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Addiction as a Systems Failure: Focus on Adolescence and Smoking

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Abstract

Objective—Scientific advances in the field of addiction have forever debunked the notion that addiction reflects a character flaw under voluntary control, demonstrating instead that it is a bona fide disease of the brain. The aim of this review is to go beyond this consensus understanding and explore the most current evidence regarding the vast number of genetic, developmental, and environmental factors whose complex interactions modulate addiction risk and trajectory.

Method—Focusing on childhood and adolescent smoking as a paradigm, we review the important risk factors for the development of addictions, starting at the level of genetics and closing with a focus on sociocultural and policy factors.

Results—A critical review of the pertinent literature provides a detailed view of the cumulative power of risk and protection factors across different phenomenological levels to modulate the risk of undesirable outcomes, particularly for young people. The result represents a compelling argument for the need to engage in comprehensive, multilevel approaches to promoting health.

Conclusions—Today, the field of medicine understands more about disease than about health; however it need not be that way. The view of drug addiction as a systems failure should help refocus our general approach to developing dynamic models and early comprehensive interventions that optimize the ways in which we prevent and treat a complex, developmental disorder such as drug addiction.

Keywords

drug abuse; addiction; dopamine; adolescence; systems biology

There seems to be a chronic tension between our growing understanding of children's emotional and physical needs and vulnerabilities and the ostensibly shrinking capacity (or eagerness) of our society to actively promote and sustain their well-being.¹

As the Institute of Medicine (IOM) report entitled “From Neurons to Neighborhoods” wisely recommends, “new investments must take advantage of nearly 50 years of research on early childhood development to improve existing policies aimed at raising and educating young children.”

Such a comprehensive, multilevel approach also rings true, of course, in the context of most models of abuse and addiction that have been developed around a “person-to-system” axis and that present reasonable, multipronged approaches for investigating and mitigating the impact of substance use disorders (SUDs).^{2–5} Most of these models have evolved from the

epidemiological triad of infectious disease causation (host–agent–environment) and are designed to shed light on the multidimensional nature of SUDs from slightly different angles (Figure 1). In one way or another, the validity of these models is predicated on the well-established fact that ecological constructs offer the best chance to deal with the staggering complexity of the living world as it affects health and disease. They all recognize the existence of mutual interactions between biological systems that are embedded inside, and strongly influenced by nested social, economic, political, and cultural spheres.

From this perspective, it would seem reasonable to propose an expansion of the scope of the IOM title in both the micro and macro directions, to arrive at the even more ambitious tagline of “From Nucleic Acids to Nations.”

METHOD

As foreshadowed by the IOM report and in response to remarkable technological advances in the past two decades, the traditional approaches to the multidimensional exploration of individual trajectories is bound to benefit from a significant expansion in the number of dimensions that it routinely takes into account. In this review, we will explore arbitrarily selected examples, from a vast recent literature, that shed important light on the multi-phenomenological nature of abuse and addiction risk at various levels of scientific inquiry.

To sharpen the focus of this review we will concentrate, whenever possible, on the science of smoking behavior and nicotine addiction. Scientists are still debating the outlines and utility of the “gateway” theory as a heuristics to frame normative patterns of experimentation with addictive substances. However, although the question “What comes first?” is unlikely to have a simple answer,⁶ we do know three critical facts pertaining to youth smoking that seem to justify our decision. First, for all practical purposes, cigarettes are freely available, so it is far easier for a young person to access tobacco products than marijuana, for example. Second, there is a strong association between early use of tobacco products and worse prognoses on a host of deleterious behavioral, social, and medical consequences, including addiction. Third, the earlier the experimentation with cigarettes, the higher the likelihood of further experimentation with marijuana and other drugs. Importantly, many of the underlying risks for initiating the use of and becoming addicted to a drug such as nicotine will be common across a spectrum of addictive substances.

We also posit, in more general terms, that the changing tobacco-use landscape⁷ should be particularly informative when trying to understand how to best leverage different points in a complex system to modify collective behavior and to improve public health outcomes.⁸ National smoking trajectories nicely illustrate this point by showing that sustained and smart interventions can and do curb the incidence of tobacco use. However, much work remains to be done.

