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

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Abstract

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.

Keywords

Addiction; Neurobiology; Adolescence; Public Health; Development

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Introduction

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 drugs have been estimated to cost the United States alone over $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 as well as families, and the impact may be felt trans-generationally 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 to 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.

The Boundaries of Addiction

Prior to embarking on a discussion of the biological factors contributing to addiction and addiction vulnerability, it is important 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 1980’s there was apparent consensus amongst some groups of experts that addiction could be defined as “compulsive drug use” [14]. However, over the past fifteen years or so, there has been debate as to whether excessive participation in non-drug 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-four-fold higher in adolescents than adults, problematic gambling, shopping, 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]. Additionally, 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]. Amongst 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 to adults (e.g., more likely to have school as compared to work be a primary emphasis, 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 non-substance behaviors like gambling might be considered within an addictions 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 DSM-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 while many of the common substances of abuse (tobacco, alcohol, and cannabis amongst the most common, with a recent rise in prescription medication abuse in some countries like the US) 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 non-addiction psychopathology) many 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 manuscript, interested readers are directed to the references cited for additional aspects of each model. Additionally, theories of addiction as related to current neurobiological understandings are reviewed in chapters 2-5 of [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, acetyl-choline, glutamate, and gamma-aminobutyric acid (GABA) [39-41]) contributes to addiction, and molecular entities (receptors, transporters) for sensing these neurotransmitters are expressed in specific brain regions (e.g., see figure 1 in [41] for details). 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 (that is, 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 hypo-functioning 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 theoretically consistency with other motivational theories like the “IRISA” (impaired response inhibition and salience attribution) and others detailed below 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 (see figure 2 in [41] for details).

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 [49-51]. In these processes, decisions to pursue typically smaller, immediate rewards (e.g., a drug-related high) 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 recruit more dorsal prefrontal cortical brain regions [52-54]. 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 amongst 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 (see figure 1 in [9]) [50, 55, 56].

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 (see figure 1 in [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 [57, 58]. The limbic loops that involve more ventral regions of 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 cortex and striatum have been proposed to be particularly relevant to habitual or compulsive behaviors [59, 60]. This model, as well as others, appears applicable to both substance and non-substance addictions, including behaviors related to excessive food intake and obesity [16, 60, 61].

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 [62]. 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 [63, 64]. 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 to reflective, "cold" states [63-65].

Given the relative immaturity in adolescents of brain regions like the prefrontal cortex involved in emotional and motivational processing including in the regulation of craving for drugs and food [66, 67], 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 [68], whereas adults show both subcortical/limbic and prefrontal cortical responses [69, 70]. In biological models focusing specifically on adolescent addiction vulnerability [50], the function of brain regions contributing to other states (for example, 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, 71, 72].

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 prior drug use (or other relevant situations) may thus provide important contextual memory contributions [50, 73-75]. 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 [76-78]. The emotional volatility of adolescents and its influence on how attention is directed thus may contribute significantly to adolescent participation in substance use and other behaviors with addictive potential, and brain regions involved in emotionally processing (e.g., the amygdala) are important contributors [79]. Importantly, input from brain regions involved in higher order executive function (for example 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, 80]. Consistently, prefrontal cortical brain regions like the inferior frontal gyrus are amongst those most frequently implicated in studies of impaired impulse control [81] as well as in the control of craving or desire [66, 67]. Taken together, adolescents may not be able to regulate emotional or motivational states to the same degree as adults given their neurodevelopmental status.

The extent to which specific neurobiological or behavioral features described above reflect normal or aberrant development is currently incompletely understood, and it appears as if 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) [82-84], and it follows that the neurobiological underpinnings would show a similar pattern. However, while some studies indicate that adolescents in general show increased reward-related and risk-taking-related responses [9, 85], other studies indicate that they show relatively diminished activation [86, 87]. Similarly, some studies indicate that adolescents with addictions as compared to those without show relatively diminished ventral striatal activation during reward anticipation, much like adults with addictions compared to those

