

How Experience Gets Under the Skin to Create Gradients in Developmental Health

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Abstract

Social environments and experiences get under the skin early in life in ways that affect the course of human development. Because most factors associated with early child development are a function of socioeconomic status, differences in early child development form a socioeconomic gradient. We are now learning how, when, and by what means early experiences influence key biological systems over the long term to produce gradients: a process known as biological embedding. Opportunities for biological embedding are tethered closely to sensitive periods in the development of neural circuitry. Epigenetic regulation is the best example of operating principles relevant to biological embedding. We are now in a position to ask how early childhood environments work together with genetic variation and epigenetic regulation to generate socially partitioned developmental trajectories with impact on health across the life course.

Developmental

trajectories: distinct life course patterns of human development (i.e., of health, well-being, learning, and behavior) from the very beginning

Pathways:

experiences at one stage of life influence the probability of others later in life, which then influence health and developmental outcomes

Biological

embedding: the processes by which human experience alters biological processes in stable and long-term ways that influence health over the life course

INTRODUCTION

Social environments and experiences get under the skin early in life, and do so in ways that affect the course of human development. Heart disease, diabetes, obesity, depression, substance abuse, school success, premature mortality, disability at retirement, and accelerated aging and memory loss all have social determinants in early life (41, 69). Furthermore, different qualities of experience in a socially partitioned world create social gradients in human developmental trajectories across the life course.

Here, the term human development encompasses the domains of health, well-being, learning, and behavior and the biological processes that underlie them. Trajectories refer to life course patterns of exposure to social environments, experiences, circumstances and also to life course patterns of human development. Social partitioning is commonly equated with socioeconomic status (SES) differences. Here the term is expanded in two ways. First, it includes other forms: social and classroom hierarchies, community organizational structures, neighborhood and family dynamics, and dominance hierarchies in adult life. Second, it recognizes that “objective” influence may be subject to cognitive interpretation by the individual and vary according to context (35).

A gradient means that as one goes from the most to the least privileged population groups in society, according to social partition, human health and developmental outcomes decline gradually, and without a threshold below or above which the relationship changes. Gradients have been observed throughout the wealthy and developing worlds alike. Their existence is no longer in doubt, but we are only now beginning to characterize the social and biological pathways that account for them by working backward from population-based observations to reinterpret human biology in its social context. This practice requires a conceptual bridge between the social and natural sciences, which we call biological embedding (44). Biological embedding occurs when experience gets under the skin and alters human biological processes; systematic differences in

experience in a socially partitioned environment lead to different bio-developmental states; the differences are stable and long term; and these differences influence health, well-being, learning, and/or behavior over the life course. That biological embedding had to exist was initially inferred entirely from patterns of human development in large populations (e.g., 81, 68, 94). It is only recently that credible candidate mechanisms for biological embedding have emerged. Accordingly, we are now in a position to understand how, when, and by what means early experiences influence key biological systems—genetic, neural, endocrine, and immunological—over the long term to produce social gradients in life course trajectories of health and human development.

THE SINGULARITY OF SOCIAL CAUSATION

An understanding of biological embedding and the social causation of disease and disorder involves several important, defining departures from habits of mind that characterize causal thinking in other epidemiologic arenas, such as infectious disease or environmental health. Among such departures are the following.

1. Social causation is nonlinear, rather than Newtonian, in character. The effects of infectious agents and toxins are thought of in principally linear terms: That is, even though virulence, vectors, and host resistance may each have roles in a given disease, it is an encounter with an infectious agent that fundamentally causes the infection. The likelihood, severity, and course of infection typically vary as a linear, monotonic function of exposure intensity. Similarly, with exposures to environmental toxins, it is the magnitude, duration, and physical occurrence of the exposure that determine the infection's pathogenicity and consequences. By contrast, exposures to social conditions bear unpredictable and sometimes nonlinear relations to their outcomes of interest. Disease outcomes,

chronic or communicable, are seen as nested within complex, dynamic systems that involve accumulations of exposures over time, complex interactions among multiple causal factors, and disease occurrence that is a nonlinear function of exposure.

2. Social causation is nonspecific, in contrast to the capacity of traditional epidemiology to link singular causes with singular outcomes, e.g., insufficient folate intake and neural tube defects, asbestos exposure and mesothelioma, the *Bordetella* bacterium with pertussis. Exposures to stressors and rearing in disadvantageous socioeconomic circumstances, by contrast, appear to augment risk for multiple categories of disorder by generating a generalized susceptibility within multiple causal paths (13, 94). Adverse social conditions yield broad, pluripotential pathogenicity rather than focal, specific morbidities, whereas salutary social environments tend to diminish liabilities to multiple diseases.
3. Social causation is iterative and recursive, in the sense of involving repeated, self-amplifying exposures over time. Social adversities often involve, for example, autocatalytic, self-organizing feedback loops in which one traumatic event follows from others, giving rise over time to intensely negative and stressful social contexts. Thus, marital conflict can presage divorce, which in turn often sequentially leads to residential moves, losses of supportive social relationships, and the onset of depression. The construct of allostatic load is another representation, at the level of stress neurobiology, of how the cumulative wear and tear of life conditions can undermine host resistance, leading to acute or chronic disease onsets (73).
4. Social causation involves mundane, rather than exceptional, exposures, i.e., the repeated, cumulative effects of wearing but otherwise unremarkable

events, as opposed, for example, to a singular, transformative encounter with a highly virulent organism such as HIV. Day-to-day child rearing in environments characterized by impoverished parent-child interactions, for example, may be implicated in the cognitive and neurobiological deficits now being identified in children from disadvantaged families (42, 54). Although physical and emotional abuse and other adverse childhood events can be reliably linked to lasting, serious health consequences (1), it is often the less memorable but hurtful and far more prevalent misfortunes of childhood that become embedded in neural circuitry and produce the vulnerabilities of adult life.

