

Conceptualizing Child Health Disparities: A Role for Developmental Neurogenomics

abstract

Biological, psychological, and social processes interact over a lifetime to influence health and vulnerability to disease. Those interested in studying and understanding how and why racial/ethnic and social disparities emerge need to focus on the intersection of these processes. Recent work exploring molecular epigenetic mechanisms of gene expression (in humans as well as other mammalian systems) has provided evidence demonstrating that the genome is subject to regulation by surrounding contexts (eg, cytoplasmic, cellular, organismic, social). The developing stress axis is exquisitely sensitive to regulation by social forces represented at the level of the epigenome. Old assumptions about an inert genome are simply incorrect. Epigenetic processes may provide the missing link that will allow us to understand how social and political conditions, along with individual subjective experiences, can directly alter gene expression and thereby contribute to observed social inequalities in health. Developmental neurogenomics may provide the direct link between the biological and social/psychological worlds. These biological mechanisms of plasticity (at the level of gene expression and regulation) may play a profound role in how we conceptualize health inequalities by informing our concepts regarding the somatization or embodiment of social inequalities. *Pediatrics* 2009;124:S196–S202

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KEY WORDS

disparities, development, stress, epigenetics

ABBREVIATIONS

SES—socioeconomic status

HPA—hypothalamic-pituitary-adrenal

CRF—corticotropin-releasing factor

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Biological, psychological, and social processes interact over a lifetime to influence health and vulnerability to disease. A wealth of epidemiologic data have documented the relationship between socioeconomic status (SES) and health, with low-SES groups faring most poorly across multiple health-outcome measures.¹ The probabilistic relationship between social phenomena and biological vulnerability seems to be in direct contrast to the commonly shared belief that the fixed genome (or genotype) plays a larger “deterministic” role in health outcomes. Indeed, a common approach to understanding disparities by exploring “social” and “biological” factors as independent agents divorced from one another has been extremely limiting. The ubiquitous study of gene \times environment interactions provides a ready example. The assertion is made that vulnerability for a given outcome measure is caused by the interaction of genes with environments, the classic nature-versus-nurture debate. Inherent in the framing of this equation is an unacknowledged directionality; genes come first in time and environments then act on them, resulting in a given vulnerability. Equally plausible but rarely explored at a molecular or mechanistic level is the hypothesis that environmental factors are acting on the genome to create differences in vulnerability (or resilience). The same variables are factored into the equation; however, the function can now be described as an environment \times gene interaction.

Recent work exploring molecular epigenetic mechanisms of gene expression (in humans and other mammalian systems) has provided evidence that the genome is subject to regulation by surrounding contexts (eg, cytoplasmic, cellular, nutritional, organismic, and sociopolitical). Environments are capable of regulating how genes are

expressed. Epigenetic processes may be the key to understanding how forces distal to an individual, such as social and political conditions, along with more proximate individual (subjective) experiences can directly alter gene expression and thereby contribute to observed social inequalities in health. The very recent and powerful new results demonstrating that the epigenome is subject to environmental regulation could provide the direct link between the biological and social or psychological worlds. Understanding how genes are differentially regulated by experience will play a profound role in how we conceptualize health inequalities by informing our concepts of the somatization or embodiment of social inequalities. As our knowledge of epigenetic processes grows, so too does our capacity to develop early-life interventions to prevent and mitigate child health disparities.

PLASTICITY OF THE GENOME

Ecological models and theories of human health that emphasize the interaction of biological, behavioral, and environmental determinants are plentiful. In reality, however, few truly multilevel research programs or projects translate at a practical level. For those studying the genome, imagining the ways in which social and societal forces might alter how genes are regulated and expressed seems formidable. Conversely, those who are interested in social disparities might find it fantastical to assume that a working knowledge of biological mechanisms, such as gene regulation and gene expression (ie, genomic plasticity), might directly inform how they fundamentally conceptualize the embodiment of social experience.

