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Review article

Biological Contributions to Addictions in Adolescents and Adults: Prevention, Treatment, and Policy Implications

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A B S T R A C T

Purpose: Despite significant advances in our understanding of the biological bases of addictions, these disorders continue to represent a huge public health burden that is associated with substantial personal suffering. Efforts to target addictions require consideration of how the improved biological understanding of addictions may lead to improved prevention, treatment, and policy initiatives.
Method: In this article, we provide a narrative review of current biological models for addictions with a goal of placing existing data and theories within a translational and developmental framework targeting the advancement of prevention, treatment, and policy strategies.
Results: Data regarding individual differences, intermediary phenotypes, and main and interactive influences of genetic and environmental contributions in the setting of developmental trajectories that may be influenced by addictive drugs or behavior indicate complex underpinnings of addictions.
Conclusions: Consideration and further elucidation of the biological etiologies of addictions hold significant potential for making important gains and reducing the public health impact of addictions.

Over the past several decades, substantial research has investigated the biological factors leading to and resulting from addictions [1,2]. The findings emanating from this work are vitally important if we are to continue to make inroads against addictions, particularly with respect to improving prevention and treatment strategies [3]. Despite significant efforts, excessive patterns of alcohol, tobacco, and other drug use have been estimated to cost the United States alone >$400 billion annually [4]. Worldwide, addictions are prevalent, and low- and middle-income countries may not have the resources to adequately address these disorders [5,6]. The impact of addictions typically is widespread, with some estimates indicating seven people being affected for each identified addicted individual, and there often exist substantial social consequences [7]. Addictions may influence employers and families, and the impact may be felt transgenerationally as parents with addictions may neglect children or model unhealthy behaviors [8]. Certain developmental groups, particularly adolescents and young adults, may be particularly vulnerable to developing addictions, as specific brain regions, specifically those involved in exerting behavioral control, typically mature less rapidly than do brain regions involved in promoting motivated behaviors like substance use [9,10]. Consistent with this notion, adolescents and young adults as compared with children and older adults have high rates of addictions [11]. As biological studies identify specific brain pathways and chemicals that may underlie specific aspects of addictions and addiction vulnerability [12], the knowledge gained holds significant potential to advance prevention, treatment, and policy interventions.

Boundaries of Addiction

Before embarking on a discussion of the biological factors contributing to addiction and addiction vulnerability, it is impor-

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tant to consider which disorders are encompassed by the term "addiction." Historically, there has been variation in the application of the word. "Addiction" is derived from the Latin verb addicere meaning "bound to" or "enslaved by," and in its original usage was not associated with substance use behaviors [13]. Dating back several hundred years, the term became linked to excessive patterns of alcohol use and later to excessive patterns of drug use such that by the 1980s, there was apparent consensus among some groups of experts that addiction could be defined as "compulsive drug use" [14]. However, over the past 15 years or so, there has been a debate as to whether excessive participation in nondrug behaviors like gambling, eating, sex, shopping, Internet use, and video gaming, to name several, might be considered addictions [15–17]. All of these domains appear to hold relevance to adolescents, as rates of problem and pathological gambling have been estimated to be two- to fourfold higher in adolescents than adults; problematic gambling, shopping, and Internet use have each been associated with adverse measures of health and functioning in adolescents; and obesity rates have risen dramatically in youth over the past several decades [17–22]. In addition, these behaviors may follow developmental frequencies similar to substance use behaviors, with high rates of use and addiction in adolescence and early adulthood and lower rates in older adulthood [11,23]. Among adolescents, it also appears important to consider levels of engagement that fall short of addiction, as subsyndromal engagement has been associated with immediate and longer-term adverse measures of health and functioning [18,24,25]. The unique characteristics of adolescents as compared with adults (e.g., more likely to have primary emphasis on school as compared with work, more likely to be influenced by parental monitoring, less likely to have head-of-household obligations, less likely to seek treatment for these behaviors, and less likely to have large sums of money to support engagement in addictive behaviors) also warrant consideration and may explain some differences in frequencies (e.g., with respect to compulsive shopping behaviors) in adolescents versus adults [26,27].

