

Using Principles of Behavioral Epigenetics to Advance Research on Early-Life Stress

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ABSTRACT—*While the negative effects of early-life stress on children’s developmental outcomes are well documented, we know little about how these processes unfold and which children are more susceptible to these exposures. In this article, I outline how studying the effects of early-life stress on children’s development can be advanced by considering how epigenetic processes may contribute to the emergence of children’s behavior. The study of epigenetics can help pinpoint the mechanisms by which early-life stress may affect developmental outcomes and identify which children may be most sensitive to the effects of these exposures. I conclude by highlighting the challenges inherent in studying epigenetics in children and offer possible solutions.*

KEYWORDS—*behavioral epigenetics; early-life stress; DNA methylation*

In the United States, at least 16 million children under age 6 experience stress early in life, ranging from abuse to neighborhood violence (1, 2). Children living in poverty are disproportionately affected by stress early in life: They are more likely to experience high levels of maternal stress in utero, have low birth weights, and experience more neighborhood and family violence

and household chaos; in addition, they are less likely to be cared for by a nurturing adult, and their caregivers are more likely to have a psychiatric problem (3), compared to their counterparts who are not raised in poverty. Exposure to childhood adversity, such as maladaptive family functioning, may account for as much as a third of adult-onset psychiatric disorders, including depression and posttraumatic stress disorder (4). Experiencing these stressors directly or indirectly can immediately affect children’s physiological and behavioral functioning, or these early exposures can lie dormant, expressing themselves years later (2). However, these findings do not tell us *how* this process unfolds and, even more puzzling, why some children raised in high-stress environments appear relatively unaffected, at least at the behavioral level. At the population level, on average, early childhood is a sensitive period for the effects of stress on development. Yet at an individual level, the effect of exposure to stress on children varies considerably. In other words, some children are apparently resilient to the factors that frequently affect other children in dramatic and damaging ways at the population level. *How* can these apparently discrepant results hold true? At a mechanistic level, the answer may lie in the study of epigenetics.

The application of epigenetic principles to developmental science is rare. Although new, it promises to advance the field of child development and research on the effects of early-life stress in several important ways. First, epigenetic processes may be one way early-life stress becomes biologically embedded, altering how children respond physiologically and behaviorally to stress (5, 6). Second, epigenetic tools may help us identify *for whom* early-life stress exerts a particularly pernicious toll, identifying which children are more sensitive to the effects of early exposure to stress.

In this article, I argue that developing these sensitivities may begin in utero, and understanding this development may help us uncover the origins of individual differences in how children respond to stress. I also discuss problems in the field of developmental behavioral epigenetics and suggest ideas for research. First, I provide a brief overview of epigenetics.

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A BRIEF OVERVIEW OF EPIGENETICS

In the absence of any unusual environmental event (e.g., exposure to radiation) that may cause specific cells to mutate, the sequence of an organism's DNA will not change over the course of its lifetime. So why do some identical twins, who share the same genetic code, look and behave differently? The answer may lie in the study of epigenetics, broadly defined as modifications to the DNA that do not alter the sequence of DNA itself (7, 8). Precisely how do epigenetic processes unfold? Epigenetic mechanisms include but are not limited to histone modifications (the binding of molecules to histone proteins, which cause the DNA to unravel and become more accessible to transcription factors), genomic imprinting, and DNA methylation. I focus here only on DNA methylation because histone modifications and genomic imprinting are relatively understudied in behavioral epigenetics (for a discussion on using genomic imprinting in fetal programming and research on early-life stress, see 9).

Furthermore, research on histone modifications is rarely used in behavioral epigenetic research, in part, because histone modifications are unstable and difficult to characterize in people.

DNA methylation is by far the most prolific mechanism in research with humans, in part, because of the ease of measuring peripheral cells and because it is relatively stable compared to histone modifications. DNA methylation is modifiable throughout life, though we do not know whether experiences have a stronger impact on DNA methylation during sensitive periods than at other points in development.