5. Social causation implicates symbolic or semiotic processes. The psychosocial determinants of disease uniquely traffic in the meaning and affective valences of life experience. The concept of weathering, for example, was introduced as a metaphorical account of how perennial, daily encounters with racial and socioeconomic discrimination can accelerate aging processes and lead to the premature onset of age-related disease. [In the African American population, the result has been higher age-specific mortality rates across a wide range of disease processes until old age, when healthy survivor effects begin to predominate and black-white mortality differentials disappear (33).] It is thus the meaning of such encounters, and their implications for assessments of self-worth, social position, and respectability, that drives the downstream, biological effects of racism and other discriminatory social interactions. The shortening of chromosomal telomeres offers a novel biological marker of such aging acceleration (3, 27), reflecting not so much the individual's encounters with physical hardships, but more so the meanings that signify positions of burden, disregard, and subordination.

Semiotic processes: processes involving signs and meaning. Social environmental causes exert effects by way of meaning, interpretation, and their capacities for conveying salient socio-affective signals

EMERGING GRADIENTS IN CHILD DEVELOPMENT

The influence of a socially partitioned world on human development is expressed early, in the form of gradients in the key domains of child development in the first five years of life. The factors associated with these gradients are well recognized and can be aggregated into three groups, from the microenvironment (most proximal) to the macroenvironment (most distal) from the child: the family (micro), the neighbourhood or local community (meso), and the broader social/economic/political environment (macro). At the level of the family, the qualities of stimulation, support, and nurturance in intimate circumstances contribute the most (81). These qualities, in turn, are influenced by the resources that families have to devote to child raising (i.e., family income and parental education), the social-emotional style of parenting, the degree of organization or chaos in the family environment, and the parents' capacity to provide a rich and responsive environment for language (often, but not necessarily, associated with parental levels of formal education) (42) and opportunities for play and active participation.

Consider, for example, the issue of play. Play is a regular activity in the daily life of young children, but that does not make it trivial. Studies in laboratory animals show that the number of playmates and the opportunity for play behavior alter the development of the prefrontal cortex. Play has clear developmental functions, relates to aggression and affiliation, is relevant to social hierarchies and relationships, is probably a significant contributor to self-perception and self-worth, and implicates key neurobiological systems and development of those systems (79). But play is experienced in qualitatively different ways according to family socioeconomic and neighborhood circumstances (47) that, in turn, lead to social gradients in access to this important developmental stimulus.

At the same time, early in life, social partitioning is not being experienced only according to family circumstances. Recent evidence

advanced by Boyce and colleagues demonstrates that, even among preschool and kindergarten children from families of comparable SES, classroom social position is related to health and health risk factors (7, 8, 34). Using naturalistic observations of classroom dominance interactions among 3–5-year-old children, this research shows that social subordination, even in the very young, is associated with heightened cardiovascular, autonomic, and adrenocortical responses to stress and with disproportionately higher rates of chronic medical conditions and injuries. Such evidence indicates, as do similar findings in nonhuman primates (16), that individuals occupying subordinate social positions are at greater physical and psychological risk than are their peers with higher social status, even after controlling for the objective socioeconomic conditions of their families and communities. Taken together, findings on the health correlates of subjective social status and peer group subordination suggest that the health disparities associated with SES may be at least partially attributable to differences in individuals' sense of identity, respect, and position within societies, small or large, marked by nonegalitarian structures and values.

At the level of the neighborhood, children growing up in safety, and where the community is cohesive in relation to children—that is, where it mobilizes resources formally (creates programs) and informally (treats its children like they belong there)—are less likely to be vulnerable in their development than are children from similar family backgrounds living in unsafe and noncohesive neighborhoods. Children who experience stable neighborhood environments during their early years tend also to be less vulnerable than those who are constantly changing their places of residence. Similarly, children from family backgrounds that harbor multiple threats to their development tend to do better growing up in mixed socioeconomic neighborhoods than in enclaves of poverty (24, 57). The contextual effects on children's development can also be characterized

according to modes of transmission: neighborhood resources, collective socialization, contagion, competition, relative deprivation, and stress due to toxins or safety concerns (18, 49, 90). From the perspective of the physical environment, noise, crowding, housing and neighborhood quality, natural settings, schools, and child-care settings have been identified (29). By focusing on the question of what constitutes a supportive community, other investigators have produced slightly different lists: quality of social services, socialization by adults, peer influences, social networks, exposure to crime and violence, physical distance, and isolation (25), or safety and cohesion, increased participation in community activities, and high levels of collective efficacy (18).

Finally, at the level of society, access to quality programs matters (83, 88). Access includes the full range of child care, family support, and family strengthening programs; public health programs for high-risk children, vision, hearing, dental, and speech/language; and broader social safety net functions such as parental leave and housing programs. Thus, the state of child development in any society is an emergent property of a complex of factors, most of them modifiable, at the intimate, community, and societal level that influence each child in unique combinations. Accordingly, by age five, as one goes from the families with the lowest to highest incomes, least to most parental education, least to most nurturing and interactive parenting style, least to most hospitable neighborhood environment, and least to most access to high-quality programs, systematic differences emerge in three broad domains of early child development (ECD): physical, social/emotional, and language/cognitive.

THE EXAMPLE OF BRITISH COLUMBIA

Because most of the nurturant factors associated with ECD are a function, directly or indirectly, of SES, differences in ECD form a socioeconomic gradient. In 2004, the province of British Columbia (Canada) became the first

jurisdiction in the world to complete a comprehensive population-based assessment of ECD (53). Assessments were done during the kindergarten year (the transition year to school at age five), and ECD was measured using the early development instrument (EDI), in which kindergarten teachers fill out a detailed checklist for each child in their class based on five scale measures of development: physical well-being, social competence, emotional maturity, language and cognitive development, and communication and general knowledge (48). The EDI allows each child to be scored as vulnerable or not vulnerable on each of these five scales. They are not used to label the child but are aggregated to the school or neighborhood level.

