Rethinking Addiction

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Abstract

Addiction is a complex and challenging condition with many contributing factors. Although addictive behaviors appear to be individual choices, behavior alterations cannot be addressed successfully without considering characteristics of the physical and social environments in which individuals live, work, and play. Exposure to chronic psychosocial stressors and the physiological response of individuals to their external environment activates the brain's neuroendocrine hypothalamic-pituitary-adrenal axis, with profound conditioning effects on behavior. This brief synopsis describes the social determinants of health; examines the interconnectedness of the psychosocial environment, behavior, and subsequent health outcomes; discusses the environment's critical influence on brain plasticity, adaptation and functioning; and explores additional factors that complicate adolescent addiction. Because the environment is both a determinant of behavior and an opportunity for intervention, in the context of addictions, it is important to incorporate these factors in the analysis of risk and design of early interventions for prevention and amelioration of addiction.

Keywords

addiction, adolescents, brain plasticity, psychosocial stressors, social determinants of health

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Introduction

Stress is a normal part of daily life, and humans have a well-honed ability to adapt, overcome, and learn from stressful events.[1] However, not as widely known are the physiological effects of chronic, adverse psychosocial stressors on brain development and structures, which have a profound effect on the parts of the brain that enable evaluation and decision-making functions, regulate emotions and impulsivity, support memory and mood, and detect, evaluate, and respond to threats in one's surroundings.[2,3] These neurological changes, which are an adaptive response known as neuroplasticity, have lifelong effects, including impaired cognitive function and poorly developed language and social-emotional skills,[2] with consequent lasting impacts on behavior, education, employment, and physical and mental health.[2,3] Adverse early life experiences also have a modifying effect on transcription of DNA and these epigenetic changes increase the risk for impaired mental and physical health later in life.[3,4] These stress-related changes are now known to also play a significant role in addiction and substance use disorders.[3,4] Thus, the stressors found in the physical and social environment where we live, work, and play may have as much or more influence on our health and behavior as our individual physical and psychological characteristics.

The focus of this review is on the pervasive effects of adverse early life experiences on behavioral choices and health outcomes, and how these experiences drive the physiological response to psychosocial stressors, which produce subsequent neurological remodeling and epigenetic changes. It then explores the role these factors play in addictive behavior, especially during adolescence, and concludes with research findings which indicate that brain remodeling precedes and may predispose to substance addiction, and that intensive, early interventions can induce corrective brain remodeling. Although a detailed discussion of the physiological mechanisms involved in such remodeling is beyond the

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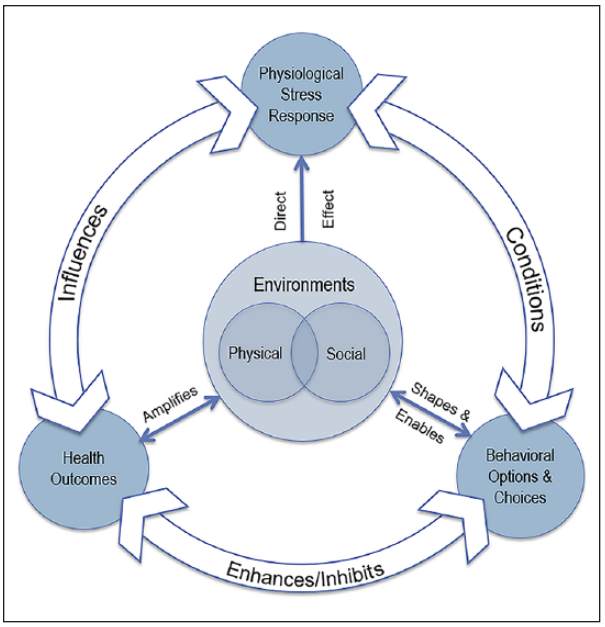

Figure 1. Environmental effects on human behaviors and health.

scope of this article, it is hoped that by showing the physiological relationship between psychosocial stressors during early life and addictive behaviors that appear later in life, at-risk youth can be identified and provided with early intensive intervention. Evidence suggests that not only could such intervention reduce their risk for becoming addicts, it may also have a positive influence on their physical and mental health later in life and may collectively begin to reduce the health disparities so prevalent among disadvantaged populations.

Effects of Environmental Factors on Human Behaviors and Health

The Social Determinants of Health

The modern health care model recognizes the reciprocal effect of a person's behavioral choices and associated health outcomes.[5,6] But behavioral choices do not occur independently from one's environment[5] and are also reciprocal. The social ecological model examines behavior through the interactions of individual, interpersonal, organizational, community, and public policy influences.[7] In this model, well-being is viewed as interdependent; the social and physical environments of a community have a direct influence on the residents' health, and the residents' collective and individual actions modify the healthfulness of their community. The social-ecological model investigates and promotes well-being through an interdisciplinary orientation, using approaches and strategies from the fields of public health, medicine, and the social and behavioral sciences.[8]

Building on this foundation, research in the United States since the 1990s has focused on the physical and social characteristics of neighborhoods as interrelated, non-medical factors, which are known as the social determinants of health.[5,6,9] As depicted in Figure 1, the physical and social environments in which people live shape behavioral options and thereby enable behavioral choices, have direct effects on physiological stress responses, and can facilitate or amplify positive and/or negative health outcomes.[6,9] The physical environment creates the settings and context for social interactions and also conditions how the social environment and social interactions among individuals are perceived.[10] These non-medical factors, which are beyond the control of the individual, can profoundly influence a person's behavioral choices and health outcomes and, more importantly, either enhance or inhibit future behavioral options and health outcomes.[5,6]

For example, studies have shown that neighborhood attributes that affect physical activity rates, such as walkability, connectivity of sidewalks and streets, road proximity, traffic safety, residential density, and recreational facilities, along with proximity to supermarkets, grocery stores, convenience stores, and fast food restaurants, are highly correlated with risk factors for cardiovascular disease such as diabetes mellitus, metabolic syndrome, blood pressure, and body mass index.[11-18] Differences in urban design and unequal distribution of neighborhood characteristics result in health disparities that disproportionately affect disadvantaged populations.[5,9,15,19] Neighborhoods that lack parks, recreational facilities, and pharmacies, and that have an abundance of fast food and alcohol outlets and deteriorated housing are associated with problematic health conditions.[10,20-22]