without [88-90]. Similar patterns of ventral striatal activation also appear to apply to risk-taking in adolescents and adults with addictions [91, 92]. 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 those showing relatively blunted activations who 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 [93]. Some of these differences might reflect study design (e.g, with respect to conflating anticipatory phases of reward processing [94]), differences in samples (e.g., with respect to substance use or other measures [95]) or other factors. As described below, 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 above-described 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 [55, 56, 96], some may reflect changes directly related to the addictive process [49, 97], and others may reflect changes related to recent or chronic substance exposure that may or may not be central to addictive processes [98, 99]. Models and studies have begun to examine these influences. One model posits that there are “allostatic” changes (that is, alterations in baseline set-points) that may occur upon repeated exposure to drugs or stressors [97, 100]. 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 (see figure 4 in [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 non-mutually exclusive possibility involves the formation of the progressive involvement of more dorsal cortico-striato-thalamo-cortical circuits as behavior moves from more consciously decision-oriented to more habitually driven with repeated engagement over time (see figures 1 in [59] and [60] and figures 1, 3 and 11 in [58]). How changes related to normal development (including the complex ones described above 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 below). Such environmental influences may come from multiple domains salient to adolescents including parents, peers, school, church, and extra-curricular involvement, to list several, and may include positive pro-social influences and negative ones such as bullying or other forms of abuse.

Predisposing Factors Versus Sequelae of Use

Disentangling the influences of chronic and recent effects of specific drugs on brain structure and function in addiction 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 prefrontal cortex [98]. Alcohol can also influence brain structure and function, and decreased gray matter and poorer white

matter integrity have been found in individuals with alcoholism [101-104]. Amongst adolescents, both structural volumetric and white matter changes have been observed in association with one to two years of drinking alcohol, particularly with respect to binge-pattern drinking [105]. 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 [106, 107]. 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 prior to 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). Upon this framework it is important to consider developmental changes in brain structure and function that occur naturally as people age [9, 55, 56]. For example, in rats, exposure to alcohol during adolescence increases risky or impulsive decision-making in adulthood [108]. 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 point in 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 [109]. For example, there exists a genetic variation 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 upon 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% to 70% of the risk for developing addictions may be genetic in nature [110], suggesting that an improved understanding of specific genetic factors relating to addictions and addiction vulnerability is relevant [111].

Moreover, environmental factors may interact with genetic factors, and these are important to consideration in the stages of addictions [112-114]. 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 [115]. Given findings linking emotional dysregulation to addictive behaviors [116], amygdala function to motivation and addictions [50, 117, 118], and serotonin transporter gene variation relating to externalizing tendencies in youth as a function of socioeconomic status [119], 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 (for example, childhood trauma) should be considered within this framework as well as within the context of developmental brain changes [120]. 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 [111, 112, 121], 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 to 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 [122]. However, some recent US data have found that girls ages 12-17 years have rates of alcohol and illicit drug abuse or dependence equal to or greater than those for boys [123, 124]. 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 women as compared to men begin engagement in the behavior on average 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 to men [125, 126]. 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) [127-129]. 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 to boys and men, respectively [130, 131]. 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 to same-sexed non-addicted 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 [132]. 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 [133]. 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 [134-137].

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 [138, 139]. 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 [137, 140]. 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 [141, 142], although the precise natures of these relationships warrant further

investigation in longitudinal studies in people [143-145]. As such, disentangling the precise contributions to addictions amongst different racial/ethnic groups is both an important and complex undertaking.

Intermediary Phenotypes

One important approach that has been employed for the past decade involves the study of intermediary phenotypes or endophenotypes [146]. 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, 61, 111, 147]. Impulsivity has been defined as propensity towards rapid, unplanned reactions to internal or external stimuli with diminished regard to the negative consequences of these reactions to the impulsive individual or others [147, 148]. Animal studies involving controlled designs indicate that impulsivity prior to drug exposure can predict the propensity to develop drug addictions [2, 149, 150], and substance exposure (for example, alcohol exposure during adolescence) can lead to increased impulsivity [108]. Thus, these animal studies indicate that impulsivity may predispose to the development of addictions and may increase following chronic substance exposure, potentially leading to worsening addiction. Amongst 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 [151]. Additionally, these similarities appear to relate to neural regions that have been linked in prior studies to poor impulse control [152]. Better impulse control in children as young as four years of age has been associated with better scholastic functioning during adolescence as well as differences in prefrontal cortical and ventral striatal functioning during performance of an impulse control task as adults [153, 154].