We will begin this discussion at the most basic level: genetics and epigenetics.

RESULTS

The Heredity of Risk

It is often said that the goal of finding genes with definite contributions to the risk of abuse and addiction has been elusive at best. Indeed, our combined search strategies have given us a steady diet of polymorphic variations that add modestly to the overall heritability/vulnerability of addiction.^{9,10} This is a recurring theme that is also seen when cataloguing genetic contributions to other complex phenotypes, such as aggressive behaviors¹¹ or depression,¹² both of which can, incidentally, also modulate abuse and addiction risk.

However, such a state of affairs is entirely consistent with the notion that addiction is a polygenic disorder. Each one of the many genes can contribute to addiction-related traits via direct or indirect influences on relevant neurotransmitter systems, drug metabolic pathways, neural circuitry, cellular physiology, and behavioral patterns (e.g., novelty seeking, impulsivity).¹³⁻¹⁵

The observed association between low or high levels of DA type 2 receptor (DR2) in the striatum and the chances that exposure to a stimulant will be rated as a pleasurable or unpleasant experience, respectively,¹⁶ is just one example of a vast and complex network of underlying genetic vulnerabilities. Variants of the dopamine and opioid receptor genes, for instance, can modulate the rewarding properties of many psychoactive drugs.¹⁷⁻¹⁹

Worth highlighting in the area of genetic risk for addiction is the substantial progress that has occurred in the past decade in teasing apart genetic contributors to smoking behavior, to an enhanced vulnerability to nicotine addiction, and to suffering some of smoking's most devastating medical consequences. For example, several converging studies have uncovered a set of addiction relevant variants within a cluster of nicotine receptor subunits.²⁰⁻²² These findings triggered a wave of excitement for their potential to spur novel and more effective predictive, preventive and therapeutic strategies. Similarly, a recent genome-wide association study (GWAS) has identified nicotine receptor and metabolizing enzyme gene variants associated with the number of cigarettes smoked per day.²³ The same group had previously identified a common variant in the nicotinic acetylcholine receptor gene cluster on chromosome 15q24 that significantly increased the risk of becoming nicotine dependent and of later developing lung cancer and peripheral arterial disease.²⁴ In addition, twin studies had shown significant heritability of smoking initiation,²⁵ although, interestingly, a meta-analysis of genetic data available in 2006, which demonstrated that genetic factors play significant role in smoking initiation, also suggested that they do more so in males than in females.²⁶ Another relevant example comes from a recent, preliminary prospective study of adolescent smoking progression that found that an allelic variation in the DAD4 receptor (D4R) gene was also linked to smoking initiation, whereas another variant in the D2R gene was associated with smoking persistence.²⁷

The science of genetic risk for abuse and addiction is advancing rapidly, thanks to a steady flow of technological breakthroughs and an increasingly cross-disciplinary approach to investigating the modulation of genetic contributors by other biological, social, and environmental variables. The resulting growing understanding is moving us closer to realizing the promise of more personalized and thus more effective prevention and treatment strategies, not only for addiction but for a host of other psychiatric disorders.

However, the emerging picture would be incomplete were we not to discuss the potential impact of epigenetic research on our understanding of addiction risk and processes. The science of epigenetics investigates the ability of external stimuli and agents to trigger chemical (epigenetic) modifications of the DNA and/or its packaging (histone) proteins to regulate (up or down) the expression of a specific gene in space and time. This critical level of biological control, well known, albeit relatively underestimated for a long time, has recently been likened to "life at the interface between a dynamic environment and a fixed genome."²⁸ Thus, epigenetic changes represent an important part of evolution's answer to a multicellular organism's need to come up with adaptive changes that do not rely on exceedingly slow genetic mutation rates.²⁹ Indeed, even the plastic changes associated with learning and memory appear to involve epigenetic modifications.³⁰

As a result, there is a growing suspicion percolating through the field that a considerable proportion of the environment's ability to shape the circuits of cognition, reward and

emotion, particularly those arising during critical periods of prenatal, postnatal, and adolescent brain development,³¹ may operate via epigenetic mechanisms.³² Research on the potential epigenetic impact of maternal smoking on their offspring provides a telling example. Recent animal studies have shown that prenatal exposure to tobacco smoke was associated with specific brain changes and behaviors later in adolescence, some of which could be traced back to methylation events in the brain-derived neurotrophic factor (BDNF) gene.³³