Mental and physical health is impaired as a result of adverse childhood experiences, including repeated or chronic exposure to psychological stressors that are present in the physical and social environments. Neighborhood stressors include high crime rates, extensive graffiti, overcrowding, inadequate infrastructure, dilapidated buildings, excessive noise, environmental pollution,[1,23] and homes with increased levels of mold and lead paint.[5] Family-related stressors include criminal activity, substance abuse, and family members who have mental illness or who are imprisoned, suicidal, or depressed.[2,3,24-28] Significant stressors during childhood include dysfunctional family dynamics, such as domestic violence,[29] especially violence directed at the mother, household chaos, trauma, physical/emotional abuse or neglect, and sexual abuse.[2,3,24-28] Dysfunctional family

dynamics can lead to continued stressful life events, such as parental divorce or separation, and loss of a job or a loved one.[23,25]

In addition to neighborhood characteristics and social relationships, individual socioeconomic status (SES) is another social determinant that is also strongly tied to one's place of residence and strongly correlated with health outcomes.[5,6] SES can be both a benefit and a hindrance to good health: there is a positive correlation between individual SES and health across all racial and ethnic groups and across all income levels, with the poorest health found among those with the least education and income.[5,9] Because one's level of education directly affects opportunities for employment and therefore income, which in turn influence one's access to and choice of housing, food, transportation, health care, and leisure activities,[5,9] it is not surprising that low income and minority populations are disproportionately affected by hypertension,[26] obesity, violence, homicide, and sexually transmitted diseases.[10,20] These correlations do not refer to an individual's social situation or SES at the time a disease or condition arises, but represent cumulative effects of consistent population patterns correlating health outcomes with socioeconomic gradients.[30]

Apart from individual SES, neighborhood SES is also a determinant of health outcomes. Neighborhood SES considers the number of adults in the neighborhood who have a college education, the number of homeowners, their household income and employment status, and the degree of poverty and economic hardship experienced by neighborhood residents, but it is not an aggregate of the individual residents' SES.[31,32] Neighborhood SES measures the impact of neighborhood-level opportunities and resources—or their lack—on individual prosperity and health outcomes, after controlling for the impact of individual SES,[31,32] with each measuring inequality of resources and achievement, but at different levels and without confounding or compounding the effects.[31]

An individual's social support from family and friends may be diminished if they live in similar neighborhoods and are exposed to similar stressors; this lack of support may range from lack of positive role models, exposure to or avoidance of family or friends who are substance users, lack of contact with or lack of positive social or emotional support from family or friends, or too many demands on the individual by financially or emotionally needy family and friends.[33] In disadvantaged and racially segregated neighborhoods, psychosocial stressors associated with income disparity can also lead to increased tension and violence between individuals.[33] All of these factors become a negative influence of the social environment for individuals where social support and trust is eroded and the potential for substance use and abuse is increased.[34,35] Because health behaviors tend to co-occur, there is an increased likelihood of related consequences such as HIV, hepatitis C virus, and overdose, thus introducing more stressors into the neighborhood environment.[34,35]

There is strong evidence that historical racial segregation in the United States has played and continues to have a significant role in racial differences in SES, and continues to limit employment and education.[19,36] The quality and availability of—or lack of opportunity for and access to—education and employment perpetuates and reinforces socioeconomic, racial, and ethnic health disparities.[5,19,36] Environmental factors such as low SES, unemployment, financial stress, marginalization, lack of access to care, neighborhood disorder, crime, violence, and racism are disproportionately experienced by African Americans, who also experience disease-related mortality and morbidity at disproportionately high rates.[5,19,33,36,37]

Neighborhood effects are social determinants of health that can take a variety of forms: in disadvantaged and racially segregated communities, which frequently have high income inequality, limited educational and economic opportunities, and less access to social and health services,[5,19,33,36] clear evidence of these effects is seen in the incidence of low-birthweight infants,[19] adverse birth and early childhood health outcomes, intimate partner violence, and depression and other mental health issues.[32] Differences in access to social services and medical care have been associated with disparities in birth outcomes, mental health, adult physical health, cardiovascular disease, and mortality.[34] Research has shown that minorities, especially African Americans, who do achieve medical care are more likely to receive inappropriate or less-than-adequate medical care, even after controlling for the type of procedure, disease severity, and differences in medical facilities, insurance, and SES.[19]

It should also be noted that physical and social factors in the external environment can arise as a result of others' actions and do not always reflect individual choice. Traumatic childhood events, whether witnessed or experienced, illustrate environmental experiences thrust on individuals. These include accidental or unintentional events, illnesses,[38] maltreatment, interpersonal physical, sexual and domestic violence,[38,39] bullying, assault, and abandonment.[39] The discussion here is intended to sensitize the reader to the significance of these reciprocal effects between an individual's environment and his or her subsequent behavior and health outcomes.

Effect of Social Determinants on Human Development and Health

From a psychological perspective, it has long been known that early life experiences shape the psyche and condition development of biological systems, and these

in turn have a lifelong influence on well-being and maladaptive responses.[2,3] Two apparently contradictory developmental pathway models explain how early life conditions and social circumstances can affect neurobiological development, resiliency, coping skills, and behavioral and health outcomes.[30] However, these models are not competing and mutually exclusive, but actually explain different aspects of the developmental challenges faced by children living in disadvantaged circumstances.[30] Both of these models are implicated in the propensity for addictive behaviors, and clearly show the long-term impact of social and environmental conditions on behavioral choices and health outcomes.[30]

The *latency model* is predicated on the idea that normal brain development occurs during critical and sensitive periods in early life.[30,40] This model posits that specific competencies are gained during each discrete period in time, and thus adverse early life socioeconomic and psychosocial circumstances can profoundly affect later life if normal development is impaired and acquisition of such competencies does not occur during the critical periods.[30,40] There can be life-long effects on health and well-being,[40] because the missed developmental competencies very early in life cannot be induced later in life, regardless of experiences during the interim years.[30]