The debate over what behaviors, and the level of engagement in such behaviors, might be considered as addictions has involved consideration of the core components of addiction [23,28]. One proposition is that central features of addiction include continued engagement in a behavior despite adverse consequences, diminished control over participation in the behavior, compulsive participation, and a craving or appetitive urge state immediately preceding engagement in the behavior [23,29]. If one adopts these features as the defining aspects of addiction, then nonsubstance behaviors like gambling might be considered within an addiction's framework. Consistent with this notion, pathological gambling is being proposed for categorization together with substance use disorders in a "Substance Use and Addictive Disorders" category in the *Diagnostic and Statistical Manual of Mental Disorders-5* [30]. Such a definition for addiction and such groupings could substantially increase the estimated costs of addictions to society. For example, if foods and food consumption might be considered addictive [31], the costs to society could increase tremendously given the high prevalence estimates of obesity and the associated health costs related to type 2 diabetes, hypertension, heart disease, and other obesity-related conditions [32]. The consumption of energy drinks and other caffeinated beverages may also be considered within an addiction framework, and this may be particularly relevant to adolescents given their patterns of consumption of these drinks [33].

It should be noted that although many of the common substances of abuse (tobacco, alcohol, and cannabis among the most common, with a recent increase in prescription medication abuse in some countries like the United States) show patterns of initiation and escalation of use during adolescence, food consumption follows a different pattern. That being said, many of the features that might converge to make adolescents vulnerable to addiction (maturation and associated hormonal and other biological changes, greater independence, greater access to addictive substances/materials, emerging nonaddiction psychopathology) may represent factors associated with altered eating behaviors and obesity.

Biological Models of Addiction

Multiple biological models have been proposed to understand addictions and addiction vulnerability, and many of these models are complementary and not mutually exclusive. As an extensive review of each of these models is beyond the scope of this article, interested readers are directed to the references cited for additional aspects of each model. In addition, theories of addiction as related to current neurobiological understandings are reviewed in chapters 2–5 of reference [34].

Early reward-centric models focused on pleasurable aspects of taking drugs and proposed that drugs may "hijack" brain circuits involved in responses to "natural" rewards like sex or food [35,36]. A central component in this circuitry is the nucleus accumbens located in the ventral striatum and receiving dopaminergic innervation from the ventral tegmental area (termed the mesolimbic dopamine system). This nucleus accumbens has at times been termed the brain's "reward center," given that all known drugs with abuse potential, as well as natural rewards, lead to dopamine release in this structure [37,38]. However, a broader range of neurotransmitters (including opioids, cannabinoids, serotonin, norepinephrine, acetylcholine, glutamate, and γ-aminobutyric acid [39–41]) contributes to addiction, and molecular entities (receptors, transporters) for sensing these neurotransmitters are expressed in specific brain regions (e.g., Figure 1 in reference [41]). Recent studies suggest that the functions of the nucleus accumbens and dopamine function therein are more complex and involve learning (particularly reward based) and reward anticipation and valuation, salience attribution (i.e., assigning degrees of relevance to items, decisions, or behaviors), as well as loss processing [1,36]. Consistent with a role for rewarding effects of drugs in addictive processes and a role for dopamine in this process, an incentive salience model of drug addiction proposes that "liking" a drug may be separated from "wanting" [42,43]. Another reward-based model suggests a "reward deficiency syndrome" in which individuals with addictions seek out and engage in addictive behaviors to compensate for hypofunctioning reward signals in the mesolimbic dopamine pathway [44]. In contrast to the incentive salience model, the reward deficiency model may be particularly relevant to self-medication theories of addiction [45,46]. Despite their differences, these two models share some theoretical consistency with other motivational theories like the "IRISA" (impaired response inhibition and salience attribution) and others detailed later in the text that describe behavioral and biological differences in transitions from initial, sporadic to regular, habitual use of drugs [2,47,48]. Specific brain regions or circuits may be particularly

important in different aspects of addiction; for example, the mesolimbic dopamine system has been proposed to be particularly relevant to initiation and binge/intoxication, noradrenergic and stress pathways particularly relevant to withdrawal and negative affect components, and prefrontal cortical, hippocampal, amygdalar, and insular contributions particularly relevant to preoccupation and craving (Figure 2 in reference [41]).

Motivation-focused models have proposed that addiction might be considered a disorder of misdirected motivation in which relatively greater priority is given to drug use and relatively lesser priority is given to other motivated behaviors like familial care, work, or school [39,49,50]. In these processes, decisions to pursue typically smaller immediate rewards (e.g., a drug-related high) are made at the expense of typically larger delayed rewards (e.g., longer-term life possibilities emanating from studying for an exam or taking children to school). These behaviors and choices may be modeled from a biological perspective, and specific brain regions including the ventral striatum and ventromedial prefrontal cortex appear closely linked to reward processing, risk/reward decision making, and the selection of smaller immediate rewards, whereas the selection of larger delayed rewards has been found to involve more dorsal prefrontal cortical brain regions [51–53]. These findings suggest that more developed brain regions involved in higher-order (so-called executive) processes are important in risk–reward decision making relevant to addictions [2]. From a developmental perspective, these prefrontal cortical brain regions are among the last to mature, and this feature of brain development may, in part, contribute to adolescent vulnerability to addictions and other risk behaviors and mental health disorders (Figure 1 in reference [9]) [50,54,55].