The involvement of the BDNF gene is tantalizing because its product plays a key role in brain development. Not surprisingly, there is indirect evidence to suggest that the epigenetic modification of BDNF may influence an adolescent's addiction vulnerability. For example, a behavioral study of 597 adolescents in Québec (half of whom had been prenatally exposed to maternal tobacco smoke) showed that those exposed were significantly more likely to use an addictive substance later in life. Furthermore, in nonexposed children, the thickness of the orbitofrontal cortex (OFC)—a brain region that is involved in decision-making-related processes—increased as a function of the number of drugs tried; but among exposed adolescents, the greater the use of substances, the thinner the OFC. Because OFC maturation is strongly influenced by the action of BDNF, it would be reasonable to hypothesize the existence of a causal link between in utero exposure to tobacco smoke, epigenetic regulation of BDNF, and an aberrant OFC development. This pathway, which is ripe for experimental evaluation, could contribute to higher substance abuse rates by causing abnormal processing of reward-associated cues that could in turn facilitate impulsive behaviors.³⁴

Importantly, by illustrating the potential behavioral impact of epigenetic modulation of a single gene, the example of BDNF underscores the enormity of the challenge for those working in this field, for they have the unenviable task of identifying and cataloguing the most relevant, consistent, and predictive alterations from among the millions of cell-type-specific epigenetic markings that are constantly taking place throughout our genomes. However, the potential benefits that we stand to reap from epigenomic intervention is equally enormous: once we begin to understand the most reliable and predictive epigenetic events related to drug abuse and addiction risk, we may be in a better position to devise ways to smartly manipulate the genetic output of an otherwise “fixed” genome via the discriminating use of key environmental variables singly or in combination with novel epigenetic pharmaceuticals.

First steps in this direction are being reported with increasing frequency. Recent experiments show how exposure to drugs of abuse can induce a remodeling of chromatin structure affecting the recruitment of transcription factors onto specific gene promoters and, ultimately, behavior.³⁵⁻³⁷ Injection of the histone deacetylase inhibitor trichostatin A has been shown to reduce the reinforcing properties of cocaine in rats³⁸ without affecting those of sucrose, a natural reinforcer.³⁹ Finally, the observations made on animal models of cross-fostering,⁴⁰ environmental enrichment,⁴¹ maternal separation,⁴² and early life adversity⁴³ provide promising additional examples of how epigenetic modulation could have an impact on drug effects and drug abuse behaviors.

Clinical Implications and Future Research—A scientific and technological revolution is currently underway that is likely to radically change the way that we practice medicine, transforming it from a reactive to a proactive discipline.⁴⁴ This dramatic shift will come on the heels of an expected surge in the number of individual genomes that will be sequenced and analyzed in coming years, and the ensuing cataloguing of rare but clinically relevant variants. Significant obstacles notwithstanding, it would be difficult to overemphasize the impact that increasingly more affordable personal genomes will have on our ability to manage diseases of addiction (and indeed most other complex disorders) far

better than we do today. Thanks to vastly improved data interpretation and a better understanding of cell and systems biology, clinical researchers will be able to rationally stratify what today look like unquestionably uniform disease phenotypes. The resulting personalization of medicine will afford it enormous predictive and preventive power, even in the face of an ostensibly intractable complex bio-behavioral disorder such as addiction. However, for this promise to be realized, researchers will need to recommit themselves to connect the rapidly expanding number of “genetic/epigenetic dots” within and among cellular networks to achieve a more global understanding of the multiple pathways by which different molecular perturbations in a system can lead to seemingly identical clinical outcomes. Eventually, but sooner rather than later, completely new approaches will be developed for clinicians to actually harness and benefit from this incredibly rich, fertile, and complex universe of personal data.