In contrast, the *pathways model* of child development theorizes that life events have cumulative effects which are reinforced or ameliorated by the various socioeconomic and psychosocial experiences and circumstances over a lifetime.[30] This model posits that successfully negotiating important transition points associated with core developmental processes builds the capacity to cope with each successive stage of life, and failure to successfully manage any given transition point causes problems coping with subsequent experiences.[41] Therefore, the most successful intervention and prevention efforts should address core developmental processes that occur during critical transition points in early childhood.[30,41]

The pathways model recognizes that there are cumulative effects of early life conditions and social circumstances which lack stability and security; these factors impair development of neurophysiological systems, produce physiological effects of chronic stress, can generate feelings of alienation or powerlessness, and may include social support systems that consist of others who have been marginalized.[40] These cumulative effects result in a cruel cycle that has both short- and long-term consequences and is self-perpetuating: in adolescence, it is associated with lack of educational achievement and a greater potential for criminal behavior, pregnancy, and drug use; in midlife, it is correlated with the quality of employment and social support, and with chronic disease; and later in life, its effects are seen in deteriorating health and degenerative conditions.[40]

Regardless of the model used, affluence or deprivation in the social, socioeconomic, and built aspects of neighborhood environments have been independently correlated with health behaviors.[22] Because early life events are the common factor in both models, these models interact in complex ways: an early life event can either have a latent effect or be the initiating factor in a series of life events that have implications for future competence, health, and well-being, and similarly, an intervention in early childhood can provide opportunity to gain competencies that would have otherwise been missed or change the developmental trajectory in ways that ultimately improve long-term health and well-being.[40] The validity of the pathways model is supported by effective early interventions, which alter subsequent early life experiences and positively influence future competencies and health outcomes, indicating that long-term effects of early life events are not predetermined at the time of the event.[41] Conversely, the importance of the latency model is underscored by evidence that the earlier an intervention occurs, the more effective it is.[41]

Effects of the Physiological Stress Response on Brain Structure, Behavior, and Health Outcomes

The previous section explored the complex relationship between environment, behaviors, and health, and discussed multiple intertwined factors that are not easily disentangled. This section shifts the focus to the top of Figure 1, recognizing the direct influence of our social and physical environments on our physiological stress response. This section will explore the physiological effects of chronic stress, delineate the structural and functional changes that arise from it in the hippocampus, amygdala, and prefrontal cortex, and discuss the cognitive and behavioral consequences of these neurological changes. It will then consider some of the ways that the physiological stress response influences health outcomes and their possible role in addiction.

The amount of support, resources, coping skills, and control that a person has determines how an experience is interpreted in the neural circuitry of the brain.[1] Whether an experience is real or perceived, the interpretation of it as benign or threatening elicits a stress response in the body, which in turn increases either resilience or risk related to future health outcomes.[1] Perceived or subjective stress has been positively correlated with higher impact on the body's stress response system, and was found to be equally or

more important than objective stressors at eliciting a physiological response.[37]

The magnitude, intensity, frequency, and duration of stressful events determines the type of stress response.[2] There are 3 types, classified as positive, tolerable, or toxic, which are distinguished by the magnitude and strength of the stress response, how frequently it occurs, and how long it takes for the body to return to its baseline, nonstressed state.[2] Positive or tolerable stress elicits an adaptive response that results in growth, beneficial development of coping skills, learning new behaviors, and future resiliency, whereas toxic stress results in a maladaptive response that elicits a cascade of physiological, neural, cognitive, and behavioral changes that increase future vulnerability and risk for stress-related diseases later in life.[1]

For children, who have little to no control over events in their lives and are learning coping skills, their greatest resources and support come from responsive, caring, nurturing adults who provide a protective buffer for them and help them learn to cope.[2] Positive and tolerable stress responses occur when such a caregiver is present: the stress response is considered positive if the physiological impact is brief and the magnitude is moderate or mild.[2] It is considered tolerable if a sudden or unusual event elicits a stronger but still temporary physiological response with greater magnitude and duration.[2] When chronic or frequent stress occurs without the presence of a supportive caregiver, it is considered toxic stress, because the absence of that protective buffer results in a prolonged or unabated physiological response that is the catalyst for a cascade of neurological, cognitive, and behavioral changes with long-term, detrimental effects.[2]

Brain Changes as a Result of Stress Response

Both pre- and postnatal experiences directly affect many neural systems in the brain. The use of alcohol, tobacco, and other drugs during pregnancy has a strong influence on neurodevelopment.[42] Intrauterine environmental stressors are known to result in disturbances to the prefrontal cortex and neuroendocrine functions, which can express as behavioral problems during childhood and adolescence.[3] Neurological systems also shown to be malleable based on human experiences include the systems involved in perceiving and responding to threats; the neural circuitry that enables executive function (needed for self-control, attention, memory, and behavioral organization); and the hypothalamic-pituitary-adrenal (HPA) axis, which coordinates and regulates physiological response to stress and return to homeostasis.[3,26] All of these neurobiological systems are important for perceiving, responding, and interacting with our environment in appropriate ways.[3,26]

Whether pre- or postnatal, the detrimental effects of unrelenting activation of the physiological stress response due to exposure to chronic environmental stressors increase the risk for dysregulation of the HPA axis, thereby influencing and amplifying health risks as shown in Figure 1, and exacerbating disease vulnerability and progression in vulnerable populations.[3] For example, dysregulation of the HPA axis has been associated with depression, with elevated activity of the HPA axis found in up to 80% of depressed patients.[43] Relatedly, children with low-SES history are known to experience increased activation of the HPA axis, differences in selective attention, and reduced differentiation of stimuli.[3] When prenatal adverse exposures are combined with postnatal adverse events, the effect on risk is cumulative.[3]

Adaptation to prolonged stress that results in alterations in the neural structures of the brain itself is known as *stress-induced plasticity*.[43] The physiological response to the external environment activates the HPA axis, which has profound effects on brain development and plasticity in critical areas that condition behavior in ways that are only beginning to be understood.[3] Much of what is known about human stress response and brain plasticity is based on evidence from animal studies, with numerous studies providing evidence of linkages and supportive of the propositions provided here.[3,27,43-48] Further exploration of the findings from animal studies to human populations will continue to benefit our understanding of the interplay between genetic influences and environmental stimuli. Such research has shown that experience-dependent plasticity results in structural and functional differences in the brain, which are not found in those without similar experiences, and this neural plasticity results in adaptive or maladaptive responses to our environment and subsequent experiences.[27]