Adolescent Addiction Vulnerability

Other motivation-focused models have proposed arguably more extensive involvement of brain regions whose functions may contribute to motivated behaviors, addiction vulnerability, and addictions. One model focusing on adolescent vulnerability to addiction separated primary and secondary motivational neurocircuitry (Figure 1 in reference [50]). The primary circuitry involves the prefrontal cortex, striatum (including the caudate and putamen), and thalamus. Parallel loops involving these structures have been proposed as primary to motivations and behaviors, including those in addictions [56,57]. The limbic loops that involve more ventral regions of the cortex and striatum have been proposed to be particularly relevant to novel or impulsive behaviors, whereas the associative and sensorimotor loops that involve more dorsal regions of the cortex and striatum have been proposed to be particularly relevant to habitual or compulsive behaviors [48,58]. This model, as well as others, appears applicable to both substance and nonsubstance addictions, including behaviors related to excessive food intake and obesity [16,58,59].

A secondary motivational neurocircuitry has been proposed to explain how other brain circuits may influence motivational decision-making processes and behaviors within the primary circuitry [50]. Specifically, multiple factors (both external influences like parental monitoring, peer behavior, and access to drugs or addictive materials, as well as internal states, all of which are particularly relevant to adolescents) may influence decisions to use drugs or engage in addictive behaviors [60]. Both internal and external influences may be relevant to adolescents' initiation and continued engagement in addictive behaviors. For example, one's emotional state may contribute, and periods of feeling upset or stressed may lead to drug use [61,62]. As such, brain regions involved in emotional processing, including the amygdala and anterior cingulate and medial prefrontal cortices, may provide important information into primary motivational circuitry and contribute to decisions to use drugs in emotionally reactive "hot" states as compared with reflective "cold" states [61–63].

Given the relative immaturity in adolescents of brain regions like the prefrontal cortex that are involved in emotional and motivational processing including in the regulation of craving for drugs and food [64,65], adolescents may be biologically vulnerable to engagement in addictive behaviors. Consistent with this notion, adolescents show largely subcortical/limbic responses to favorite food cues and individualized stress cues [66], whereas adults show both subcortical/limbic and prefrontal cortical responses [67,68]. In biological models focusing specifically on adolescent addiction vulnerability [50], the function of brain regions contributing to other states (e.g., relating to hunger, thirst, or sex drive) relating to motivational drives and behaviors has been cited as important. For example, brain regions such as the hypothalamus and septum that are involved in these homeostatic processes may contribute importantly [50,69,70].

Personally relevant experiences may also influence motivations and decisions to use drugs, and in the setting of relatively smaller contributions of prefrontal cortically mediated self-control in adolescence, such experiential recollection may play a relatively larger role in adolescent decision making related to addictive behaviors. Brain regions such as the hippocampus or temporal cortices that have been implicated in storing and recalling memories, particularly emotional ones, related to previous drug use (or other relevant situations) may thus provide important contextual memory contributions [50,71–73]. Other brain regions such as the insula (involved in sensing physical or somatic states) and parietal cortex (involved in attentional processing) may also participate by influencing motivations and decisions to engage in addictive behaviors [74–76]. Thus, the emotional volatility of adolescents and its influence on how attention is directed may contribute significantly to adolescent participation in substance use and other behaviors with addictive potential, and brain regions involved in emotional processing (e.g., the amygdala) are important contributors [77]. Importantly, input from brain regions involved in higher-order executive function (e.g., the dorsolateral prefrontal cortex) may allow for "top-down" control over motivations, in part driven by "bottom-up" subcortical processes, to engage in addictive behaviors [2,78]. Consistently, prefrontal cortical brain regions like the inferior frontal gyrus are among those most frequently implicated in studies of impaired impulse control [79], as well as in the control of craving or desire [64,65]. Taken together, given their neurodevelopmental status, adolescents may not be able to regulate emotional or motivational states to the same degree as adults.