The first wave of data (collected between 2000 and 2004) included ~44,000 kindergarten children from all walks of life across British Columbia (53); between 90% and 100% of kindergarten-age children from at least one school entry cohort were included from every geographic school district in the province. **Table 1** shows the strength of the gradient in vulnerability on the five scales of the EDI, according to the socioeconomic characteristics of all 478 residential neighborhoods in the province. On each scale, the proportion of vulnerable children by neighborhood ranged from 0% to 22% to 35% (depending on the scale), and the proportion vulnerable on one or more scales of the EDI ranged from 5% to 67%. As **Table 1** shows, the proportion of variance explained by neighborhood socioeconomic characteristics ranges from approximately one-fifth to nearly one-half, depending on the scale.

Table 1 Variation in EDI vulnerability by BC neighborhood explained by neighborhood socioeconomic characteristics

EDI scale	Proportion of variance explained
Physical health and well-being	33.8%
Social competence	20.9%
Emotional maturity	23.4%
Language and cognitive	27.2%
Communication skills and general knowledge	46.9%
One or more EDI vulnerabilities	42.7%

ECD: early child development

Socioeconomic gradient: from the most to the least privileged groups in society human health and developmental outcomes decline gradually, without a threshold

EDI: early development instrument

Latency:

relationships between an exposure at one point in the life course and a developmental outcome that it influences years or decades later, irrespective of intervening experience

Cumulative: multiple exposures over the life course whose effects on development combine

HPA: hypothalamic-pituitary-adrenal

More than 40% of the variance for vulnerability on one or more scales can be explained by neighborhood socioeconomic characteristics, which clearly demonstrates the strength of the emerging gradient in basic developmental competencies.

FROM CHILD DEVELOPMENT TO THE LIFE COURSE

One of the most useful advances of the past 15 years has been the merging of the developmental and the epidemiological perspectives to address the emergence of gradients across the life course. The latter perspective is best suited for studying discrete phenomena (i.e., extraordinary and nonquotidian) whose statistical association with health outcomes meets epidemiological criteria for causation (60). In contrast, the developmental perspective presumes that the experiences of infants and children who are candidates to produce social-gradient-distributed differences in outcome have the properties of being common (all children experience them), frequent or iterative, and basic in the sense of being relevant to essential needs, part and parcel of early experience, and perhaps, critical for survival. These are distinguishing features of social causation, described above. These mundane, quotidian experiences drive human development and are the principal agents mediating the relationship between life course and outcome (81, 90). The human development perspective thus complements social epidemiology by characterizing the population in terms of trajectories of experience and comparing these with trajectories of expression that accommodate gradations of change in human developmental outcomes.

Exposure to both beneficial and adverse experiences over the life course will vary for each individual and will constitute a unique life exposure trajectory, which will, in turn, be expressed as a unique trajectory of human development. Studies that collect data from the earliest stages of life and follow individuals over time provide the best lens on the relative importance of, and interaction among, these exposure-to-

expression relationships. They tend to cluster into three types of relationships, which have been labeled latency, cumulative, and pathway (45). Latency refers to relationships between an exposure at one point in the life course and a developmental outcome that it influences years or decades later, irrespective of intervening experience. Cumulative refers to multiple exposures over the life course whose effects on development combine. These may be either multiple exposures to a single recurrent factor (e.g., chronic poverty) or a series of exposures to different factors. They may act synergistically, such that children with multiple exposures (e.g., poor parenting style, residential instability, low SES) may have much more challenging trajectories than the effects of individual exposures might predict. Exposures may also have different influences on developmental trajectories depending on the character of the broader social environment in which the individual develops. Finally, the term pathways refers to dependent sequences, such that an exposure/experience at one stage of the life course influences the probability of others later in the life course, as well as associated health and developmental outcomes. This is akin to the notion of chains of risk (85). For example, the divorce of someone's parents in early childhood may reduce that child's readiness to learn at school entry, which may, in turn, affect school performance, which could then affect the subsequent life course trajectory.

In the real world, latent, pathway, and cumulative influences coexist. Early experiences can produce small changes in trajectories, which can become magnified as the individual develops. As a hypothetical example, attachment is under considerable social control, but failure of the environment to properly signal and set up the reactions of positive attachment in the hypothalamic-pituitary-adrenal axis (HPA) and brain of the child means that the child will be at risk of missing significant social cues. Lack of social cues, in turn, can make the child less easy for caregivers and peers to relate to, which, in turn, can lead to deterioration of the child's immediate social environment, making it more

stressful. This vicious cycle, in turn, can have significant consequences for his or her social, emotional, and cognitive development.

Human development can be examined in the context of a socially partitioned world by incorporating the concept of macro/meso/microlevels of influence, described earlier, into a parsimonious model of the individual life course embedded in society. The model presented in **Figure 1** illustrates the determinants of self-rated health at age 33 in the 1958 British Birth Cohort (46). It conceptualizes life course development as an arrow, encompassing latent, pathway, and cumulative effects, intersecting a bullseye that represents society at the micro, meso, and macrolevels of aggregation. Although difficult to display graphically, the model is meant to convey the notion of a day-to-day interplay between the developmental stage of individuals and their experiences at each level of social aggregation. In this case, the measured outcome at age 33 was self-rated health, a simple measure of well-being that is predictive of subsequent mortality. There were strong associations between childhood factors—latent, pathway, and cumulative—and self-rated health at age 33, expressed as odds ratios in **Figure 1**. Similarly, there were strong associations between factors at two of three levels of social aggregation (meso and macro) at age 33 and self-rated health. But the most relevant finding was the following: The life course odds ratios given in **Figure 1** are after controlling for all factors at age 33. Experiences earlier in the life course exerted a statistically independent influence on current well-being. Of greatest interest here is the character of the latent factors that entered the model (with a combined odds ratio of 5.03). The latent factors were those that occurred between age zero and seven, but continued to independently influence health and well-being three decades later. The factors were whether the child was read to on a regular basis by his or her parents, whether the child adjusted easily when first attending school, and what proportion of ultimate adult height the child had reached by age seven. None of these

factors reflects dramatic departures from normative experience.