Brain Development

The BDNF example described above nicely illustrates the power of otherwise subtle genetic variations and epigenetic modifications, even at the level of a single gene, to “bubble up” and profoundly affect performance in key behavioral circuits and, through them, abuse and addiction risk. Developmental trajectories constitute the organizational substrate in which those circuits are being shaped constantly by the interaction between genes and experience, and put together into attitudes, temperaments, and more or less rigid patterns of behaviors. The vast number of overlapping and carefully choreographed processes taking place during this active maturation process offers a particularly fertile substrate of opportunities for either increasing risk or building resilience into the system. The outcome of complex developmental processes, for example, will greatly influence the final balance (at maturity) of reactivities between subcortical (e.g., emotion, reward/motivation) and cortical (e.g., cognitive control) circuits, which will, in turn, modulate an individual's ability to inhibit prepotent responses and his/her tendencies to seek novelty or engage in risky behaviors.⁴⁵

Many of these processes, which are exquisitely sensitive to external influences, take place at exceedingly slow speeds, covering a period that begins in utero and continues well past adolescence.⁴⁶ Such a protracted time course of change in the maturing brain helps explain the long window of vulnerability in adolescence (between the ages of 15 and 20 years, approximately), a period during which substance use initiation is known to dramatically increase the risk of developing an addiction later in life.⁴⁷ To make matters worse, this period is characterized by an evolutionarily determined tendency for engaging in risky behaviors, combined with a relatively high level of access to and experimentation with psychoactive substances.

It is difficult to overestimate the disproportionate influence that the psychosocial processes taking place during childhood and adolescent development will exert on future life trajectories. This notion is important because it helps explain the origins of problem behaviors and substance use throughout individuals' lives.⁴⁸ Early temperamental dispositions, family experiences, and interactions with the larger environment influence whether adolescents will develop individual characteristics that will make them more or less vulnerable to using and becoming dependent on drugs. For example, antisocial, aggressive and other externalizing behaviors appear to be moderately stable from childhood through adolescence, as well as predictive of substance abuse.^{49,50} Disturbingly, the phenomenon has many of the properties that one would expect of a self-perpetuating cycle: for example, early initiation of daily cigarette smoking, as well as the age of first antisocial/conduct disorder symptom, have been linked to adolescent parenthood.⁵¹

Childhood psychopathology is a major risk factor for later problem behaviors, including substance abuse. Research shows that psychiatric disorders in childhood and adolescence,

including conduct and oppositional disorder, anxiety disorders, particularly major depressive disorder and attention-deficit/hyperactivity disorder (ADHD), are all related to an increased risk of alcoholism and drug abuse.^{52,53} Of particular concern, in light of its high prevalence,⁵⁴ is the observation that children with ADHD are at significantly higher risk for smoking during adolescence, particularly if left untreated and/or in combination with conduct disorder.⁵⁵ Aggression, of the type associated with externalizing conduct disorders (CD) is, in addition, strongly predictive of future deviant behavior, including antisocial peers, impoverished social ties, and early substance use.^{56,57}

The intense interactions between genetic and external factors during development have a profound and long lasting effect in establishing the types of individual-level features that exert the most proximal influence on the likelihood of drug abuse.⁵⁸ These can be grouped into four domains: a) unconventionality (e.g., risk tolerance, deviant attitudes and behaviors)⁵⁷; b) emotional undercontrol (e.g., impulsivity, novelty seeking)⁵⁹; c) psychological maladjustment/psychopathology (e.g., depressive symptoms, mood disorders)^{60, 61}; and d) difficulties in relating to others.⁶² A number of recent longitudinal studies have explored several of these individual-level constructs as predictors not only of substance use disorders but also of the trajectories of substance use comorbidities. For example, similar individual-level characteristics (i.e., externalizing and internalizing) were found to be predictive of joint trajectories of chronic tobacco and marijuana use.⁶³ These findings are consistent with other reports documenting high levels of comorbidity among different substance use disorders (SUDs). In addition, it is well known that SUDs are frequently comorbid with other psychiatric conditions such as bipolar disorder,⁶⁴ schizophrenia, and eating disorders.⁶⁵

Clinical Implications and Future Research—A better recognition of the interacting biological and environmental factors that impinge upon brain development and its behavioral outputs is essential for the proper assessment of individual addiction risk trajectories in the clinic. Important insight has been gained, mostly from animal studies, about the ontogeny of sensitivity to addictive substances and about the neurobiological and cognitive consequences of adolescent drug exposure. However, new technologies, particularly, high-resolution, real time, and noninvasive brain imaging techniques (i.e., resting state connectivity) are poised to vastly extend our understanding of these interactions and their impact on individual risk in humans. This knowledge will greatly facilitate the design and implementation of more effective substance abuse prevention and treatment programs.