The extent to which the aforementioned specific neurobiological or behavioral features reflect normal or aberrant development is currently incompletely understood, and it appears as though arguments for both cases could be made. Importantly, characteristics that are developmentally appropriate (e.g., increased risk taking) are also associated with real-life measures of adverse functioning (including with respect to addictive behaviors) [80–82], and it follows that the neurobiological underpinnings would show a similar pattern. However, some studies

indicate that adolescents in general show increased reward-related and risk taking-related responses [9,83], whereas other studies indicate that they show relatively diminished activation [84,85]. Similarly, some studies indicate that adolescents with addictions as compared with those without addictions show relatively diminished ventral striatal activation during reward anticipation, much like adults with addictions compared with those without addictions [86–88]. Similar patterns of ventral striatal activation also appear to apply to risk taking in adolescents and adults with addictions [89,90]. Thus, although adolescents in general may show exaggerated reward- or risk-related brain activations in reward circuitry, it is possible that those who may be showing relatively blunted activations are most important to target with respect to addictions. However, other data suggest that features associated with substance abuse (e.g., externalizing tendencies) correlate positively with reward anticipation-related activation of the ventral striatum in adolescence [91]. Some of these differences might reflect study design (e.g., with respect to conflating anticipatory phases of reward processing [92]), differences in samples (e.g., with respect to substance use or other measures [93]), or other factors. As described later in the text, understanding the biological correlates of such individual differences represents a major area of research in that it might help advance individualized interventions. Despite these gaps in our understanding, given that some of the normative developmental features of adolescence may represent risk factors for addiction and adolescent engagement is associated with poorer outcome, navigation through this developmental epoch in a healthy fashion is important.

How Might Drug Use or the Addictive Process Influence Brain Structure and Function?

Using the aforementioned frameworks to consider the neurocircuitry involved in addictions, it is important to consider that changes may occur over time in the structure and function of these brain motivational pathways. Some changes may reflect normative developmental processes [54,55,94]; some may reflect changes directly related to the addictive process [49,95]; and others may reflect changes related to recent or long-term substance exposure that may or may not be central to addictive processes [96,97]. Models and studies have begun to examine these influences. One model posits that there are "allostatic" changes (i.e., alterations in baseline set points) that may occur on repeated exposure to drugs or stressors [95,98]. Such exposures may differentially influence specific neural structures, with initial involvement of the mesolimbic dopamine system progressing to the nucleus accumbens, prefrontal cortex, and extended amygdala with continued drug exposure and increasing compulsivity (Figure 4 in reference [41]). Such progressive involvement of brain regions and their function in brain circuits may underlie a recalibration of baseline set points in the functioning of motivational circuitry that could contribute importantly to repeated drug taking and complicate attempts to cease engagement in addictive behaviors. A nonmutually exclusive possibility involves the progressive involvement of more dorsal corticostriatothalamocortical circuits as behavior moves from more consciously decision oriented to more habitually driven with repeated engagement over time (Figure 1 in references [48,58] and Figures 1, 3, and 11 in reference [57]). How changes related to normal development (including the aforementioned complex ones during adolescence) interact with behavioral engagement and substance use thus may involve complex interactions, particularly when one considers individual differences in genetic composition and life experiences and their interactive effects (see later in the text). Such environmental influences may come from multiple domains salient to adolescents, including parents, peers, school, church, and extracurricular involvement, to list several, and may include positive prosocial influences and negative ones, such as bullying or other forms of abuse.

Predisposing Factors Versus Sequelae of Use

In addiction, disentangling the influences of long-term and recent effects of specific drugs on brain structure and function can be complicated. That being said, drugs like cocaine appear to have significant influences on cortical structures, with repeated exposure progressively involving ventral to lateral to dorsal regions of the prefrontal cortex [96]. Alcohol can also influence brain structure and function, and decreased gray matter and poorer white matter integrity have been found in individuals with alcoholism [99–102]. Among adolescents, both structural, volumetric, and white matter changes have been observed in association with 1–2 years of drinking alcohol, particularly with respect to binge-pattern drinking [103]. Both gray matter and white matter integrity are important to brain function, with the latter particularly relevant to how brain regions connect and therefore operate in conjunction with one another. Alcohol's influences on gray and white matter structures may explain, in part, differences seen in performance on cognitive tests in groups of individuals with different addictions [104,105]. However, longitudinal studies in people with carefully assessed measures of drug-taking behaviors will help further clarify to what extent differences may reflect characteristics (e.g., neurobiological features related to impulsive tendencies) existing before drug exposure, those relating to drug exposure, those relating more precisely to changes in the addictive process, or a combination thereof (possibly evolving in an interactive fashion). On this framework, it is important to consider developmental changes in brain structure and function that occur naturally as people age [9,54,55]. For example, in rats, exposure to alcohol during adolescence increases risky or impulsive decision making in adulthood [106]. These findings suggest that if adolescents consume alcohol, such consumption may lead to tendencies promoting alcohol consumption, generating a vicious cycle of addictive behavior. However, controlled studies investigating such questions are lacking in humans. Thus, at this time, it is important to be cautious about inferring causality, particularly as many human studies involve associational rather than longitudinal designs.