LIFE COURSE DEVELOPMENT AND THE OPPORTUNITY FOR BIOLOGICAL EMBEDDING

The developmental perspective allows a story of early life to be told in a way that points toward windows of opportunity for biological embedding. At the beginning, socially partitioned experiences play a crucial role in the early phases of conception and the prenatal and postnatal periods of children's development (93, 97). Sensitive periods in brain and biological development start in the prenatal period, reach a peak in the first few years of life, and continue at a declining rate throughout childhood and adolescence. Early sensory stimulation activates specific genes in different parts of the brain to differentiate neuron functions and establish sensory pathways. Sensory pathways, in turn, influence the development of neural pathways to other parts of the brain involved in coping, movement, language, cognition, and biological pathways, including the immune and hormone systems. Early environments are mediated through relationships with primary caregivers. A prime example is infant attachment to a parental figure (usually, the mother) in both higher primates and humans. Attachment drives the development of neural pathways that help the baby's brain become attuned to its immediate environment (69). A failure to provide the full set of necessary visual, tactile, and auditory—and, perhaps, olfactory—inputs during sensitive early windows of infant development may lead to profound developmental delay (19). Indeed, in cases of severe neglect, this deprivation can result in adult stunting or even death, despite the availability of theoretically adequate physical nourishment, warmth, and other material necessities. Furthermore, there is much less effect of this form of psychosocial deprivation when it occurs at later ages, as if the infant is prewired to require this input at precisely a certain developmental stage (19).

Evidence from neurosciences, developmental and experimental psychology, and cell biology has been integrated to provide the following scenario. The brain continues to sculpt itself, albeit at a declining rate, such that it does not reach its adult state until the end of the second or beginning of the third decade of life. For example, key executive functions, regarding how an individual responds to social and emotional stimuli, develop in the prefrontal cortex from approximately age three to age nine, whereas neural connections to the prefrontal cortex, from centers in the midbrain that sense environmental threats, develop earlier. Thus, whereas the physiological sense of threat is developed at a very young age, the repertoire of responses to threatening circumstances may develop later (19, 37, 55, 56, 90). Overall, this is a story of early life providing a roughly ordered sequence of developmental windows of opportunity that, in turn, allow both mundane and extraordinary experiences to get under the skin at the right time to alter biological functions, which, in turn, have the capacity to alter life course trajectories.

HOW EXPERIENCE GETS UNDER THE SKIN

What might be the biological character of the receptors behind these windows of opportunity? Experience most definitely does get under the skin and is expressed at all levels, from gene expression to behavior. But to meet the test of biological embedding not only must experiences have biological effects, but also these effects must, in turn, influence long-term human developmental outcomes and the expression of gradients in human development. Experiential impact on certain biological pathways passes this test better than others. We call these biological pathways “candidate systems” because their physiological functions make them transducers between the social environment and those aspects of human biology that have the capacity to embed and influence the rest of the life course. Candidate systems have four basic

characteristics: The system can be influenced by daily experiences (often early in life), such that differential qualities of experience have the capacity to lead to a differently functioning system; the system responds to such experiences throughout the life course; the system, if dysfunctional, has the biological capacity to influence health, well-being, learning, and/or behavior; and differential functioning of the system across the life course, to the extent that outcomes are affected, may derive from early experience.

Four candidate systems have so far been shown to have these characteristics: the HPA axis and its accompanying secretion of cortisol; the autonomic nervous system (ANS) in association with epinephrine and norepinephrine; the development of memory, attention, and other executive functions in the prefrontal cortex; and the systems of social affiliation involving the primitive amygdala and locus coeruleus with accompanying higher-order cerebral connections, mediated by serotonin and other hormones (4). Here we highlight the best documented system, the HPA axis, to illustrate how biological embedding might play out across the life course.

The Life Course Development of the HPA Axis in Society

The HPA axis is highly relevant because of its role in our perception of, and response to, stressful circumstances. HPA stimulation leads to the secretion of the hormone cortisol, which, in turn, has metabolic effects on the brain and the immune, gastrointestinal, cardiovascular, and reproductive systems. These effects are adaptive in the acute stress-response phase, focusing the body’s energy on the immediate task at hand and reducing metabolic processes that do not contribute to the immediate response. But over the long term, dysregulation of cortisol could damage these same organ systems (71).

Animal studies provide an intriguing model of the role the HPA axis may play in influencing

developmental trajectories. In rats, the apparently minimal intervention of removal from the mother for short time periods early in the rat pup's life can bring about a cascade of events that permanently conditions the way the HPA axis functions over the remainder of the life course (86). This conditioning effect can be created only by intervention during a narrow window of days in early life, which suggests that it depends on appropriate stimulation/deprivation during a highly circumscribed window of opportunity in brain and biological development (i.e., a critical period). Most important, once the HPA axis has been conditioned, the effects appear to be lifelong.

The underlying nature of the intervention was revealed when the researchers returned the rat pups to their cages. Their mothers, who had been without them, then engaged in extra licking, grooming, and arch-backed nursing (LG-ABN) that was not offered as frequently to the unhandled rat pups. Subsequent biochemical studies have shown that, after the intervention, the handled rats showed a more adaptive or functional corticosterone response pattern to stress: a low basal corticosterone level, an abrupt response to acutely stressful circumstances, and an abrupt decline to baseline thereafter. Among the nonhandled rats, there was a much broader range of responses, typified by higher baseline levels and a more blunted response to stressful circumstances. Thus, the handled rats had reduced total lifetime secretion of corticosterone compared with the nonhandled rats. Chronic overexposure to corticosterone, in turn, endangered selected neurons in the brain's hippocampus (86), such that the rate of loss of hippocampal neurons was reduced in the handled rats over their whole life span. Because of cognitive functions' sensitivity to relatively small degrees of hippocampal damage, the handled rats, by 24 months of age (elderly by rat standards), had been spared some of the cognitive deterioration typical of aging. Rats not handled as pups showed a progressive deterioration in their memory, cognitive processing, and learning performance with age; in

contrast, much less deterioration occurred in aged rats handled in infancy (74).