These adaptations result in changes to neural connectivity, structure, and function, which in turn influence how the brain perceives and interprets the environment and sensitize the brain to adverse environmental factors.[26] Stress-induced changes in brain function can have long-lasting consequences, including heightened awareness of potential threats, increased emotional reactivity, impaired cognitive development, and reduced ability to adapt to challenging conditions.[26] Adverse childhood experiences can not only affect these neurobiological systems but can also result in epigenetic modifications that alter expression of genes, and increase risk for psychiatric disorders.[3,26] Ultimately, responses to stress are highly individualized, depending on the person's genetic heritage, early life experiences, and prior exposure to

stressors, thus the magnitude, duration, and physiological consequences, and ultimately resilience or susceptibility to stress, can be quite different.[43]

There are measurable differences in the biological structures of the brain in individuals who have experienced adverse early life conditions, when compared with those who have not had these experiences.[3] Although a detailed description of all stress-induced neurobiological changes and their mechanisms is beyond the scope of this article, a brief discussion of cortisol and its effects on brain function and behavior follows as an example of the complexity and far-reaching impact of such changes. Cortisol is the hormone released by the adrenal glands in response to long-term stressors,[3,26] such as adverse early childhood experiences and other types of ongoing environmental and psychosocial stressors previously discussed.

Perhaps the greatest effect of early adversity is seen in the HPA axis, which normally has a diurnal rhythm with higher cortisol levels in the morning and decreasing levels throughout the day, but is inherently sensitive to the environment as well.[3,49] In addition to the diurnal rhythm, cortisol reactivity independently occurs when perceived or actual stressors elicit release of a series of sequential hormone signals from the hypothalamus to the pituitary, and then from the pituitary to the adrenal cortex, which in turn releases the stress hormone cortisol.[3,49] Cortisol circulates in the blood throughout the body and brain, binds with receptors in the amygdala, the prefrontal cortex, and the hippocampus, and coordinates both behavioral and physiological responses to these stressors.[3,26]

Normal cortisol production beneficially primes the body to cope with stress by changing glucose metabolism, enhancing cardiovascular function, stimulating the anti-inflammatory immune system, and sharpening cognitive function.[3,37] However, in a stressful environment, the stress response results in overactivation of the sympathetic nervous system and the HPA axis, leading to greater secretion of catecholamines and glucocorticoids and higher serum cortisol levels.[3,50] High levels of cortisol usually act as a negative feedback loop to shut down cortisol production, but in environments with continuous, ongoing, or extreme real or perceived stressors, especially if the threats are unpredictable, ongoing cortisol reactivity keeps cortisol levels from returning to baseline.[3,37] Prolonged periods of relentless exposure to stressors increases reactivity and reduces recovery, dysregulating the normal feedback loop; in addition to blunted or heightened reactivity of the HPA axis, physiological changes in the individual's HPA axis result in greater cortisol variability, increased stress sensitization,[3,37] more aggressive or disruptive behavior,[3] and increased risk of stress-related diseases.[37]

Research has shown a smaller volume of gray matter (neurological capacity for information processing) in the amygdala, resulting in greater activation or failure to suppress activity in response to stressful experiences or strong emotions.[26] The amygdala is the neural region that detects and responds to threats in the environment by generating a fear response, which can escalate to anxiety or excessive fear if the threat or perceived threat is ongoing or repeatedly experienced.[3]

The prefrontal cortex is the region that enables cognitive control, attention to stimuli, memory, and executive function.[26] Early adverse events have also been associated with smaller volume of gray matter and less activation of the prefrontal cortex, as well as delayed processing and reduced performance monitoring.[3,26] The amygdala and prefrontal cortex are 2 areas of the brain that regulate and condition individual decision making about risky behavior and are also most susceptible to substance use and abuse.[4] Stress-induced changes in the structure and function of these areas of the brain are associated with vulnerability to addiction during adolescence, which is discussed in the later section titled "Adolescent Brain Changes and Vulnerability to Substance Use."

The hippocampus is another area of the brain that has been found to have a smaller volume of gray matter in those who experienced early adverse life conditions.[26] The hippocampus plays an important role in regulating cortisol production and returning the HPA axis to homeostasis following an acutely stressful event.[1] Research has shown that chronic stress and continuously elevated cortisol levels impair both the structure and function of the hippocampus, and therefore its ability to maintain homeostasis.[26,43]

Severe neglect is one of the most extreme and damaging environments a child can experience; studies of children from orphanages, who experienced extreme neglect with very little interaction from caregivers, have provided a wealth of epidemiological evidence for the negative effects on the brain of unrelentingly stressful physical and social environments.[3,27] This extreme neglect had pronounced effects on the children's HPA axis function, as measured by blunting of the diurnal rhythm and elevated evening cortisol levels; additionally, the length of time that the children were in the orphanage and the extent of the social neglect correlated with the severity of the diurnal cortisol blunting.[3] These children exhibited growth delays, serious impairments in cognitive function, language ability, emotional and personality development, and greater vulnerability to disease, collectively known as *institutionalization syndrome*.[27]

How the Physiological Stress Response Influences Health Outcomes

The previous sections discussed how the physiological response of individuals to chronic psychosocial stressors and adverse childhood experiences results in impaired mental and physical health, with greater health disparities seen among minorities and disadvantaged populations, and explored how the social determinants of health and the physiological stress response interact to influence behavioral choices and health outcomes. Throughout these sections, correlations with specific diseases and other adverse health outcomes were given, but these findings came from studies of adults. In this section, the focus will be on some of the adverse health conditions experienced by adolescents.