For many social scientists a working knowledge of genetics is limited to a classical mendelian perspective; genes are the physical units of heredity, they

are transmitted across generations, alleles are different “versions” of a gene (they exist in 2 forms; dominant or recessive), and a given genotype is related to an observable phenotype. This view of genetics has expanded dramatically since the early 1900s, yet most scientists who do not work at the level of the genome have had little or no exposure to recent findings in the field. As a consequence, we remain saddled with the antiquated central dogma that (1) the flow of information is unidirectional, from genes to environment, and (2) biological vulnerabilities are classically inherited (in contrast to being created by “vulnerable” environments or experience).² This limited perspective of the genome has had a large influence on the theoretical framework of many academic disciplines. Table 1 shows the units of study or focus for some classic academic disciplines.

The number of genes predicted (by molecular biologists and geneticists) to exist in the human genome was far higher ($\sim 150\,000$) than the number reported ($\sim 25\,000$) in the first draft of the Human Genome Project report.^{3,4} To provide an example, humans and the worm *Caenorhabditis elegans* have a similar number of genes, 20 000 to 25 000, despite large differences in organism size and complexity. Both species have significantly fewer genes than the corn plant, which has 40 000.⁵ Clearly, humans are greater than the sum of their genes. The emerging field of epigenetics focuses on the study of changes in gene expression that are not caused by changes in DNA sequence.⁶ The epigenome consists of DNA marks and modifications that control gene expression.⁷ The epigenome is innately plastic and can be programmed or reprogrammed by environmental experiences such as nutrition and stress.^{8–10} These epigenetic mechanisms provide the means

TABLE 1 Focus of Classic Academic Disciplines

Academic Discipline	Focus	Environment
Genetics	Gene transmission and genotypes	Cell nucleus, DNA
Molecular and cellular biology	Gene-cell regulation	System, cell, RNA, and DNA
Neuroscience	Nervous system and neurons	Brain
Medicine	Individual diseases	Individual person
Psychology and social psychology	Behavioral and individual differences	Individual person or animal and social space (SES, gender, race)
Sociology	Group processes	Individuals in groups
Ecology	Organisms and their environment	Physical world
Public health	Health protection, promotion, and restoration	Populations
Public policy	Effects of government decisions and indecision	Decision-making bodies

through which social experiences can fundamentally and profoundly alter the regulation and expression of the genome without altering genotypes. Epigenetic processes are extremely active during early developmental windows when a young organism is growing. The epigenome, therefore, is extremely sensitive to dysregulation during early development when DNA synthesis rates are highest.⁷

The environment column in Table 1 helps in visualizing and understanding how environmental characteristics at every level (individual, family, community, etc) can potentially affect genome regulation. Again, the salient role of early life experiences is evident. We begin to mechanistically understand how both biological vulnerability and resilience can emerge from differences in the social experience.

STRESS AXIS AS A LOCUS OF VULNERABILITY OR RESILIENCY

Stress is a risk factor for several illnesses such as cardiovascular disease, type 2 diabetes, and depression.¹¹ The pathways through which stressful events can promote the development of such divergent illnesses and compromised health seem to be mediated by activation of the same systems that ensure survival. Activation of the hypothalamic-pituitary-adrenal (HPA) axis in response to stress is a basic adaptive mechanism

in mammals. This response governs the metabolic and cardiovascular responses to the challenges of everyday stressors and those associated with more prevailing chronic stress.

During stress, the hypothalamus (in the brain) releases corticotropin-releasing factor (CRF). CRF provokes the release of corticotropin from the pituitary gland, which, in turn, causes the release of glucocorticoids from the adrenal gland.¹² The highly catabolic glucocorticoids act in synergy with catecholamines to produce lipolysis, glycogenolysis, and protein catabolism, which result in increased blood glucoses. These processes contribute to the survival of an organism during stress, in part by increasing the availability of energy substrates.¹³

Prolonged exposure to elevated stress hormones, however, can become problematic. Glucocorticoids, along with catecholamines, promote the suppression of anabolic processes, muscle atrophy, decreased insulin sensitivity, hypertension, amenorrhea, impotence, and impaired tissue repair. Cognitive and emotional states also change during stress.¹¹ CRF release in the brain activates pathways that enhance vigilance when the organism is challenged. Again, activation of these pathways is quite adaptive under acute challenge or stress, but continued activation of these circuits can

lead to impairments.¹⁴ Increased “wear and tear” on an organism that is subjected to repeated challenge or stress might chronically tax the HPA axis and ultimately lead to disease vulnerability (both mental and physical).