It is striking that when the researchers tried the handling protocol later in life, rather than during the early critical window, it had no biological effect. That is, they did not detect the prolonged change in the corticosterone response pattern or the differential aging of learning and memory functions. This research presents a model of variations in an experience (maternal nurturance) occurring at a circumscribed time in early development that affects a basic biological function relevant to host stress response, defense, and organ-system aging—a latent effect that then had lifelong consequences for trajectories of learning and behavior.

A second series of experiments added important depth to this story. By comparing the development of rat pups that were frequently, versus infrequently, licked and groomed by their mothers, researchers have elucidated a mechanism by which systematic differences in the function of the HPA axis emerge (74). LG-ABN behaviors initiate a biochemical cascade that leads to long-term alterations in the expression of genes through epigenetic changes, that is, through modification of the DNA or associated proteins, other than DNA sequence variation, that carry information during cell division (31). In this case, the epigenetic mechanism was methylation of a region of DNA that regulates HPA axis function and, also, higher-order executive functions in the brain (23, 95, 98). In colloquial terms, this situation has been referred to informally as a “life is going to suck” pattern, wherein the less-licked and -suckled rats end up with a more highly reactive HPA axis (good for fight or flight, but bad for sustaining learning and memory functions over time) and a reduction of the density of synapses in the cerebral cortex. It is a model wherein high-quality early nurturance leads, through mediation of gene expression, to a more tranquil HPA axis, greater capacity for complex learning, and reduced age-related declines in learning and memory capacity. However, the life-is-going-to-suck pattern has short-term survival and procreation

LG-ABN: licking, grooming, and arch-backed nursing

advantages in environments that resemble the natural habitat of the rat. Either way, the early nurturant environment has been “biologically embedded” (95).

This series of experiments has also shown that patterns of licking and grooming can be transmitted from one generation to the next. It began with distinct subgroups of rats that had histories of either high or low licking and suckling. However, when female rat pups from the low-licking and -suckling group were cross-fostered with high-licking and -suckling mothers, they experienced the same benefits did as the natural offspring. Most important, these female offspring adopted the high-licking and -suckling behavior when they became mothers. A pattern of intergenerational learning was taking place that transmitted the more adaptive nurturing pattern to those who had been predisposed to the nonadaptive pattern (14). Taken as a whole, this research presents a complete working model of how experience can get under the skin and influence aspects of well-being across the life course and also from generation to generation.

Does the HPA axis actually have the same sort of life story in human society that it seems to have among rats? In particular, does a socially partitioned human society biologically embed via HPA axis regulation? Evidence on this point has been much slower to accumulate. However, several lines of inquiry converge with the evidence just presented.

The quality of early maternal-child attachment affects both the HPA axis function and behavior, such that poorly attached toddlers have more reactive HPA axes and less adaptive behavioral responses in social conflict situations (37). An extreme example of this is the plight of Romanian orphans (36). After neglect during the first six months since birth in state-run orphanages, these children have tended to become high cortisol reactors and to suffer profound social-emotional, as well as cognitive, developmental disturbances that persist at least into early adolescence (58). Romanian children orphaned later in life, or for briefer periods, tend to show less profound,

and more easily reversible, developmental disturbances.

Under much less extreme conditions in North America, social class differences in basal cortisol levels have been found among both primary and secondary school children (67). Systematic differences in cortisol levels have been reported according to parental income, education, and employment status (65, 66); the mother’s depressive symptoms (28, 67); childhood adversity (11, 30, 38); and the stressfulness of social environments (32, 38). Low socioeconomic position is also related to higher levels of basal cortisol in children, emerging between ages 6 and 10 years (65). However, this relationship may be unstable thereafter: Between age 10 and 14 years, the direct association between basal cortisol and socioeconomic position is superseded by an indirect effect whereby it is associated with differences in cognitive processing style that, in turn, are associated with basal cortisol (65). Elsewhere, cortisol levels were associated with adult SES (10, 15, 17, 59, 61, 92) and chronic stress due to unemployment (77). Others (64) found that the impact of a less advantaged socioeconomic position over a lifetime would lead to an approximate doubling of the proportion of extreme postwaking cortisol levels, an 8%–10% increase in cumulative cortisol secretion during the early hours of the day, and a 60%–91% increased risk of having an abnormal cortisol secretion pattern.

Taken as a whole, the human studies suggest that distress and psychopathology are associated with hypersecretion of cortisol over the short term but that, over a prolonged period, there may be a blunted or hyposecretory pattern, reflecting burnout of the system. Another hypothesis proposes that the HPA axis becomes dysregulated over time, as a result of social stressors, suggested by studies of low SES, adversity, and maltreatment in childhood. The stresses of daily living, as well as chronic repeated adversity, are thought to exert wear and tear on the HPA axis, leading to dysregulation (71, 72). In turn, dysregulation of the HPA axis can lead to either hypo- or hypersecretion of cortisol, either of which may have adverse

consequences, such as depression; the mid-range would have the most favorable outcomes (5, 21, 39, 43). Work on the 1958 British Birth Cohort has demonstrated an association between low cognitive performance in childhood (as measured by standardized tests of core academic skills at ages 7–16 years) with hyposecretion of cortisol at age 45 (82). Studies of socioeconomic position and cortisol at different stages in childhood suggest a dynamic bidirectional relationship between cortisol and cognition evolving over time. Reduced cognitive trajectories in childhood may lead to lower socioeconomic position in adulthood and, through that, to altered cortisol patterns. Finally, with respect to cortisol and cognition at later stages of the life course, chronic exposure to high levels of cortisol is associated with memory impairments in the elderly (52, 65, 89).