DNA is made up of four nucleotides: cytosine, guanine, adenine, and thymine. Gene expression typically occurs in a region of the gene called a promoter, where many cytosine and guanine nucleotides cluster. These clusters are called CpG islands. DNA methylation occurs when a methyl molecule is added to a cytosine preceding a guanine along this gene promoter. When a methyl molecule is added to cytosine in the promoter region, this typically blocks transcription, and therefore is more likely

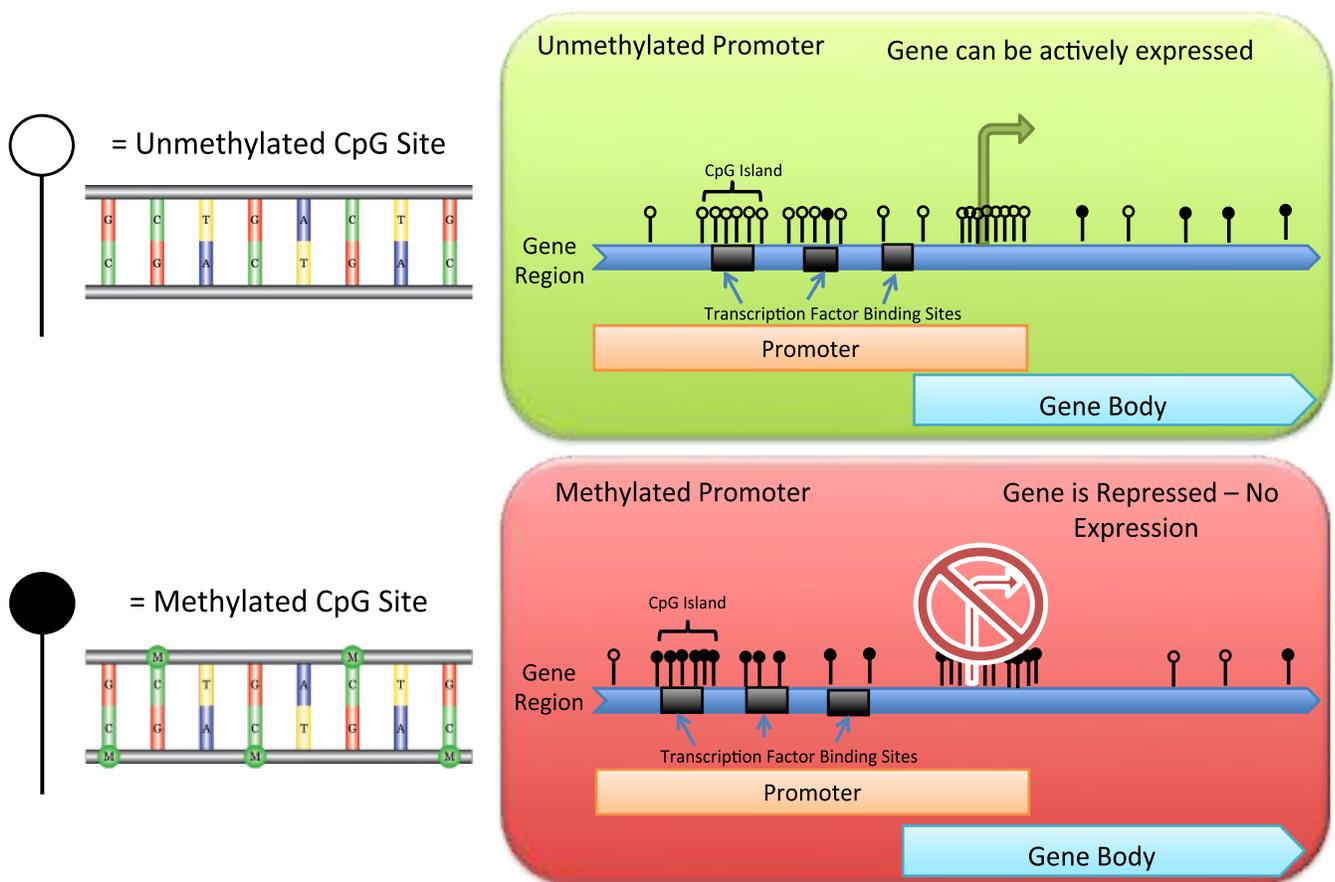


Figure 1. Effects of DNA methylation in the promoter region on gene expression.