DEVELOPMENTAL PLASTICITY OF THE STRESS AXIS

The quality of early family-life events can influence the health of human, nonhuman primate, and other mammalian offspring throughout their lifetimes. Rodent models provide the best demonstration of parental calibration of the developing stress axis in young animals. In the rat, variations in maternal care are associated with the development of differences in behavioral and endocrine responses to stress in the offspring. Naturally occurring variations in maternal licking (the largest source of tactile stimulation) are associated with the development of individual differences in the HPA axis and behavioral responses to stress in the offspring.^{15,16} As adults, offspring of high-licking mothers are behaviorally less fearful and exhibit a more modest HPA-axis response to stress than offspring of low-licking mothers.¹⁶ High-licking adult offspring have lower corticotropin and corticosterone responses after an acute challenge or stressor than low-licking adult offspring. These responses are believed to be mediated, in part, by differential regulation and expression of the glucocorticoid receptor gene in the brain. Extremely relevant is the plasticity inherent in the quality of parent-offspring interactions. The simple procedure of rat pup cross-fostering at birth is sufficient to reverse the phenotypes described above. Rat pups born to a high-licking mother but reared by a low-licking mother exhibit stress reactivity as adults that are indistinguishable from that of offspring born to and reared by a low-licking mother.

Conversely, offspring born to a low-licking mother but reared in a high-licking and grooming maternal environment exhibit stress-reactivity profiles of offspring born to and reared by a high-licking mother.^{17,18} The simple environmental intervention (adoption) affected not only the existing generation of animals growing up but also subsequent generations.

The cross-fostering of offspring early in life alters adult behavioral, hormonal, and neurobiological profiles. This finding suggests that the quality of maternal care early in life is directly involved in the development and programming of the HPA axis. Events or experiences that alter maternal care are thus capable of directly altering the development of the offspring. High-licking mothers (characterized while rearing a first litter) subjected to stress during gestation for a second litter exhibit decreased licking profiles once offspring are born. Thus, these offspring are reared under low-licking conditions and, as adults, exhibit exaggerated stress-reactivity profiles.¹⁹

Early postnatal experiences can calibrate the developing brain and neuroendocrine axis in expectation of future similar environments. The HPA axis profiles described above persist into adulthood and old age if environmental conditions remain stable.^{20,21} Very recent findings using the laboratory rat as a model report that differences in early life events are specifically altering the epigenetic processes that regulate expression of the glucocorticoid receptor in the brain. The genotypes of the developing animals are intact; however, their epigenomes are dramatically altered.^{22–24}

RACIAL/ETHNIC DISPARITIES AND THE STRESS RESPONSE

Conceptualizing race as a product of environment × gene interactions

(mediated by epigenetic processes) allows us to retreat from the discourse that focuses on biological or psychosocial vulnerabilities. An understanding of developmental neurogenomics allows us to transcend this debate and readily observe how the social experience of chronic and pervasive racism and discrimination is experienced somatically as a chronic stressor with inevitable deleterious outcomes. Blacks have higher disease rates relative to whites even when controlling for SES.^{25,26} The “weathering hypothesis” suggests that racial disparities exist with respect to the burden of stressors that accumulate over the lifetime.²⁵ Those individuals who are subjected to the greatest levels of racial discrimination (ie, stress) have the worst mental health outcomes.^{27,28} If we approach the question of racial/ethnic disparities in health from the perspective of developmental neurogenomics, we can begin to understand how different lived social experiences leave their epigenomic imprint on an organism. The genotype is fixed. What remains plastic, and therefore subject to environmental regulation, is the epigenome. If we hypothesize that racial discrimination is capable of directly altering the epigenomic profiles of genes that are important to the stress response, we can then predict that targeting and ameliorating discrimination and racism should have an equally direct, potent, and protective effect on the stress-axis epigenome. This hypothesis would extend to other socially disadvantaged groups subject to the stress associated with discrimination.^{29–31} Rather than engaging in the nature-versus-nurture debate concerning race as a genetic or social construct, we now define race as an epigenomic construct in which genotype and the socially experienced world are perpetually entwined.