Perhaps the most compelling evidence of the HPA axis as a biological pathway between the social environment and health comes from comparisons between 50-year-old Swedish and Lithuanian men (59). During the final 30 years of the Soviet period, the rates of heart disease between these two populations diverged from parity to a fourfold higher rate in the Lithuanians over the Swedes. When subjected to laboratory stress tests, the Swedish men's cortisol levels were reminiscent of the handled rats, whereas the Lithuanian men tended to have cortisol profiles of nonhandled rats (87). Moreover, the Lithuanian pattern tended to be associated with low self-esteem, lower sense of coherence (that is, a sense of conjunction between one's lived experience and one's sense of what life should bring) (2), and increased reported job strain, according to the Karasek model (51). In general, the Lithuanians showed decreased decision latitude in their jobs, increased "vital exhaustion," and increased depression. This psychosocial risk factor complex association with coronary heart disease risk was closely associated with HPA axis function but not with any other heart disease risk factors that were measured at the time (59).

BIOLOGICAL EMBEDDING TO UNDERLYING MECHANISMS

The case for the existence of biological embedding is substantial. Yet, validating its mechanisms necessitates making the relationships among socially partitioned experiences, brain and biological development, and outcomes in health, learning, and behavior transparent in humans. One challenge here concerns levels of description. In particular, relevant activity occurs at a number of levels of biological organization. To characterize fully the underlying mechanisms, it is necessary to move up and down these levels, from human development to neurobiology, physiological pathways, genes, and gene regulation, combining animal and human evidence to determine where there is substantial convergence, emerging suggestions of convergence, or no convergence across all levels with respect to the influences of socially partitioned environments.

CRITICAL AND SENSITIVE PERIODS

Opportunities for the biological embedding of early social experiences are likely tethered closely to so-called sensitive periods in the development of neural circuitry. Sensitive periods are limited spans of developmental time when specific brain systems and the cognitive, emotional, or behavioral capacities they subserve are maximally receptive to environmental tuning and input (56). Such periods are specific in length and timing, with respect to both circuit and species, but can be influenced by perinatal experiences. Psychoactive drugs (e.g., diazepam) and sensory experiences (e.g., auditory or tactile stimulation) can shift sensitive periods in cerebral development (19). Sensitive periods may be temporally overlapping but occupy specific developmental epochs within auditory, visual, and other systems; furthermore, the sensitive period for the visual cortex within one species may correspond only moderately, or not at all, to that of another species.

Most elegantly studied in animal models, the opening and closing of sensitive periods have been explored experimentally at the levels of complex behavior, histological change within specific brain areas, neuronal structure and function, and the differential expression of neuroregulatory genes. Human children, for example (see **Figure 2**), show highly competent acquisition of a second language up until around seven years of age, beyond which accurate, proficient language learning rapidly declines. Although sufficient cortical plasticity remains throughout the life course to enable humans of any age to learn and master a second language, never again beyond middle childhood is fidelity to the usage and pronunciation of a native speaker possible.

Many neurocognitive functions (self awareness and social understanding, language, memory, executive function) appear to depend heavily on enculturation/socialization. With respect to the prefrontal cortex, D'Angiulli and his colleagues (20) investigated the relationship among socioeconomic position, performance, and the neural correlates of auditory selective attention by comparing event-related potentials (ERPs) in lower- and higher-socioeconomic preadolescent children during a task in which they had to attend to two types of pure tones but ignore two other types. The hypothesis was that, at comparable performance levels, higher-SES children would easily ignore distracters (the unattended, irrelevant tones), whereas lower-SES children would attend equally to distracters and target tones. Indeed, they found that ERP waveform differences between attended and unattended tones were significant in the higher-SES but not in the lower-SES group. Despite the fact that the groups did not differ in reaction times or accuracy, electroencephalographic power analysis revealed that the high- and low-SES children recruited different neural processes to achieve the task. Lower-SES children seemed to deploy supplementary resources to attend to irrelevant information, consistent with what D'Angiulli calls the "ear to the ground hypothesis." That is, lower-SES children may,

on average, experience more chaos, disorganization, and threat in their environments than do higher-SES children. If so, biological embedding of a more distractible or vigilant executive function system would be adaptive for the lower-SES children in their daily lives but would likely make school success more difficult to achieve over the long term.

In another example of a sensitive period, rhesus monkey infants deprived of their mothers show distinctive levels and types of behavioral deficits depending on the timing of the maternal separation (70). Those separated at one month of age showed dramatically greater deficits and self-soothing behaviors than did infants separated at two months. Similarly, barn owls have a sensitive developmental period for acquiring the ability to locate objects in three-dimensional space using convergent auditory and visual signals (55). Such changes in capacity—the ability, for example, to compute interaural time and level differences to localize sound—coincide with microanatomical and histological changes in the functional linkages among circuitry components and in the patterns of neuronal projections within auditory and visual cortex. Finally, as elucidated in the rat model studied by Meaney & Szyf (75, 96), epigenetic changes in expression of the gene encoding the glucocorticoid receptor (GR) are mediated, during an early sensitive period, by naturally occurring differences in maternal behavior, specifically the intensity and frequency of LG-ABN of the pups. Natural or induced low levels of maternal LG-ABN behavior are associated, among the mother's offspring, with downregulation of GR expression, resultant increases in HPA reactivity, and temperamental characteristics suggesting more fearful and anxious behavior. High LG-ABN, by contrast, results in downregulation of HPA reactivity and bolder, less fearful behavior, characteristics that, from a public health standpoint, are more adaptive in a safer modern environment that presents manageable risks. Moreover, these characteristics are subsequently passed on to a subsequent generation through epigenetic or behavioral means.