Responses to stress differ by the adolescent's age, gender, and coping style but, independent of addiction or substance use, increased stress is generally associated with greater cortisol response, elevated inflammatory responses, less physical activity, and more emotional eating.[51] Independent of other known risk factors, environments that are perceived as dangerous, unsafe, or threatening can evoke psychological, behavioral, and physiological stress response mechanisms that directly influence health outcomes by increasing the adolescent's risk for obesity, diabetes, hypertension, anxiety, and depression.[50,51] Because the risk factors are co-occurring and reciprocal, overweight and obese children are shown to have a higher risk of depression and suicidal thoughts, and this risk is even greater for disadvantaged youth.[52]

The risk for excessive weight gain is higher for children in disadvantaged environments and lower-resource communities; these children have 20% to 60% higher odds of being overweight or obese.[53] Although obesity rates appear to have stabilized in the general population of children aged 2 to 19 years, racial and ethnic disparities persist; overweight and obesity rates are 35.9% and 38.2%, respectively, among African American and Hispanic children, and significantly less (29.3%) among white children.[53] Among adolescents aged 12 to 19 years, the prevalence of overweight and obesity is 41.2% among African Americans compared with 30.0% among whites,[54] and 4% to 6% of youth are classified as severely obese, with minority and disadvantaged youth having a higher prevalence of severe obesity.[52]

Pediatric hypertension is highly correlated with overweight and obesity and there is a direct correlation between the degree of pediatric hypertension and the risk for hypertension, stroke, and kidney disease in adulthood, however, only about 50% of adolescents with hypertension are obese; unfortunately, pediatric hypertension that occurs in the absence of excess weight is often not diagnosed or treated before permanent organ damage has occurred.[52] Pediatric hypertension estimates range from 3% to 14% for normal weight children and from 11% to 30% for obese children, but these rates are likely to be seriously understated; studies have shown that hypertension is diagnosed in only 13% to 26% of children.[52]

The health disparities reflected in the foregoing show how the physiological stress response that is evoked by adverse early life conditions can directly and powerfully affect health outcomes that are evident by adolescence and continue into adulthood, as discussed in previous sections. It should come as no surprise that adolescents' behavioral choices, including substance use or abuse, are also conditioned by these early life conditions. The *stress reduction hypothesis* posits that substance use is a coping response to heightened psychological and physiological stress.[33]

Factors in Adolescent Addiction

Genetic and Environmental Influences on Addiction

The tendency for drug use and misuse is strongly influenced by factors as diverse as gender, age, psychological and neurobiological factors that affect impulsivity and sensation seeking, and genetic vulnerability,[55] which is also supported by animal studies.[3,27,43-48] Various researchers have sought to clarify the role of genetic and environmental influences on addiction by means of twin studies, longitudinal research, and meta-analyses.[56-59] The pattern of results indicates that factors such as a common environment are most important in the initiation of substance use, whereas genetic and unique environmental influences appear to be more important in the progression to problem use.[59]

Genetic predispositions and vulnerabilities partially influence susceptibility to social and environmental stressors, interact with personality traits and comorbid psychiatric disorders, and influence the trajectory of addiction at varying stages (e.g., acquisition, maintenance, relapse).[57] Epidemiological studies estimate 30% to 60% heritability of genes that predispose to addiction, but genetic vulnerability is strongly influenced by environmental factors and drug availability, and does not predict actual substance use or addiction.[57] Clearly, there is a reciprocal determinism between genes and environment and both are important; part of the question being addressed by researchers is the degree to which they are co-occurring. Environmental factors appear to have greater influence during early development, whereas

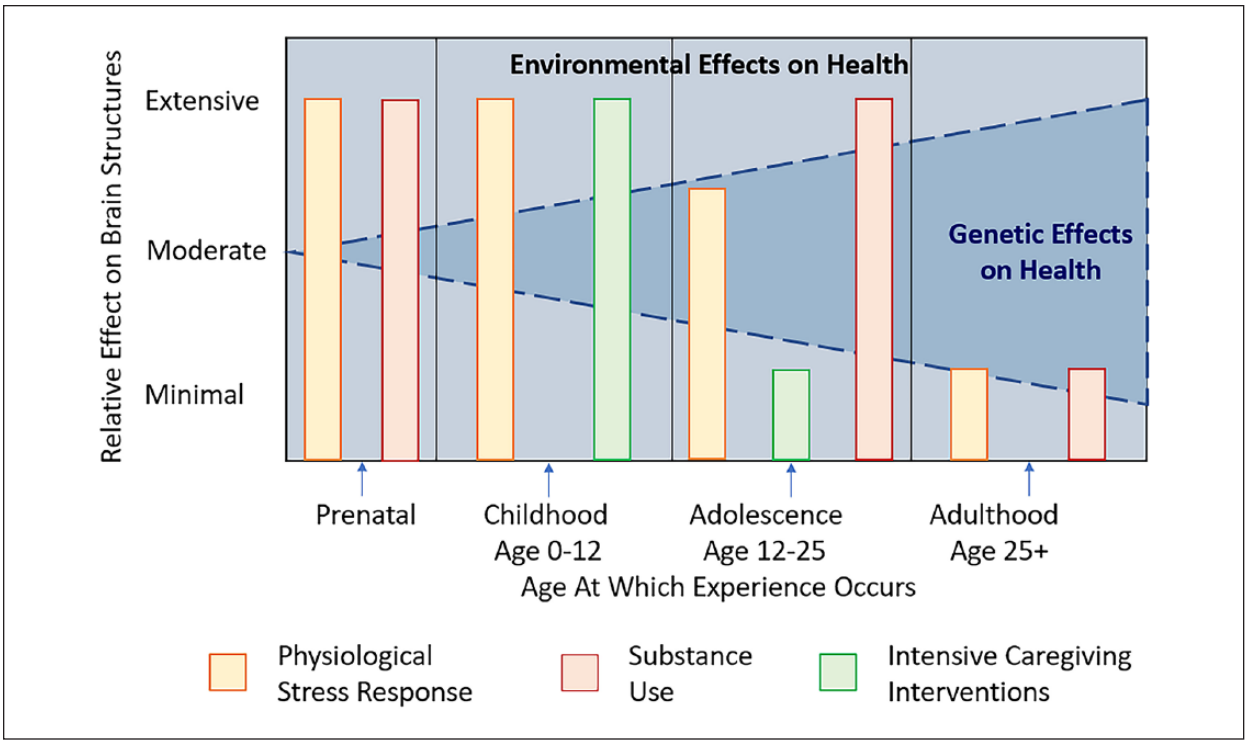

Figure 2. The relative influence of environmental and genetic factors on health changes over time. Environmental effects are greater during early development whereas genetic effects increase with age due to increased opportunity for environmental interactions, thus the physiological effects of experiences differ according to the age at which they occur. Prenatal: Physiological stressors and parental substance abuse have significant effects on fetal brain development. Childhood: Physiological stressors and intensive caregiving interventions (discussed later) have significant effects on the developing brain, with greater effects occurring among the youngest children. Adolescence: Physiological stressors still moderately affect the developing brain, but intensive caregiving interventions have only minimal effects. Substance use during this period has extensive effects on the developing brain. Adulthood: Physiological stressors and substance use have minimal effects on brain development.

genetic factors have greater influence later in life[60] and gradually increase their effect as individuals age[56] and as opportunity for interaction with the environment increases, as shown in Figure 2.