SES AND THE STRESS RESPONSE

Epidemiologic studies have identified a graded, continuous association between socioeconomic conditions and morbidity in adults and children of widely varied SES levels.³² This gradient of SES-health relationships leads to differences in morbidity at all SES levels. People in each class have poorer health outcomes than those in the class just above theirs and better outcomes than those in the class just below. This gradient suggests a nuanced link between SES and health that extends beyond the common effects of extreme poverty, which often includes poor nutrition, inadequate housing, environmental exposures, and lack of access to health services.

One plausible explanation for the SES-health association is that chronic activation of the stress response (stemming from the experiences of adversity that accompany lower and disadvantaged social positions) could compromise health.^{22,33,34} This hypothesis is consistent with evidence that relates lower SES with elevated basal activation of the stress axis in children^{35–37} and heightened neural reactivity to stressful challenges.^{38–41} An association of stress with subordinate social positions is also consistent with the previous finding that subjective estimates of social class might be a stronger predictor of health outcomes than objective indicators, such as job status, income, or wealth.^{42–44} Previous research has also shown that dominance status in primate social hierarchies is similarly associated with health, even among captive animals with equal access to food, open environments, and veterinary care.^{35,45–47}

Stress and adversity among young children of low SES come in many forms and varieties. Poor children are routinely exposed to neighborhood violence; disorganized, dysfunctional schools; family turmoil; household

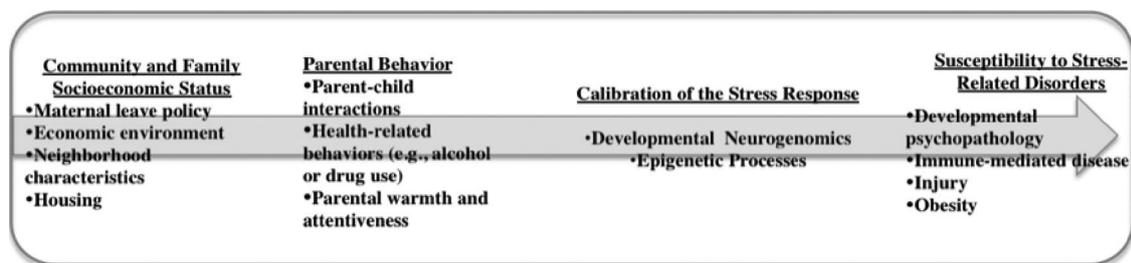


FIGURE 1
Social calibration of the stress response. (Figure courtesy of W. T. Boyce, MD.)

chaos; and parental divorce.⁴⁸ Among the most proximate stressors in the lives of poor children are the common experiences with harsh, unresponsive, and authoritarian parenting. Children of lower SES experience a disproportionate share of conflictive and punitive parent behavior, even in infancy.^{48–50} Disadvantaged homes produce not only more experiences with negative parenting but also fewer positive parent-child experiences. Class-based differences in children’s disciplinary, socioemotional, cognitive, and linguistic experiences with primary caregivers are demonstrably related to brain development, particularly in the neural structures that are tied most closely to the ontogeny of reasoning capacity and language. Specifically, these experiences are linked to the executive functions involved in strategic planning and the regulation of emotion and social behavior.⁵¹ Figure 1 illustrates how broader social forces such as SES can modulate parenting profiles, which are critically involved in calibrating the stress axis in the developing child. We see how larger social forces in concert with more proximate social factors are able to impinge on the developing child to create biological vulnerabilities (another example of an environment × gene interaction).⁵²

A ROLE FOR DEVELOPMENTAL NEUROGENOMICS IN DISPARITIES RESEARCH?