GENETIC AND EPIGENETIC PROCESSES

Socially partitioned pre- and postnatal experiences in both humans and laboratory animals can influence developmental trajectories, and can do so through a variety of mechanisms, including epigenetic changes. The model, described earlier, of the ways that parental care early in life influences epigenetic regulation in infant rats, including cross-generational transmission, is a striking result and, to date, probably the most well articulated example of operating principles relevant to biological embedding. At the same time, the relatively tight developmental window of influence, the highly specific promoter region on a specific gene that is affected, and the problems of interspecies reliability all raise important questions about the generalizability of the phenomenon to human populations.

As exemplified above, genomic regulation of brain growth and development is a core process by which environmental signals, both beneficial and adverse, sculpt and determine the configuration and function of neural circuits. This shaping of neurodevelopment engages both genetic and epigenetic processes. Allelic variation in key neuroregulatory genes can bias the maturation of important circuits and provide a substrate for important temperamental and behavioral differences, as well as for differences in risk for disorders of mental health. The functional circuit linking the anterior cingulate cortex (ACC) and the amygdala, for example, appears to play an important role in the capacity for extinguishing negative affect and cognition. Carriers of the short allele of a functional 5' promoter polymorphism in the serotonin transporter gene, who have known predispositions to anxiety and depression, also show on functional MRI a relative uncoupling of the ACC-amygdala circuit, which is thought to play a role in the extinction of negative affect (80). Thus, sequence variation in the heritable genome is likely centrally important to the development of individual differences in behavior, personality, and risk for psychopathology.

Yet, the preponderance of the evidence to date shows that it is not genes or environment, nor is it genes and environment, but rather it is gene-by-environment interactions that influence developmental trajectories (4). The best-studied examples of this are found in the expression of antisocial behavior. A very small fraction of the population accounts for the majority of criminal offenses. In the first instance, this statistic suggests a strong genetic influence, but an extensive body of research has now redirected our attention to gene-by-environment interactions. The Dunedin birth cohort study showed that there is a genetic polymorphism in the monoamine oxidase A (MAOA) promoter region of the genome, whose metabolic contribution gives it a high level of biological plausibility for being on the aggression pathway. The low-MAOA activity allele in association with severe maltreatment in childhood led to antisocial outcomes in 85% of males. Although they constituted only 12% of the Dunedin cohort, they had 44% of the violent convictions in the cohort. However, the contribution of the genetic polymorphism in the absence of childhood maltreatment was virtually nil (76). Similarly, research on the Dunedin birth cohort has shown that the serotonin transporter polymorphism (12) expresses itself in risk of depression in adulthood only under conditions of moderate-to-severe child maltreatment. When early nurturant conditions were strong, there was no independent effect of the polymorphism. Gene-by-environment interactions predominate over gene-only effects in the function of the dopamine transporter gene and attention-deficit hyperactivity (62), in the association of genes mediating HPA axis function and posttraumatic stress disorder symptoms in adults (6), and in the expression of academic readiness for school (63). Interactions are not confined to conditions in the intimate environment. For example, some evidence shows that environmental factors as remote as urban versus rural residency can interact with the serotonin receptor 2A gene in the expression of depression symptoms (50). In this study, urban residency was associated with low depressive

Epigenetic regulation:

environmental signals may cause long-term changes in gene expression through modifying DNA or associated proteins, but not DNA sequence variation

Gene-by-environment interaction:

Contrasting with genetic or environmental main effects, specific genotypes may produce systematically different human characteristics, depending upon the individual's environment

symptoms in individuals carrying the T/T or T/C genotype of the T102C polymorphism, but not in those carrying the C/C genotype. The T allele was associated with high depressive symptoms in remote rural areas but with low depressive symptoms in urban or suburban areas.

Biological embedding is also consistent with the adaptations through which early environmental influences affect the calibration of biological systems. These adaptations are evolved mechanisms that monitor early environments, including during the prenatal period, to adjust set points within important brain circuits. Such adaptations produce “phenotypic plasticity,” which refers to the capacity of a single genome to produce a range of physically or functionally adaptive traits. For example, fetal responses to prenatal nutritional conditions may promote an adjustment of postnatal metabolic expectations that are appropriate to anticipated circumstances (40). Thus, fetuses in intrauterine environments that are characterized by poor nutrition undergo adaptive, energy-sparing, metabolic changes because they anticipate that the postnatal environment will also be characterized by food scarcity. Although such metabolic changes may be adaptive in the short run, problems can arise when the adaptive prediction regarding postnatal life is wrong, and the early childhood environment is characterized instead by energy abundance, a carbohydrate-rich diet, and a sedentary life style.

The cell-level processes by which conditional adaptations occur include developmental, ontogenic changes in the expression of regulatory genes. As shown in **Figure 3**, developmental changes in DNA methylation, at specific CpG sites,¹ occur throughout the sequential ontogeny of germ cell development, fertilization, and embryogenesis. Such changes guide, for example, stem cell differentiation into tissue-specific histological

structures and functions. The same epigenetic processes—including, but not limited to, DNA methylation—are likely key mechanisms by which early environmental signals are transmuted into conditionally adaptive changes in metabolic, endocrine, and neuroregulatory pathways. These changes, in turn, are responsible for systematic developmental biases toward adaptive, although not uniformly protective, profiles of growth, metabolism, immune responsivity, developmental pace, and behavior. Epigenetic modifications of the genome, which occur both prenatally and postnatally in response to environmental cues, are also likely to be implicated in the genesis of developmental psychopathology and chronic biomedical disorders (22). Although epigenetic marks, derived from environmental exposures, are capable of modifying gene expression, allelic variation in the actual exonic, coding DNA sequence can also be associated with differences in transcription rates (78).