Note. Upper panel depicts unmethylated CpG dinucleotides (open circles) with the absence of methyl molecules attached to cytosines. This allows access to transcription factor binding sites and gene expression in the promoter region. Lower panel depicts methylated CpG dinucleotides (filled circles) and methyl molecules attached to cytosines. This blocks transcription factor binding and the repression of gene expression. Adapted from Lester et al. (35).

to turn off the anticipated activity of that gene (Figure 1). Methylation in other regions of the genome (e.g., the gene body) may stimulate gene expression (10).

DNA methylation does not necessarily lead to a behavioral outcome (11). In many instances, DNA methylation has no functional significance, resulting in behavioral changes only when methylation occurs on or near a transcription factor binding site (12), because transcription factors ultimately induce gene expression. This idea is important for developmental researchers because it suggests we should select, a priori, specific CpG sites that are on or near transcription factors rather than examining all possible CpG sites on a region of a gene, thus reducing the number of comparisons per study. DNA methylation can also occur outside the CpG context, but its function is less well defined and has not been studied as it relates to human behavior. In addition, other mechanisms, such as neuron growth and branching, can result in different phenotypes independent of epigenetic processes.

In their introduction to the field of developmental behavioral epigenetics, van Ijzendoorn et al. defined child development as “experiences being sculpted in the organism’s DNA through methylation” (13, p. 305). For children growing up in stressful conditions, DNA methylation is one of the major mechanisms that may lead to psychological and physical disease. Thus, early-life stress may result in changes in DNA methylation that in turn may lead to psychological and physical disease (Figure 2).

EPIGENETIC PROCESSES MAY HELP EXPLAIN HOW EARLY-LIFE STRESS BECOMES BIOLOGICALLY EMBEDDED

Much attention has been paid to how early-life stress can become biologically embedded to affect disease outcomes. Many researchers assert that an experience has been biologically embedded when an association is found between a stressor (broadly defined) and a physiological marker. Although certainly compelling, we know little scientifically about *how* these processes occur. One mechanism may be epigenetic (5, 6).

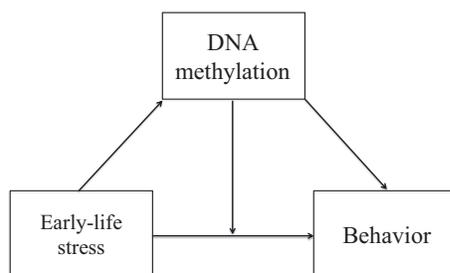


Figure 2. DNA methylation as a moderator and mediator of early-life stress on behavioral outcomes.

Note. Early-life stress encompasses the prenatal and early childhood developmental periods.

Some of the most important evidence for epigenetic mediators of disease outcomes stems from the work of Meaney et al. with rodents (14). In this work, frequent maternal licking and grooming and arched-back nursing led to lower levels of DNA methylation in Exon 1_F of the promoter region of the glucocorticoid receptor gene, *NR3CI*, which in turn resulted in greater expression of glucocorticoid receptors and improved efficiency of the hypothalamic–pituitary–adrenal (HPA) axis (which regulates the amount of stress hormone cortisol releases in our bloodstream). This region corresponds to the most widely studied region of the *NR3CI* gene in humans, Exon 1_F, and correlates with expression of the *NR3CI* gene (15). Compared to rats whose mothers lick and groom them infrequently, the offspring of mothers who frequently lick and groom their young appeared less stressed and anxious, explored more, and were less reactive in terms of cortisol when placed in novel environments. These results generated excitement in the scientific community and researchers have tried to translate the research to humans through experiments that partially replicate the original study in human children (16–19). But an inherent difficulty of translating this work is that studies of rats can examine the brain, while studies of humans must use peripheral tissues (e.g., from buccal cells or blood).

In 2008, Oberlander et al. provided the first evidence for this partial replication in infants exposed to maternal depression in utero (17). Three-month-olds of mothers with many symptoms of depression during pregnancy had greater cord blood methylation of Exon 1_F of the promoter region of *NR3CI*, and in turn greater levels of cortisol reactivity to an arm restraint procedure. In an independent study (16), placental DNA methylation of specific CpG sites of Exon 1_F of the promoter region of *NR3CI* were also related to greater cortisol reactivity in response to a social stressor when infants were 5 months old, and in turn less optimal behavioral self-regulation in response to this task.