Researchers, clinicians, and practitioners with an interest in understanding

and ameliorating child health disparities necessarily represent a diverse group of professionals with broad notions of what matters most. By default, most of us have inherited the theoretical framework of our academic disciplines (captured in Table 1). We tend to focus on the levels of analyses most familiar to us. We acknowledge that disparities arise from the intersectionality and interactions of the genome with experiences as they occur in time; however, we rarely get to study them. The calibration and regulation of the stress axis in response to social forces provides us the opportunity to directly investigate this intersection. Developmental neurogenomic processes contribute to disparities in child health and well-being. Chronic stressors embedded in proximate family experiences (such as maternal depression and decreased parental care) are themselves subject to regulation by ultimate forces, including economic hardship, neighborhood safety, and high-quality housing. Proximate- and ultimate-level forces are biologically calibrating critical developmental processes in children, thereby influencing their vulnerability to and risk of pathology and illness. A developmental neurogenomics approach makes it possible to begin conceptualizing and understanding childhood health disparities from multiple perspectives and dimensions.

A fundamental understanding of the mechanisms by which social pro-

cesses are embodied and represented biologically free us from the constraints of having to defend a biological or psychosocial argument to explain disparities in health. The evidence at hand overwhelmingly demonstrates that the biological and psychosocial arguments are, indeed, one and the same. Moreover, because the genotype of an organism is fixed and immutable, all interventions should be targeted to optimize those variables and features that promote plasticity. For policy makers it should now be clear that efforts to eliminate or minimize social inequalities (caused by racism, SES, and class) would have direct biological effects on an individual. Moreover, interventions or programs that target the earliest developmental windows in the young child may prevent or significantly attenuate the cumulative effects of social disadvantage, which we know emerge over the life span. Funding mechanisms rarely target these most biologically plastic and labile developmental windows. Informed by biological mechanisms such as those described in this article, policies that create economic, social, or political change can all fundamentally affect the biological development of a single individual as well as whole populations. To grasp a full understanding of why and how social disparities emerge, we need to collectively move beyond the false dichotomy of the biological-psychosocial divide. An understanding of developmental

neurogenomics provides us with the tools to do just that.

THE NEXT FRONTIER OF CHILD HEALTH DISPARITIES RESEARCH

Recent advances in the area of developmental biology and neurogenomics have provided evidence to demonstrate, mechanistically, how challenging or compromised early experiences can create biological vulnerabilities that affect both physical and mental health outcomes in the developing child. Shonkoff et al⁵² have made an excellent case for building a new framework of health promotion and disease prevention with neuroscience, molecular biology, and childhood roots of health disparities at the core. Evidence of this novel agenda is beginning to emerge at the levels of

research,⁵³ policy,⁵⁴ and practice.⁵⁵ However, educational or training opportunities that marry the disciplines of neuroscience, molecular biology, and childhood health disparities are virtually nonexistent (at least at the level of graduate education). A pedagogical approach inclusive of basic developmental biology, molecular biology, and neuroscience offered to the next generation of health-disparities researchers would create a powerful element for change. A breadth of biological training early in an academic trajectory should serve to “lessen” the silo-based approaches often used to address disparities-related research. No longer would the framework be one of biological, psychological, or social vulnerabilities but, rather, a framework focused on how these processes

intersect to create vulnerability (or resilience). Students taught the fundamental concepts of neuroscience, developmental genomics, and HPA/stress-axis function as they relate to social inequalities and health can take the basic biological knowledge they have acquired and immediately translate it to disciplines as diverse as public policy, community health, medicine, clinical psychology, social work, and education. By providing the current generation of health-disparities researchers with a solid background in relevant biological mechanisms we will, in essence, be cultivating the next generation of researchers, practitioners, and policy makers who can readily endorse the assertion that early adversity can create health vulnerabilities.

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