Consideration of Individual Differences

It is reasonable to consider that certain factors (including individual differences in genetic composition and/or environmental exposures) may exist, develop, or be experienced early in life, precede the exposure to addictive substances or engagement in addictive behaviors, and thus predispose to addiction vulnerability or resilience [107]. For example, there exists a genetic variant coding for an enzyme (acetylaldehyde dehydrogenase) involved in the metabolism of alcohol. Individuals with the variant that is associated with slower metabolism of alcohol and the accumulation of acetylaldehyde on alcohol consumption (leading to an unpleasant or aversive response) are protected against the development of alcoholism. The ways in which

other genetic differences may contribute to the development of addictions are arguably less clear. However, twin data suggest that 30%–70% of the risk for developing addictions may be genetic [108], suggesting that an improved understanding of specific genetic factors relating to addictions and addiction vulnerability is relevant [109].

Moreover, environmental factors may interact with genetic factors, and these are important to consider in the stages of addictions [110–112]. That is, individuals with one type of genetic background may respond differently than individuals of another genetic background to the same environmental stimulus. Such gene-by-environment interactions have been suggested in brain-imaging studies and may have relevance to addictions and other mental health conditions. For example, specific variants of the gene coding for the serotonin transporter that are associated with different functioning of the transporter protein are associated with differences in amygdala activation to emotional stimuli [113]. Given findings linking emotional dysregulation to addictive behaviors [114], amygdala function to motivation and addictions [50,115,116], and serotonin transporter gene variation relating to externalizing tendencies in youth as a function of socioeconomic status [117], such variations may, in part, explain how different individuals respond differently to environments with respect to developing addictions. Furthermore, the timing of exposure to specific environmental stimuli (e.g., childhood trauma) should be considered within this framework and within the context of developmental brain changes [118]. This example is meant to reflect one of multiple possible genes and gene–environment interactions that may contribute to addictions and other conditions. As many genes with commonly occurring variations have been proposed to contribute to aspects of addiction [109,110,119], it will be important to examine a broad range of genetic and environmental factors relating to addiction vulnerability and resilience.

Sex/Gender

Other individual differences also warrant consideration. For example, males as compared with females tend to more frequently encounter problems with addiction, although the gender composition varies somewhat according to addictive substance or behavior and developmental stage. For example, alcohol and cocaine dependence and pathological gambling are typically male predominant, whereas compulsive shopping is more typically identified in females across the lifespan [120]. However, some recent U.S. data have found that girls aged 12–17 years have rates of alcohol and illicit drug abuse or dependence equal to or greater than those for boys [121,122]. Despite these differences, some gender-related differences appear relatively consistent across disorders. For example, a telescoping phenomenon, initially described for alcoholism, later for drug use, and more recently for gambling, exists whereby, on average, women as compared with men begin engagement in the behavior later in life than do men, but the time between initial participation and development of a problem is shorter (or telescoped) in women as compared with men [123,124]. Differences in motivations for engaging in addictive behaviors also exist between females and males, with women more likely to participate to escape from negative mood states (negative reinforcement) and men more likely to participate to experience positive feelings (positive reinforcement) [125–127]. These differences have important implications. First, they may relate to important differences in co-occurring disorders whereby addictive behaviors like gambling are more closely linked to depression in girls and women as compared with boys and men [67,128]. Second, they suggest that differences exist in biological underpinnings of addictions in women and men, particularly with respect to responses to negative (stress/anxiety) and positive (addiction cue) responses. Consistently, as compared with same-sexed nonaddicted comparison subjects, women with cocaine dependence show more robust patterns of brain activation differences in brain motivation circuitry in responses to stress cues, and men with cocaine dependence show more robust patterns of brain activation differences in brain motivation circuitry in responses to drug cues [129]. Third, these findings have treatment implications, as interventions like mindfulness-based approaches that target stress reduction might be differentially helpful for women and men with addictions [130]. The extent to which gender-related differences relate to biological sex hormones (e.g., progesterone, estrogens, testosterone) and/or environmental factors like gender-related differences in social acceptability of specific behaviors warrants additional investigation, as well as does how these might best be targeted in interventions [131–134].

