailed characterization of social, physical, nutritional, and toxicological environmental exposures is combined with measures of the stability and change of epigenetic marks throughout development, would provide an opportunity to address critical questions regarding the shifting epigenetic landscape. Overall, this approach would enhance our understanding of the interplay among genetics, epigenetics, and environmental experiences and possibly lead to a more integrated notion of the biological basis of risk and resilience.

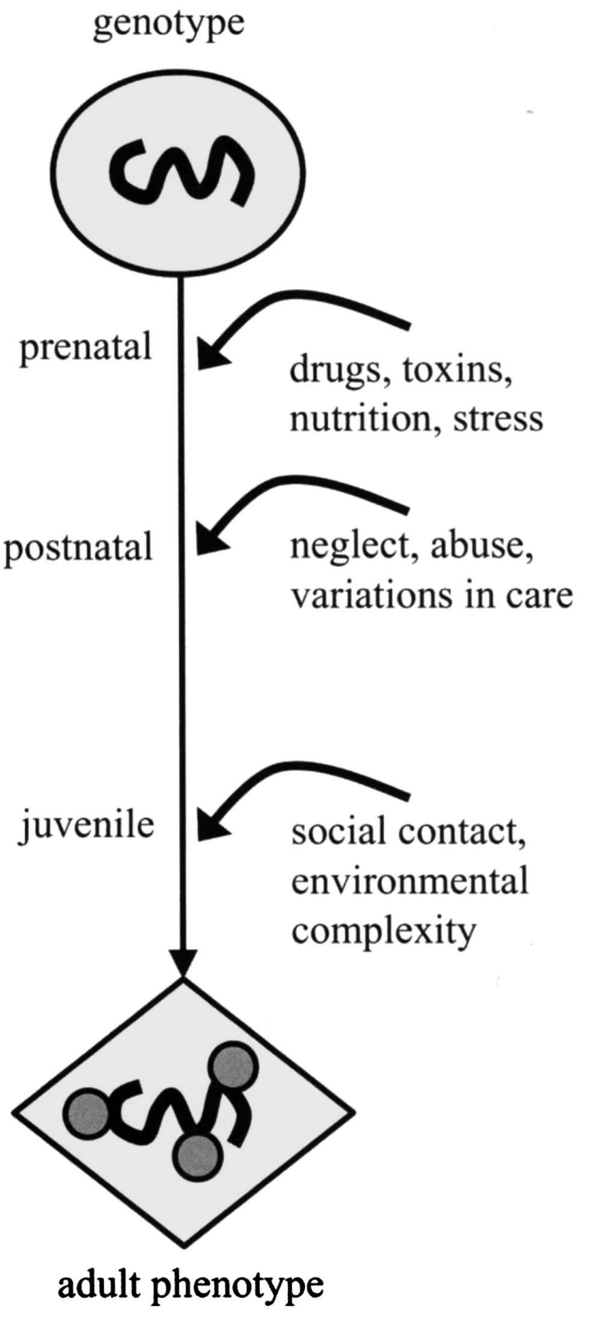

Fig. 1. Potential influences during the prenatal, postnatal, and juvenile periods of development on the pathway from genotype to adult phenotype. Although experiences across the life span may not change the underlying genotype (*coiled black line*), through DNA methylation (*round gray circles*) there may be stable changes in the functioning of the genotype in response to environmental experiences that lead to variations in adult phenotype.

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