Adding to the complexity, genetic risk factors can be modified by environmental factors, differences in genetic inheritance can mediate responses to environmental factors,[56,58] and the effect of environmental influences can become greater over time if they are enhanced by gene-environment correlations.[58] There is also a correlation between genetic risk, which is transmitted by parents, and environmental risk, which is shaped by parents, thus any evaluation of gene-environment correlation that involves the family environment may be at least partially genetically mediated.[58] Specific genetic influences, such as the rate of drug metabolism, are associated with risk for specific substance use disorders (SUDs), while non-specific risks for SUDs are associated with environmental risk factors.[60] In addition, risk for SUDs is thought to be additive, with the number of exposures over time being more important than a single exposure at one point in time.[60] This is consistent with the *cumulative risk hypothesis*, which states that there is a positive correlation between the number of risk factors and the frequency of clinical problems,[61] as illustrated in Figure 2.

Effect of Social Factors on Adolescent Addiction Behavior

Both interpersonal and community influences affect adolescent behavioral choices and health outcomes.[7,8] Highlighting the importance of these influences, researchers have identified unique risk and protective factors during young adulthood that predict the likelihood of problem substance use.[42,62] Individual risk factors that promote problem substance use include having a favorable opinion of substance use, early initiation of substance use, peer substance use, parental substance dependence, lack of dedication to school, poor scholastic achievement, rebelliousness, rejecting conformity, and male gender.[42,62] Social contexts reflect changes in

life circumstances: problem use is predicted by changes that provide increased personal freedom and limit social controls, such as beginning college or university, and moving out of the family home; conversely, lower usage is predicted by college graduation, cohabitation or marriage, and employment.[42,62] Community factors include cultural values, norms and expectations; laws regarding how and to whom substances are sold; substance cost, legality and availability; and the degree of neighborhood disorganization, deterioration, and instability.[42,62]

Social and familial environmental factors are critical in influencing psychoactive substance use in early adolescence.[56] Neighborhoods with high rates of poverty, assault, or public assistance are considered high-risk environments.[63] When high-risk environments are combined with unhealthy, high-risk peer influences, parental influence may become the most important factor in determining whether an adolescent will turn to substance use or abuse.[63] Thus it is important to consider a child's socioeconomic and built environment, social influences from peer networks, influences of the parent-child relationship, and interactions between all of these as mitigating or exacerbating factors affecting health behaviors.[63] In young adulthood, being unemployed and out of school are risk factors for both substance use and abuse, suggesting that parents, employers, and community organizations that support employment and schooling can contribute to reducing substance use.[42]

Childhood traumatic events have been associated with development of post-traumatic stress disorder (PTSD).[38] PTSD is characterized by the development of specific symptoms following exposure to one-time or ongoing traumatic experience, which cause significant functional impairment or distress and last for more than a month.[64] PTSD can consist of 3 core symptoms (intrusion or re-experiencing, avoidance, and hyperarousal or reactivity), or in those who have experienced long-term trauma, a more complex form of PTSD can also include affective dysregulation, relationship avoidance, and negative self-concept which is specifically trauma related.[65] Childhood traumatic events are strongly associated with multiple behavioral and psychiatric outcomes during adolescence, including substance use and addiction.[38]

A nationally representative study found that traumatic events that occurred prior to the age of 11 years were associated with alcohol and drug use beginning at a younger age, drinking as a way of coping, with heavier alcohol use by boys who survived sexual assault, and specific types of drug use during adolescence.[38] Exposure to any traumatic event during childhood increased the risk for lifetime use of drugs, ranging from marijuana to cocaine, other illegal drugs, nonmedical prescription drugs, and polydrug use.[38] Although there were different relative risks for each type of trauma, there was a dose-response relationship with adolescent drug use as the number of exposures to childhood traumatic events increased: compared with children who were not exposed to traumatic events, the relative risk of lifetime illicit drug use increased as the number of exposures increased, with the greatest effect seen for cocaine use.[38]

Because drug use is a social activity, neighborhood social networks can also be a determinant of drug use,[34] as shown by the "shaping and enabling" relationship in Figure 1. In neighborhoods with high population density where sales of illicit drugs are more likely, income inequality, race/ethnicity, neighborhood characteristics, peer influence, and cultural and social norms within one's family and community of residence can be moderating and mediating factors.[34,55,66] Although population density is lower, greater risk for alcohol and tobacco use among rural youth occurs in conjunction with social and cultural aspects of rural living, including greater use and acceptance by adults in the community, isolation, loneliness, limited recreational opportunities, and less access to health care.[34] In rural areas, a more relaxed or permissive attitude about alcohol and tobacco use by adolescents is common, especially when used at home or in social settings, with adults either not restricting access or actually supplying these substances.[67]

Although population density may play an important role in behaviors that affect health, social norms and group practices both contribute to social learning.[34] The combined influences of population density, social norms, and social learning can increase or reduce the risk for use or abuse of illicit drugs, alcohol, or cigarettes, and exposure to sexually transmitted diseases, including HIV.[34,35] In more densely populated neighborhoods, common resources are shared, and the behaviors of one group can influence the behaviors and thus affect the health of other groups.[34] For example, it has been shown that students at schools with more violence, fewer health resources, and a stressful school climate are more likely to form unhealthy peer relationships, have poorer physical and mental health, and experience more behavioral problems.[50]

Those who experiment with substances usually obtain them from friends or social contacts when they first begin using.[67,68] Among high school students, risk factors include increased age, perceived availability of alcohol and other drugs, perceived prevalence of peer use, social support or acceptance of use, and physical availability and use.[67,69] The risk of adolescent substance abuse is increased when parents, friends, or role models use substances or are supportive of substance use, when

unsupervised time is spent with peers, and when parents use harsh, inconsistent discipline.[28,70] Independent of individual and family characteristics, there is a positive association between drug and alcohol use and the degree of neighborhood disorganization, indicated by residential instability, drug selling activity, and crime.[70]