Race, Culture, and Ethnicity

Factors related to culture, race, and ethnicity also warrant consideration in the propensity to develop addictions. Differences in genetic compositions may vary according to race and, in part, explain differences observed in rates of addictions across racial and ethnic groups [135,136]. Environmental factors related to differences in acculturation, cultural expectations, socioeconomics, stress exposure, and other domains also warrant consideration, as these might differ across cultural groups [134,137]. Some of these factors (e.g., stress exposure like childhood trauma) have been linked both to the propensity to develop addictions and to brain structure and function, including in regions implicated in reward, motivation, and addictions [138,139], although the precise natures of these relationships warrant further investigation in longitudinal studies in people [140–142]. As such, disentangling the precise contributions to addictions among different racial/ethnic groups is both an important and complex undertaking.

Intermediary Phenotypes

One important approach that has been used for the past decade involves the study of intermediary phenotypes or endophenotypes [143]. This approach considers that multiple factors, including multiple gene variations, likely contribute to psychiatric disorders like addictions, and that these disorders represent heterogeneous groupings. Intermediary phenotypes or endophenotypes represent constructs that are not readily visible but represent measurable constructs that may more closely link to biological factors (and by extension, their prevention and treatment) than do the heterogeneous diagnostic groupings. Endophenotypes also are proposed to be identifiable, albeit to a lesser extent, in unaffected family members of people with the disorder.

An example of an endophenotype that has been proposed for addictions and some other psychiatric disorders is impulsivity [2,59,109,144]. Impulsivity has been defined as propensity toward rapid unplanned reactions to internal or external stimuli with diminished regard to the negative consequences of these

reactions to the impulsive individual or others [144,145]. Animal studies involving controlled designs indicate that impulsivity before drug exposure can predict the propensity to develop drug addictions [2,146,147], and substance exposure (e.g., alcohol exposure during adolescence) can lead to increased impulsivity [106]. Thus, these animal studies indicate that impulsivity may predispose to the development of addictions and may increase after long-term substance exposure, potentially leading to worsening addiction. Among people, impulsivity measures are higher not only in stimulant-dependent individuals but also in their siblings, consistent with the notion that impulsivity represents an endophenotype for addictions [148]. In addition, these similarities appear to relate to neural regions that have been linked in previous studies to poor impulse control [149]. Better impulse control in children as young as 4 years has been associated with better scholastic functioning during adolescence and differences in prefrontal cortical and ventral striatal functioning during performance of an impulse control task as adults [150,151].

Although these findings are encouraging and suggest that impulsivity may represent a relevant target for treatment development in addictions [3,152–154], caution should be noted for several reasons.

First, impulsivity is a complex construct that can be fractionated, and components related to decision making (choice impulsivity) and action (response impulsivity) have been identified in multiple studies [155–157]. Thus, facets of impulsivity may represent separate and dissociable endophenotypic constructs. Choice and response impulsivity often do not associate, may involve different neurochemical contributions, and appear to relate differentially to aspects of addiction [2,154,156,158,159]. For instance, although response impulsivity has been found in animal models to predict compulsive or addictive drug use [2,146], choice impulsivity has not and has rather been associated with resistance to extinction and propensity to relapse [160]. As such, these aspects of impulsivity may relate specifically to different aspects of addictive processes (e.g., initiation vs. persistence).

Similarly, "hot" and "cold" processes that might contribute to impulsive tendencies and behaviors may have different neural underpinnings that reflect different genetic, environmental, and interactive components (refer to the aforementioned description and Figure 1 in reference [9] describing subcortical/limbic and prefrontal cortical contributions to motivated behaviors and their changes during adolescence). In addition, in this context, it is important to consider genetic factors that may influence adolescent behavior including psychopathic tendencies, risk taking, and distress tolerance [117,161,162], as well as gene–environment interactions, such as with respect to brain responses and psychopathology related to early childhood trauma [113,163,164]. Such interactions appear to have important clinical implications with respect to addictive behaviors in adolescents; for example, greater stress-induced risk taking has been linked to poorer treatment outcome in adolescent smokers [165].