The Social Environment

This level of the *system* consists of multiple compartments that comprise the dynamic set of environmental and behavioral interactions that support the connections among individuals, such as parent and child, schoolmates, husband and wife, interest groups, institutions, and societies. In turn, these connections form the *social network*, a recognized powerful modulator of gene expression, brain development and function, cognition, emotion, and behavior.

The overall quality of family and friends contributes to some of the deepest and longest-lasting influences on an individual's development across the lifespan. Indeed, the family of origin is the primary developmental context, in which individual characteristics are shaped that is related to later drug use and abuse (see Family Interactional Theory for a more formal theory of development encompassing these dimensions⁶⁶). Several aspects of the family context are known to be important in influencing adolescent drug use and other problem behaviors, including parental substance use and abuse,⁶⁷⁻⁶⁹ and parenting style.^{70,71} For

example, clear behavioral expectations, parental monitoring, high levels of parental involvement (all aspects of firm parenting) and a nonconflictual relationship have all been linked to adolescents' psychological well-being, including nonuse of drugs.^{66,72-75} The quality of the parent-child relationship has been shown to be a crucial link in the chain of risk transmission from one generation to the next,⁶⁶ as it not only serves as a model for other relationships, but also shapes the child's personality and sense of self.^{76,77}

Such intergenerational transmission may be influenced by genetic^{78,79} or epigenetic²⁹ factors, and/or may reflect parental modeling of substance use.^{80,81} Indirect effects of parental drug use and abuse on the adolescent's own use of drugs include adolescents' selection of friends who use drugs, which in turn is related to their own drug use.⁸² Indeed, a twin study that used an extended kinship design to dissect the contribution of genetic and environmental factors in smoking initiation corroborated a significant level of heritability that was partly due to assortment, but also demonstrated the significant role of nonparental shared environments, introducing the powerful notion of peer group effects that may be even more important for smoking initiation in adolescence than in adulthood.²⁵

Peers provide a crucial developmental context in the pathways to substance use and, ultimately, dependence. In general, the importance of the peer group in shaping adolescent substance use is consistent across a variety of studies and cultures.⁸³⁻⁸⁵ One mechanism responsible for the link between peer and self substance use may be assortative peer selection, which refers to the process of selecting friends who are similar to oneself.⁸⁶ Indeed, unconventional adolescents tend to select deviant peers who share with them selected characteristics, and deviant peers, in turn, could reinforce deviant attitudes and behaviors via role modeling, which further increases the probability of adolescent substance use. However, peer influence may be more important in drug use than in the establishment of drug abuse and dependence. Although substance-abusing individuals tend to socialize with other substance abusers, peer drug use does not seem to lead directly to drug abuse as much as other factors do (e.g., frequent use, biological vulnerabilities, parental drug use). A study by Brook et al., for example, found that peer drug use was directly related to adolescent drug use, but indirectly related to SUDs.⁸⁷ Furthermore, a latent growth curve analysis of more than 1,300 youths followed from sixth through ninth grade corroborated the impact of assortment (i.e., selecting friends who smoke) but also found that parental involvement, monitoring, and expectations had direct protective effects against smoking progression.⁸⁸ Clearly, a more comprehensive understanding of the complex and dynamic interactions between peers and families would help to explain why some adolescents thrive even under the most adverse circumstances.⁸⁹

Consider a child attending a school in which the peer pressure to experiment with alcohol or drugs is persistent and strong but successfully neutralized by the affective support, clearly stated expectations, and consistent monitoring and guidance provided by that child's family.⁹⁰ Potential opportunities for effective policy intervention are also suggested by recent evidence that the timing of family breakdown (e.g., paternal absence) has a profound and differential impact on a long list of youth deviant behaviors that include smoking, drinking, engaging in risky sexual behaviors, marijuana use, and conviction before the age of 15 years.⁹¹