Prevalence of Adolescent Substance Use

Changing social norms and perceptions are also a factor in adolescent substance use. In their 2011 report on adolescent substance use, the National Center on Addiction and Substance Abuse (CASA) at Columbia University reported that 25% of adolescents and 21% of parents considered marijuana to be harmless and 17% of adolescents considered marijuana to be medicinal.[28] Because these changes in perception have not occurred for substances like heroin, cocaine, or hallucinogens, research that includes marijuana use in the category of "other drugs" or "any illicit drug use" may not capture changes in marijuana usage patterns, risk factors, or other associated relationships.[70] Nevertheless, research consistently shows that the substances used most frequently by adolescents are alcohol, tobacco, and marijuana.[67,71,72] Although alcohol is the substance most widely used by young people,[67,71] marijuana use has become more socially accepted, and adolescents' perceptions of the harmfulness of its use have decreased by nearly 80% since the 1990s.[70]

The 2012 National Survey on Drug Use and Health reported that, among adolescents aged 12 to 17 years, "fairly or very easy" access was reported by 48% for marijuana, 26% for cocaine, 16% for heroin, and 15% for LSD (lysergic acid diethylamide).[67] The 2012 Monitoring the Future Survey indicated higher percentages for high school seniors, with easy access reported by 91% for alcohol, 82% for marijuana, and 30% for cocaine.[67] In their report on adolescent substance use, CASA found that more than 82% of high school seniors and 75% of all high school students had used addictive substances (alcohol, cigarettes, marijuana, or cocaine), and of those students, nearly 20% had a clinical SUD.[28] CASA also found that 46% of all high school students were current users of these addictive substances, and of current users, one-third had a clinical SUD.[28] The prevalence of clinical SUD was nearly 1 in 8 (12%) for all high school students, but for high school seniors, it was more than 1 in 6 (18%).[28]

In their report, CASA found that, despite the scientific studies showing that addiction is a disease, only about one third of students and their parents perceived addiction as a physical or mental health problem, whereas about 40% viewed it as a behavioral problem, and about 60% saw it as an emotional crutch; addiction was seen as a lack of willpower or self-control by 63% of students and 54% of parents.[28] These misperceptions are a barrier to successful addiction treatment, which distract from attention to the potentially bigger barrier, that substance use causes significant physiological changes in the adolescent brain.

Adolescent Brain Changes and Vulnerability to Substance Use

Because the human brain is not fully developed until young adulthood, in the mid-20s,[28] the still-maturing adolescent brain is particularly vulnerable to addiction as a result of stress-related physiological changes,[4,28] which were previously discussed in the section "Brain Changes as a Result of Stress Response." In the adolescent brain, the connections are still being established between the prefrontal cortex, the amygdala, and the hippocampus; the neurotransmitter dopamine plays an important role in these processes.[73] Dopamine increases the sensation of pleasure, and during early adolescence, the prefrontal cortex has the most dopamine receptors[74,75] and the highest levels of dopamine.[28,74] These developmental stages of the brain during adolescence occur at the same time that sensation-seeking and risk-taking behaviors are most likely, including experimenting with addictive substances, and the heightened dopamine feedback response reinforces these behaviors.[4,28] There is also evidence that substance use has a more powerful and long-lasting effect on the brain during adolescence than after the brain has matured, resulting in functional deficits that affect learning, memory, attention, judgment, and cognitive performance and increasing the risk of lifelong addiction and substance use disorders.[28,74]

Evidence suggests that changes to the neural systems of the brain as a result of adverse early environments, which produce altered behaviors such as impulsivity and sensation seeking, may precede drug seeking behavior rather than result from it.[60] This idea is reinforced by the finding that these changes in neural or behavioral characteristics were shared by non–drug using first-degree relatives of drug abusers but were not found in controls.[60] Substance abusers and their non-using siblings were also found to have similar changes in brain structure in the amygdala and frontal regions that resulted in impaired inhibitory control.[60] These shared behavioral and neural characteristics, known as *endophenotypes*, which precede substance use, are often attributed to genetic influences but may also arise from shared environmental effects, and can be exacerbated with substance use.[60]

Such changes in the structure and function of the brain, whether they precede or follow exposure to

addictive substances, make it very difficult for substance users to change their behavior; not only is cognitive function affected, but so is the ability to control compulsive or pleasure-seeking behavior.[28] Even when the individual is able to stop using, memories can be triggered by environmental cues, resulting in ongoing or recurring cravings for the substance.[28,60] The prevalence of substance use and addiction in adolescents, despite decades of prevention and treatment programs, indicates that it is time to reconsider addiction approaches.

The Importance of Targeted Early Interventions

Decades of animal and human research have shown that, compared to other interventions, the strongest influence on neural structures and neurobiological systems was the quality of caregiving that was received; evidence from these studies suggests detrimental effects on brain structures when consistent, predictable, nurturing, responsive parenting is lacking.[3,27,43-48] One of the most exciting aspects of such research is that, because the brain's neural systems exhibit plasticity, it is possible to recover at least some of the lost functions associated with stress-induced structural changes (as previously discussed in the section "Brain Changes as a Result of Stress Response") through intensive targeted interventions and environmental adjustments, as summarized in the following studies.