Second, self-report and behavioral measures of impulsivity, even within the same domain, may not correlate, suggesting that how people perceive their behavioral tendencies may differ from their actual behavior [154]. Thus, these measures may relate differentially to specific aspects of addictions relevant to prevention and treatment efforts [3,154]. They may also relate differentially to the interaction between environmental exposures and substance use behaviors. For example, self-reported but not behavioral measures of impulsivity have been reported to mediate the relationships between different forms of stress (trauma, major and recent life events, and chronic stressors) and alcohol consumption [166]. Among adolescents seeking treatment for addictive behaviors, real-life behavioral and hypothetical self-report measures of discounting at treatment onset have been associated with treatment outcome in tobacco and marijuana smokers, respectively, indicating that these constructs relate importantly to clinically relevant measures and have the potential to identify subgroups of adolescents warranting particular attention [154,167]. Additional therapies (e.g., those like dialectical behavioral therapy or mindfulness-based stress reduction) may be helpful for adolescents who show impaired impulse control during emotionally arousing or stressful states [168,169].

Third, impulsivity, and facets thereof, appears to follow developmental trajectories that are important to consider [170]. For example, although self-reported impulsivity has been reported to decrease in a linear fashion from adolescence to adulthood, sensation-seeking appears to follow a curvilinear pattern, increasing during early adolescence and decreasing thereafter [171]. Individual differences in impulsivity appear important to substance use behavior; for example, during late adolescence/early adulthood (age 18–25 years), groups showing the greatest decreases in impulsivity demonstrated accelerated decreases in alcohol involvement [172].

Fourth, impulsivity represents only one of multiple potential endophenotypes relevant to addictions. Other constructs (e.g., compulsivity, emotional reactivity, stress responsiveness) represent other potential endophenotypes that warrant consideration in understanding the biologies of addictions [2,61]. Each of these intermediary phenotypes has potential relevance for adolescent addiction vulnerability, particularly given the neurobiological and behavioral changes during this developmental epoch.

Prevention, Treatment, and Policy Implications

A major goal in advancing our understanding of the biologies of addictions involves the translation of this knowledge into improved prevention, treatment, and policy strategies. Arguably, these efforts might be most easily understood for treatment development, particularly with respect to pharmacological therapies (Figure 1 in reference [3]). That is, an improved understanding of the neurobiological underpinnings of addictions, for example, with respect to the function of specific neurotransmitters in specific brain regions, might help to develop medications for the specific receptors or transporters they target. In some ways, efforts in this area have fallen short. Specifically, despite the findings that mesolimbic dopamine release in the nucleus accumbens is considered a central component of drug addictions, medications that block dopamine receptors in this brain region have shown limited efficacy in the treatment of addictions, and in nonsubstance addictions like pathological gambling have been associated with progambling motivations and behaviors [3,173]. However, drugs that may influence mesolimbic dopamine function indirectly, such as opioid receptor antagonists like naltrexone and nalmefene and glutamatergic compounds like *N*-acetyl cysteine, have shown more consistent findings in both substance and nonsubstance addictions like pathological gambling [16,174,175]. Other molecular targets that may influence mesolimbic dopamine function, like the serotonin 1B receptor, show similarities in substance and nonsubstance addictions [176,177], and these entities may represent better targets for

treatment development than do less specific serotonergic proteins like the serotonin transporter targeted by serotonin reuptake inhibitors, a class of compounds that has shown only modest effects in treating addictions [16,175]. Given the biological links between substance addictions and obesity (e.g., with respect to striatal dopamine function), some of these targets may extend to excessive eating behaviors [16]. Given the involvement of cannabinoids in both eating behaviors and substance use disorders [16,178], medication development targeting cannabinoid function also warrants consideration across addictive behaviors. The cross-addiction targeting of cannabinoids would fit with their roles in ventral striatal functioning and stress system responsiveness, as well as the clinical population of adolescent cannabis users who tend to use multiple substances. It is also important to consider heterogeneities with respect to patterns of excessive food consumption, and that some patterns (e.g., those related to binge-eating disorder or "food addiction") might help identify important subgroups with respect to underlying biologies and effective prevention and treatment strategies [179].

Intermediary phenotypes or endophenotypes also warrant consideration as treatment targets, and preliminary findings with impulsivity appear encouraging [152,153]. Specific groups of individuals (e.g., adolescents who demonstrate greater choice impulsivity as demonstrated by steeper discounting) may respond preferentially to different interventions like contingency management [167,180]. In addition, medications and behavioral treatments that target cognitive enhancement may help improve decision making and behavioral control in addictions, and these may operate by influencing the brain circuits underlying impulse control [3,181,182].