Abuse experienced early in life is an extreme form of caregiving stress with devastating consequences for the behavioral and psychological health of children. These effects also manifest at the level of the epigenome. In 11- to 14-year-olds, greater methylation of specific CpG sites of Exon 1_F of the *NR3CI* promoter was related to physical abuse (19). These findings were replicated in an independent laboratory and sample, and extended to show that, among maltreated preschoolers, greater methylation of Exon 1_F of *NR3CI* mediated the effect of maltreatment on internalizing behavior among 3- to 5-year-olds, providing the first evidence in children of epigenetic processes as mediators of later problem behaviors (18).

Few translational studies with children have measured the behavior of caregivers as a potential proxy for licking and grooming. Gunnar and Loman (20) suggested that maternal sensitivity may be analogous to rat licking and grooming given that both regulate and even buffer infants’ responses to stress. To test this hypothesis, my colleagues and I examined whether maternal sensitivity, maternal depression (which is typically highly correlated with maternal sensitivity), or both are directly related to

DNA methylation of Exon 1_F of the *NR3C1* promoter (21). We found that the combined effects of maternal sensitivity and maternal depression predicted DNA methylation of specific CpG sites of *NR3C1*. What mattered most with respect to DNA methylation was whether the infant was raised by a caregiver who was both insensitive *and* had many symptoms of depression. Mothers who had high levels of depressive symptoms *and* who were less sensitive had infants with greater methylation of *NR3C1*, potentially reflecting less optimal functioning of the HPA axis, compared to infants of mothers who had high levels of depression but interacted sensitively with their infants. In humans, who are raised in more complex environments than laboratory rats, the associations between parenting and methylation may be less straightforward. The diversity of the parenting environment, as well as the temperamental traits of the infant, need careful study. Researchers should also consider the potential protective effect of maternal sensitivity as a buffer for the effects of exposure to maternal depression, which can be studied at the level of the epigenome.

DNA methylation, particularly in the glucocorticoid receptor gene, may be one mechanism linking early-life stress to biobehavioral reactivity and self-regulation. The behavioral epigenetic research addresses in more detail theories about *how* early-life stress and even toxic stress affect physiological systems associated with reactivity and self-regulation, and in turn human behavior. However, not all forms of early-life stress are the same, and stress that affects the caregiving environment may predict methylation more potently than more distal forms of stress that target psychosocial or prenatal processes (22).

EPIGENETIC PROCESSES MAY BE USED TO IDENTIFY WHO IS MOST SUSCEPTIBLE TO THE EFFECTS OF EARLY-LIFE STRESS

Compared to mediation research, less attention has been paid to the study of epigenetic processes as moderators or markers of early exposure to stress. Researchers have long been interested in identifying genetic moderators in $G \times E$ interactions, and a growing body of research suggests that epigenetic moderators may be operating, too (23). This research can help us identify *for whom* early stressful experiences may be problematic, that is, who is most susceptible to the effects of early-life stress.

Only four studies with humans have examined epigenetic processes as moderators of early-life stress on behavioral outcomes (23–26). We wondered whether the effect of exposure to prenatal maternal depression on newborns' behavior depended on DNA methylation of *NR3C1*, given that methylation of this gene may be related to altered neuroendocrine responses to stress (24). In our study, mothers reported whether they were depressed prenatally, DNA methylation was assessed via the placenta, and newborn behavior was examined using the NICU Network Neurobehavioral Scale at birth. Exposure to prenatal depression was associated with less self-regulation, more

lethargy, and hypotonia (low tone or floppiness) in newborns, but only if the infants had high levels of methylation of a specific CpG site of *NR3C1*. In other research with epigenetic moderators, the effect of birth status (infants born at term vs. those born preterm) on temperamental indicators (duration of orienting and approach) depended on DNA methylation of the serotonin transporter gene *SLC6A4* (25). Only preterm infants with greater methylation of *SLC6A4* had poorer attention and were more inhibited.

In related work, van Ijzendoorn et al. (23) identified a Gene \times Epigenome interaction: A variant (*ss*) of the serotonin transporter gene predicted more unresolved loss or trauma in adulthood, but only among individuals with lower levels of DNA methylation in the serotonin transporter. Methylation of the oxytocin receptor gene *OXTR* interacted with a history of abuse to predict depression or anxiety (26). Findings were mixed, with abuse predicting more depression and anxiety in individuals with low methylation at a particular CpG site, while greater methylation at other sites was related to greater depression and anxiety among adults with histories of abuse. This work suggests that epigenetic processes should also be considered as moderators, and not simply as mechanisms of exposure on a particular maladaptive outcome. Thus, the impact of prenatal exposure to maternal depression on newborns' behavior may depend on epigenetic processes.