Perhaps the most well-known intervention is the Bucharest Early Intervention Project, a randomized controlled trial (RCT) in which some of the children from Bucharest orphanages were randomly assigned to therapeutic foster care in which they received enhanced caregiving; despite the severe neglect they had survived, the children in the intervention experienced markedly improved cognitive outcomes and greatly reduced developmental disturbances suggestive of changes in brain function, with the children who were youngest at the time of foster placement having the most improvement.[76] A meta-analysis of 14 additional orphanage-based interventions in 7 countries over a span of 70 years found a large effect size, $d = 0.84$ (CI 0.65-1.04, $N = 826$), indicating considerable success in improving cognitive development in these children, with the most effective interventions starting prior to the child's first birthday ($d = 1.03$, $k = 8$, $N = 468$); the effectiveness of the interventions decreased as the child's age at start of intervention increased.[77]

Further supporting the environment as an intervention, the Multidimensional Treatment Foster Care for Preschoolers program provided a behavior management intervention that incorporated strategies to reduce stress and increase consistent, positive parenting for children aged 3 to 6 years in foster care.[78] A 1-year long RCT compared children in this program with children in regular foster care; when measured, the diurnal cortisol rhythm was blunted for children in foster care who did not receive the intervention, but children in the program who received effective, highly responsive caregiving showed cortisol patterns consistent with children *in the community control group*.[79-81] It is notable that foster parents in the intervention group also experienced reduced stress levels, whereas the stress level increased for foster parents who did not receive the intervention.[82]

The 10-week long Attachment and Biobehavioral Catch-up (ABC) intervention,[49] which focused on infants and toddlers at risk of neglect, used an attachment-based approach to address parents' issues, teach them how to recognize their children's needs, and how to interact in a highly effective and responsive way. This intervention was designed to affect the children's regulatory capacity and in turn assess HPA axis functioning. An RCT of the ABC intervention compared children who had received this intervention with children who had received a nonattachment-based educationally focused intervention intended to improve cognitive function.[49] Children who received the ABC intervention, which shaped the child's environment as the active ingredient of the intervention, had more variation in their diurnal cortisol rhythm; whereas, the children who received the educational intervention had a more blunted pattern.[49] Furthermore, these effects were maintained through preschool, demonstrating that responsive parenting has a long-term normalizing influence on HPA axis functioning.[83]

Another RCT intervention was conducted with maltreated infants approximately 13 months old who still lived with their biological caregivers.[84] Infants were randomly assigned to 3 different intervention methods: child-parent psychotherapy, psychoeducational parenting intervention, and a community standard intervention; a control group consisted of demographically similar children who were not maltreated. Infants receiving the community standard intervention showed declining morning cortisol levels over the course of the study, whereas children in the other 2 intervention groups showed morning cortisol levels that were similar to the control group; these normalized morning cortisol levels were still evident 1 year post-intervention.[84]

These studies and others provide consistent evidence supporting the brain's capacity to be repaired through environmental interventions that occur during critical developmental windows, while brain plasticity enables repair to the HPA axis and reversal of early adversity effects on brain structures.[3,49] The finding that siblings of

substance users shared biological changes associated with early environmental influences shows the importance of interventions that include non-substance using relatives prior to environmental opportunities for substance use.[60]

Rethinking Addiction

Clearly, the physical and social environments are powerful determinants for the adoption and continuation of addictive behaviors.[34] Although these behaviors appear to be individual choices, the influences on our behavioral choices are much more complex. This means behavior alterations cannot be addressed successfully without considering the characteristics of the environment in which the individual lives, works, and plays because it shapes adolescent development and individual-risk factors.[34,35,70] Despite decades of educational and prevention programs, there is scant evidence that individually targeted prevention efforts among adolescents are effective or that they mitigate health and social harms that result from substance use,[85] suggesting that more comprehensive approaches for amelioration are needed.

There is growing evidence that drug prevention efforts in high-risk populations are more effective when implemented in early childhood, rather than waiting until adolescence.[86] For example, interventions in childhood and adolescence that target the family management skills of parents and adolescent academic performance have reduced adolescent substance use and continued impacting use into young adulthood.[62] Although substance use and abuse peak during young adulthood, longitudinal research suggests that opportunities to ameliorate harms by means of modifying risk and protective factors begin prior to birth and continue through young adulthood.[42] Adequate and appropriate early interventions in at-risk children are cost-effective and have been shown to increase employment potential and reduce criminal behavior and drug abuse in adolescence and beyond.[87,88] These findings argue against waiting until adolescence to initiate drug prevention efforts.

Addiction is a complex and challenging condition with many contributing factors. The previous sections have presented clear and compelling evidence that the neurodevelopmental consequences of the physiological stress response and the changes it induces in the brain can be mitigated or even reversed through early interventions using intensive, consistent, supportive caregiving; until this is recognized, the effectiveness of treatment approaches to addiction and substance use disorders will continue to be limited. One of the most effective approaches is *trauma-informed care*, which recognizes and addresses the long-lasting residual effects of adverse early life experiences.[89,90]

Because of the physiological effect of environment on brain plasticity and behavior, it is unsurprising that clinical interventions which focus solely on changing individual behaviors have been insufficient to reduce substance use and addiction.[85,91] Successful prevention and intervention programs need to focus on social and environmental factors found in neighborhoods and communities, and the influence of community and neighborhood environments on the individual.[35,56,59,62,72,92] Rather than the current medical model of treating addiction one person at a time, researchers, interventionists, and policy makers who take a much more comprehensive view of the etiology of additions, recognize that environmental stressors lead to biological and neurological changes and addictions, and direct their focus toward primary prevention modalities, can potentially alter the trajectory of health for entire populations.

Conclusion

The physical and social environment should be seen as both a determinant and as an opportunity for intervention. Although the physiological stress response to the environment can have detrimental effects on brain functioning, with consequent effects on addictive behaviors and health outcomes, human and animal studies have demonstrated unequivocally that we can make changes to the environment that have positive effects on brain function[3,27,43-48] and therefore positively influence behavioral choices and health outcomes. In the context of addictions, it is important to incorporate these factors in the analysis of risk and design of early interventions for prevention and amelioration of addiction. In light of the foregoing, the social ecological model can reorient and inform the approach to professional interventions and allow conversations to expand beyond individually-targeted treatment approaches. This broader view of addiction behaviors that incorporates the environmental contexts in which individuals live, work and, play, combined with what is now known about stress-induced neurobiological changes, creates an unprecedented opportunity to find new strategies that include intervention leverage points beyond the individual.

Author Contributions

DRE contributed to design, research, acquisition, analysis, and interpretation; drafted manuscript; critically revised manuscript; gave final approval; and agrees to be accountable for all aspects of work ensuring integrity and accuracy. RWS contributed to conception, design, analysis, and interpretation; critically revised manuscript; gave final approval; and agrees to be accountable for all aspects of work ensuring integrity and accuracy. MMO contributed to analysis and interpretation;

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