Further progress in the area of social neuroscience will be critical to better understand the specific pathways by which such socio-behavioral processes and experiences influence and are influenced by brain function, particularly during adolescence. Of increasing importance in this context is the recognition of the dominant power of images, mass media, and online social networks as a source of information and influence for young people.⁹²⁻⁹⁴

There is a good chance that a focused effort, designed to elucidate the neural basis of psychosocial processes, and attentive to the revolutionary impact that digital social environments and related new technologies have had on the communication's landscape, could yield meaningful insights for developing more effective strategies to better protect vulnerable adolescents. However, to be effective, any new intervention would have to take into account the physical realities of the broader, physical, cultural and political environments, which have and undeniable power to facilitate or hinder the implementation of even the simplest programs.

Clinical Implications and Future Research—There is little doubt that to truly understand substance use disorders, their risks, and their consequences, we must first understand the reciprocal interactions—largely modulated by the mesocorticolimbic dopamine system—between addictive drugs and social behaviors.⁹⁵

Neuroscientific research is paying increasing attention to the multidimensional context in which these interactions take place. This is particularly important when investigating the etiology of psychopathologies that result from dys-functional interactions between neurogenetic and psychosocial factors.⁹⁶ The budding field of Social Neuroscience is a perfect example of how the simultaneous attention to multiple processes, taking place at various, interacting phenomenological levels (e.g., emotional, behavioral, cognitive, and neurobiological) can lead to a more meaningful explanation of social behavior and how it influences, or is influenced by, substance abuse. By extension, we can predict that future diagnostic tools will become increasingly more accurate and predictive if they become the types of comprehensive biosocial screens that incorporate validated parameters from multiple key domains.⁹⁷

The Broader Environment

The proportion of city dwellers has been increasing steadily since the beginning of the 19th century: 2007 has been estimated to be the first year in history in which more than half of the human population lived in urban areas. By most accounts, the accelerating move of human beings into cities and mega-cities is becoming a growing factor in determining the prevalence of risky behaviors and overall health status.⁹⁸ In a disturbing example of urban dysfunction, a recent report found that longer incarceration times were associated with homelessness, co-occurring severe mental disorders, and substance-related disorders. Some authors have gone so far as to suggest that the criminal justice system may be assuming, at times, the responsibility for a population whose needs ought to be addressed through entirely different service delivery channels.⁹⁹ However, although the urban face of drug abuse presents a particularly ominous countenance, it is also clear from the epidemiology of alcohol and methamphetamine abuse disorders,¹⁰⁰ for example, that rural life is not always the idealized environment that it was once purported to be.¹⁰¹

Macro-contextual factors, such as drug availability, adverse economic conditions, high levels of crime, and neighborhood disorganization have all been found to be related to substance use.¹⁰²⁻¹⁰⁴ In addition, the media, advertising, and social and legal policies, have important effects on adolescent substance use and, ultimately, addiction. The influence of these cultural and ecological factors on drug use and abuse is at least in part mediated by their effects on family relationships, peer group norms, and individual-level characteristics, such as attitudes and behaviors. For example, a large body of research has linked the representations of tobacco use in popular media, such as movies and magazines, to adolescent tobacco use.¹⁰⁵ Not surprisingly, a recent study has found that individuals' receptivity to media images of tobacco use (an individual-level variable) was related to nicotine dependence among adolescents.¹⁰⁶

There is some evidence that comprehensive tobacco control programs, including mass-media campaigns, can be effective in changing adult smoking behavior.¹⁰⁷ However, it is less clear whether the millions of dollars spent in countermeasures targeting young smokers are effective. For example, analysis of Florida's youth-targeted anti-tobacco media "truth" campaign seemed to indicate that any positive results were rather transient.^{108,109} In addition, one of the largest and most rigorous school-based programs for the prevention of smoking, the Hutchinson Smoking Prevention Project, found no long-term effect on smoking behavior.¹¹⁰ In a media landscape that is virtually reinventing itself with increasing frequency, prevention strategies will need to continuously revisit their approaches to message crafting and delivery so as to make them relevant and effective. Moreover, while doing so, future strategies would benefit greatly from taking advantage of brain neuroimaging tools to maximize, for example, the impact and recall value of novel public health communication strategies.¹¹¹