Research on epigenetic moderators could help identify the origins of individual differences in reactivity to stress. According to the theory of differential susceptibility (27), a fetus that is particularly susceptible to the environment may have more methylation in genes depending on environmental inputs received in utero. These inputs may include exposure to maternal stress hormones such as cortisol (28). This response may be adaptive even if the fetus is exposed to high levels of maternal stress in utero because it may prepare the fetus for the type of environment in which he or she will be raised (27). No direct test of this process exists in humans or animals; studies that examine prenatal associations between stress and epigenetics test this hypothesis only indirectly. In fact, few studies have examined epigenetic effects prenatally. And few researchers have examined prenatal epigenetic effects, possibly because of the challenges collecting placental data; as this field grows, I anticipate more prenatal effects will be uncovered.

CHALLENGES IN THE FIELD OF EPIGENETICS AND POTENTIAL SOLUTIONS

Epigenetic research as it applies to human behavior is just beginning. Several challenges must be addressed if we are to apply this method appropriately to research on child development:

An Overreliance on Candidate Genes

Despite exceptions (5, 29), most epigenetic research with children relies on candidate genes, particularly *NR3C1*. Given the

complexity and plasticity of human behavior, many additional genes and CpG sites should be analyzed. Researchers may want to focus on genes involved in specific physiological systems of interest, such as the neuroendocrine system.

Need for Studies of Normative Developmental Trajectories

We know little about the typical trajectory of DNA methylation, though we would expect methylation to increase over time (30). Researchers should identify typical trajectories to find patterns that deviate from this trend and possibly predict disease outcomes.

Tissue Type

All of the published studies examining epigenetic effects with children have used peripheral tissue (e.g., the placenta, buccal cells, or blood) to infer that similar epigenetic processes occur in the brain. However, using these peripheral measures is potentially problematic because they may not parallel neural tissue.

Independent Replication

We have learned from research on molecular genetics the importance of independent replication, ideally in different populations and laboratories. This is important because some epigenetic studies may have reported false positives (i.e., Type I errors), whereas other studies may have reported false negatives (i.e., Type II errors; 31, 32).

Measuring Phenotype

Behavioral epigenetic researchers need to associate an epigenetic process with a phenotype of interest (e.g., temperament or stress reactivity). Until we can measure these behavioral and physiological traits more precisely, it will be difficult to measure associations between epigenetic processes and these traits.

Assumptions of Causality

It is tempting to assume that a particular early-life stressor causes epigenetic changes in a child. However, we cannot assume causality without intervention research (and even then, claims of causality may be dubious). If a goal of epigenetic research in humans is to inform mechanisms of disease expression to guide intervention, then we may not be able to conclusively identify epigenetic mediators unless we conduct intervention work to determine if our intervention affected the proposed mechanism.

CONCLUSIONS

Exposure to early-life stress is a major public health concern affecting physiological, behavioral, cognitive, and emotional aspects of human functioning, and leading to a variety of diseases ranging from diabetes to depression (2). It is time to target specific mechanisms and markers of this exposure and one of the most promising processes to do so is epigenetics. Therefore,

epigenetic research can advance research on early-life stress because epigenetic processes may help explain *how* early-life stress becomes biologically embedded and which children are most susceptible to this stress.

Policymakers may want to consider how epigenetic findings in research on early-life stress can inform social policy. As detailed in a Canadian report to policymakers (6), people may be more inclined to support policies to ameliorate children's exposure to early-life stress if they understand how this exposure is linked to later problematic health outcomes, and particularly if the link has a strong biological basis. In the United Kingdom, epigenetic research is shaping social policy, with such studies influencing guidelines on prenatal nutrition for low-income women (33). In the United States, where policymakers emphasize the importance of early childhood education beginning at age 3 on later outcomes, research on early-life stress suggests that by that age, many physiological systems underlying self-regulation have been shaped in part by epigenetic processes (17, 18, 21). In light of the research I have presented, investing in programs to ameliorate exposure to early-life stress prenatally or in infancy should be an important priority (34).

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