It will be important to consider neurodevelopmental changes, particularly with respect to adolescence and adolescent addiction vulnerability, and how this may impact adult functioning, and how differences in maturational rates of cortical and subcortical regions may influence both addiction and other mental health vulnerabilities and the mechanisms of actions (and effectiveness) of specific therapies [9,10,50,183,184]. For example, the use of instructions derived from cognitive behavioral therapies for addictions in adult tobacco smokers has been shown to increase connectivity between prefrontal cortical regions implicated in behavioral control and subcortical regions implicated in cravings [64]. The extent to which these strategies might work in adolescents who may as a group show less prefrontal cortical maturity and ability to harness such cortical control may offer both challenges and opportunities. However, preliminary data indicate that adolescents demonstrate benefit from cognitive behavioral therapies (e.g., with respect to smoking cessation). Similarly, the efficacy and tolerability of medications in the treatment of youth warrant consideration, for example, potential risks associated with widely used medications like serotonin reuptake inhibitors or stimulants. Specific medications effective in adults need to be evaluated separately in youth for efficacy and tolerability, with both short-term and long-term outcomes in mind. Individual differences (e.g., with respect to past trauma exposure) also warrant consideration [185].

Multiple interventions for adolescents have received empirical support. The prevention strategies with the most empirical support involve targeting important risk factors and bolstering important protective factors at individual, familial, and community levels [186]. Multiple behavioral approaches, including contingency management, motivational interviewing, and cognitive behavioral and family therapies, have empirical support, with varying levels of data to support each approach in specific populations [180,187,188]. Comparatively, few medications have been tested for their efficacy and tolerability among adolescents with substance abuse or dependence [189], and even less research has examined the extent to which pharmacotherapies might be helpful among nonsubstance addictions [190]. As in adults, other considerations (e.g., co-occurring disorders and aftercare) are important in the treatment of adolescent addictions [191,192].

Other potential targets exist. For example, poor white matter integrity has been found to contribute to both substance and nonsubstance addictions like pathological gambling, as well as to obesity [105,193–196]. The extent to which pharmacological and behavioral mechanisms might alter white matter integrity to improve treatment outcome warrants consideration [3,197–199].

Biological knowledge of addictions may help inform advances in policy and prevention [200]. An improved understanding of genetic factors or related endophenotypes might help identify individuals with vulnerability factors that could be targeted preventively for interventions. Similarly, an improved understanding of gene–environment interactions, and how specific environmental exposures may influence gene expression (epigenetic phenomena), may also improve prevention strategies. Identification of brain-imaging measures that reliably link to addictions could aid in both prevention and treatment strategies. Such prevention and treatment interventions would be most effective with policies and related resources that facilitate their enactment, and this may be particularly difficult in countries that devote limited resources to mental health interventions [5,201].

Other considerations relevant to prevention, treatment, and policy, such as the potential influences of low socioeconomic status, may also be informed by biological advances. For example, early life adversity has been linked to altered brain structure and function [138,139]. In addition, individuals lower in social status show hypofunctioning striatal systems, and this may influence reward- and motivation-related behaviors including addiction propensity [202]. The extent to which this impact operates at a communal or national level warrants consideration.

Importantly, policy may be informed across addictive behaviors in a manner that benefits from effective interventions in other domains. For example, effective tax strategies that have helped curtail tobacco use, particularly among adolescents and young adults, may be used to model similar efforts with respect to food taxation [31,203]. It may also be that certain foods (e.g., highly caloric, "hyperpalatable" processed foods) may possess greater addictive potential than do other foods and thus may warrant increased attention from public health and policy perspectives [31]. With respect to adolescents, limiting fast food and sugared sodas (e.g., in school cafeterias and vending machines) warrants consideration. Similarly, policy efforts could restrict the availability of substances with addictive potential that might lead to greater adolescent initiation or use ("bidis" or flavored cigarettes and alcohol-containing caffeinated beverages). Using information related to individual differences in biologies may help to optimize such policies, and the resulting policies may have substantial impact on reducing the societal burdens of addictions. From a global perspective, having resources and policies that would help increase the currently scarce mental health and addiction efforts in low- and middle-income countries could have a major impact on world health [204–206].

Conclusions

The growing body of data on the neurobiology of addiction has the potential to address more effectively one of the major public health problems facing societies today. A neurodevelopmental perspective with a focus on youth vulnerability could help advance efforts related to early interventions.

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