CONCLUSION

Experience affects individuals differently. From early in life, ~15% of children are more highly biologically reactive to their immediate social context than others are. Over the life course, the effects of being a highly reactive individual on psychiatric and biomedical outcomes are bivalent, rather than univalent, in character because they can be protective in some contexts and risk-augmenting in other contexts. Heightened stress reactivity may reflect not simply exaggerated arousal under challenge, but rather an increased biological sensitivity to context, regardless of the context. For example, in child-care populations there is a curvilinear, U-shaped relation between early exposures to adversity and the development of stress-reactive profiles; high reactivity phenotypes disproportionately emerge within both highly stressful and highly protected early social environments (9, 26). When this observation is juxtaposed against the body of this review, the following working hypothesis emerges: Being

¹CpG sites are places in the linear genome sequence where cytosine and guanine nucleotides occur adjacent to each other, separated and linked by a phosphate moiety.

biologically sensitive to context will serve as a bellwether in a socially partitioned world. That is, those who are biologically sensitive to context will be distributed broadly across social partitions, but those from less privileged backgrounds will tend to find themselves in risk-augmenting contexts, whereas those from more privileged backgrounds will tend to find themselves in protective environments. Over time, the differences in developmental trajectories of those biologically sensitive to context will drive the expression of gradients.

We are now in a position to ask how early childhood environments work together with genetic variation and epigenetic regulation to generate socially partitioned developmental trajectories in early life. Using a broad range of data—from assessments of gene polymorphisms and DNA methylation to population-level information on social class and developmental status at school entry—we

can now examine the stability of epigenetic modifications from the newborn period to primary school entry, generate hypotheses regarding differential epigenetic expression of stress-related genes for neurodevelopmental vulnerability in different social partitions, and seek further evidence for social environment-related functional differences in prefrontal cortex neural circuitry. A generation of studies like this will help elucidate interactions among social environmental, genomic, and neurobiological factors in the preservation of healthy development and the genesis of disease; will demonstrate linkages between social disparities in children's early parenting experiences and the development and calibration of stress-responsive neural circuitry; and will help show the timing and character of early interventions among children from compromised backgrounds that could interrupt generational cycles of disadvantage and disorder.

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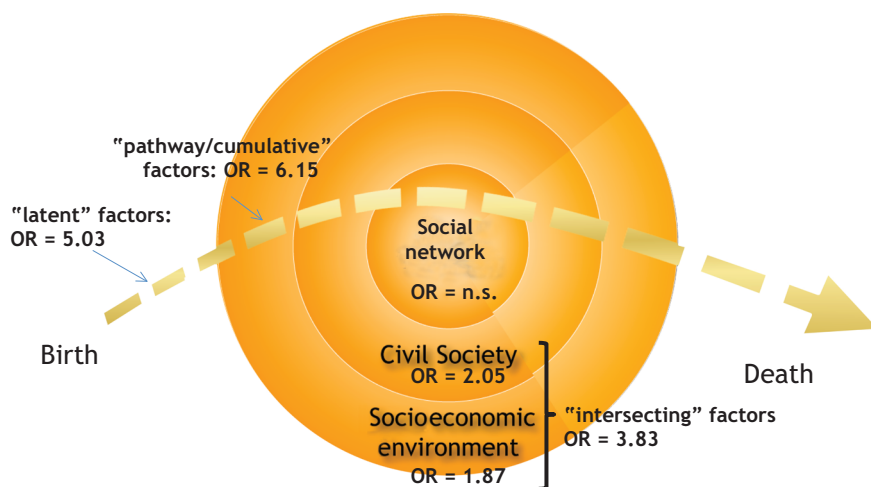


Figure 1

Contributions to self-rated health at age 33 1958 birth cohort. N.S., nonsignificant; OR, odds ratio.

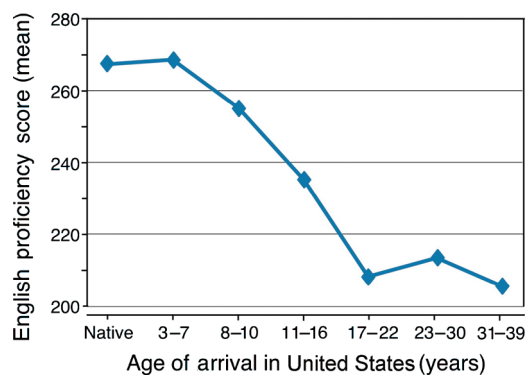


Figure 2

Proficiency in English language learning by age of arrival in the United States.

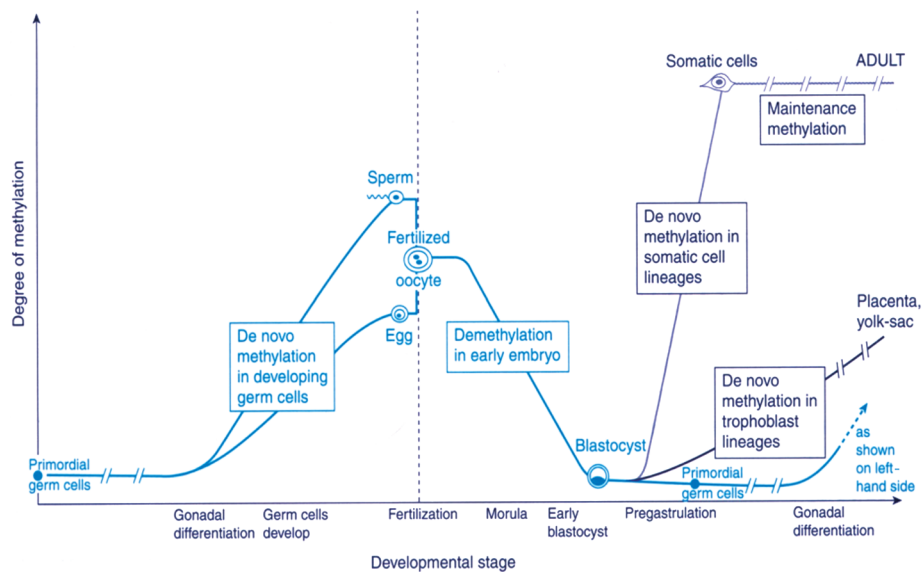


Figure 3

Epigenetic methylation events in early human gestation. From Reference 84.



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