In a more physical context, it would be a serious mistake not to take into account (and advantage of) the impact that the built environment can have on drug use behaviors. Some key variables to consider are those that affect collective efficacy, physical activity, availability and price of drugs, access to education and jobs, after-school programs, health care, information technologies, and social networks. A dramatic example can be found in a recent (unpublished) secondary analysis of the 2009 Monitoring the Future data, which clearly showed that adolescents who exercise regularly had lower rates of legal and illegal drug use. Specifically, 12 graders who rarely or never exercised had more than double the prevalence of daily smoking than those who exercise on a daily or almost daily basis.¹¹² This simple observation demonstrates that there are many challenges but also great opportunities in our broadly defined "environments" to purposefully and cost-efficiently engineer prevention and safety into the system.

Finally, it is critical to consider the central role played by new media in the lives of today's children and adolescents. Their homes (indeed, their bedrooms) are saturated with digital windows into the virtual world. Many young people carry with them miniaturized, portable devices wherever they go. Children and teenagers comprise the primary audience for popular music; they form important niche audiences for television, movies, video games, and print media (each of these industries produces extensive content that targets primarily young people); they typically are among the early adopters of personal computers (indeed, of most new media) and are a primary target of much of the content of the World Wide Web. Importantly, it seems that meaningful supervision is increasingly becoming as unrealistic as forcing children to lead "unplugged" lives.

Clearly, the long periods of time that young people spend in virtual environments warrant that adults and clinicians pay increasingly more attention to any signs of impending mental health trouble. These concerns are amply justified, yet they belie a unique opportunity for influencing young people's lives that should not be ignored, particularly when we consider that, because of media multitasking, for every hour that young people use media, they are exposed to 1.25 hours of media content.¹¹³

It is time to begin a serious discussion about, and design a new research agenda to explore and fully harness, the potential of modern technologies to rewire the human brain, particularly during the developmental years. Interactive media exposure or unbridled multitasking, for example, are quickly becoming chronic and ubiquitous, despite the growing evidence that human cognition may not be well suited for the simultaneous processing of multiple streams of information.¹¹⁴ Clearly, it would be impossible to predict the eventual impact of these recent developments on society, but our lack of understanding of the potential consequences suggests that we would ignore this gap at our own peril.

Clinical Implications—Our rapidly changing world presents unprecedented challenges for parents, educators, and medical practitioners whose combined task is to keep our children healthy and, paradoxically, to prepare them to function optimally in an environment that is becoming less predictable with every passing day. The broader environment is itself becoming a digital landscape. The implications of this *virtualization* for creating, evaluating, and counteracting addiction risk are far reaching. It seems reasonable to predict that, by choosing the business-as-usual approach, we will be increasingly unable to meet these responsibilities. Smart research and new models will be needed to bring our understanding of how the changing environmental forces impact abuse and addiction risk and trajectories up to speed.

DISCUSSION

We have attempted to present an updated bird's-eye view of the multilayered nature of substance abuse and addiction landscape confronted by young people during some of the most critical years of development. In mapping out this landscape of risk, we were heavily influenced by Kaplan's multilevel approach to promoting health³ (Figure 1), which hints at the cumulative power of risk and protection factors across different phenomenological levels to modulate the risk of undesirable outcomes. The field stands to benefit greatly from the continuous refinement of this and related models, under the light of increasingly detailed scientific information, with the ultimate goal of devising next-generation interventions that are multipronged, individualized, and effective.

Today, the field of medicine understands more about disease than about health. However, it need not be that way: The view of drug addiction as a “systems failure” should help to refocus our general approach to developing dynamic models and early comprehensive interventions that optimize the ways in which we prevent and treat this complex and developmental brain disorder.

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FIGURE 1.

The model introduced by Kaplan et al. in 2000 is a well established model that captures key aspects of the multilevel contributors to a systems failure in the context of health outcomes. Reprinted from *Promoting Health: Intervention Strategies from Social and Behavioral Research*, Brian D. Smedley and S. Leonard Syme, eds., page 43, copyright 2000, with permission from The National Academies Press.³