Although these findings are encouraging and suggest that impulsivity may represent a relevant target for treatment development in addictions [3, 155-157], 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 [158-160]. 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, 157, 159, 161, 162]. For instance, while response impulsivity has been found in animal models to predict compulsive or addictive drug use [2, 149], choice impulsivity has not and has rather been associated with resistance to extinction and propensity to relapse [163]. As such, these aspects of impulsivity may relate specifically to different aspects of addictive processes (e.g., initiation versus 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 (see description above and figure 1 in [9] describing subcortical/limbic and prefrontal cortical contributions to motivated behaviors and their changes during adolescence). Additionally, it is important to consider in this

context genetic factors that may influence adolescent behavior including psychopathic tendencies, risk-taking and distress tolerance [119, 164, 165], as well as gene-environment interactions, such as with respect to brain responses and psychopathology related to early childhood trauma [115, 166, 167]. 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 [168].

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 [157]. These measures may thus relate differentially to specific aspects of addictions relevant to prevention and treatment efforts [3, 157]. 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 [169]. Amongst 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 [157, 170]. 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 [171, 172].

Third, impulsivity, and facets thereof, appear to follow developmental trajectories that are important to consider [173]. For example, while self-reported impulsivity has been reported to decrease in a linear fashion from adolescence to adulthood, sensation-seeking appears to follow a curvi-linear pattern, increasing during early adolescence and decreasing thereafter [174]. Individual differences in impulsivity appear important to substance use behavior; for example, during late adolescence/early adulthood (ages 18-25 years), groups showing the greatest decreases in impulsivity demonstrated accelerated decreases in alcohol involvement [175].

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, 63]. 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 (see figure 1 in [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 non-substance addictions like pathological gambling have been associated with pro-gambling motivations and behaviors [3, 176]. 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 non-substance addictions like pathological gambling [16, 177, 178]. Other molecular targets that may influence mesolimbic dopamine function, like the serotonin 1B receptor, show similarities in substance and non-substance addictions [179, 180], 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 which has shown only modest effects in treating addictions [16, 178]. 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, 181], 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 sub-groups with respect to underlying biologies and effective prevention and treatment strategies [182].

Intermediary phenotypes or endophenotypes also warrant consideration as treatment targets, and preliminary findings with impulsivity appear encouraging [155, 156]. Specific groups of individuals (e.g., adolescents who demonstrate greater choice impulsivity as evidenced by steeper discounting) may respond preferentially to different interventions like contingency management [170, 183]. Additionally, 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, 184, 185].

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, 186, 187]. For example, the utilization of instructions derived from cognitive behavioral therapies for addictions have been shown in adult tobacco smokers to increase connectivity between prefrontal cortical regions implicated in behavioral control and subcortical regions implicated in cravings [66]. 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 (for example, with respect to smoking cessation). Similarly, the efficacy and tolerability of medications in the treatment of youth warrant consideration; e.g., 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 [188].

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 [189]. 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 [183, 190, 191]. Comparatively few medications have been tested for their efficacy and tolerability amongst adolescents with substance abuse or dependence [192], and even less research has examined the extent to which pharmacotherapies might be helpful amongst non-substance addictions [193]. As in adults, other considerations (e.g., co-occurring disorders and after-care) are important in the treatment of adolescent addictions [194, 195].

Other potential targets exist. For example, poor white matter integrity has been found to contribute to both substance and non-substance addictions like pathological gambling as well as to obesity [107, 196-199]. The extent to which pharmacological and behavioral mechanisms might alter white matter integrity to improve treatment outcome warrants consideration [3, 200-202].

Biological knowledge of addictions may help inform advances in policy and prevention [203]. 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-by-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, 204].

Other considerations relevant to prevention, treatment and policy, such as the potential influences of low socio-economic status, may also be informed by biological advances. For example, early life adversity has been linked to altered brain structure and function [141, 142]. Additionally, individuals lower in social status show hypo-functioning striatal systems, and this may influence reward- and motivation-related behaviors including addiction propensity [205]. 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 amongst adolescents and young adults may be used to model similar efforts with respect to food taxation [31, 206]. It may also be that certain foods (e.g., highly caloric, “hyper-palatable” 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) warrant 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 [207-209].

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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