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ADOLESCENT/YOUNG ADULT ADDICTION (M HEITZEG, SECTION EDITOR)

Risks Versus Consequences of Adolescent and Young Adult Substance Use: a Focus on Executive Control

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Abstract

Purpose of Review This review examines the role of executive control processes in the liability for substance misuse and whether substance use, once initiated, leads to subsequent decrements as proposed by neurotoxicity models of substance use disorder (SUD).

Recent Findings As indicated by a number of recent meta-analyses, executive control processes, which include working memory, cognitive flexibility, and numerous aspects of attentional, behavioral, and emotional control, are impaired in the context of active SUD. Longitudinal studies of behaviorally disinhibited children, individuals with familial risks for SUD, and twins within whom genetic versus environmental influences on behavior can be modeled robustly indicate that relatively poor control is a vulnerability factor for early substance use initiation, binge patterns of use, and subsequent SUD. Evidence of further declines in executive control, once substance use is initiated, is mixed, although a growing number of neuroimaging studies indicate that frontostriatal, frontolimbic, and frontocerebellar systems are altered as a consequence of use.

Summary Together these patterns suggest strategies for identifying children and adolescents at high risk for SUD, avenues through which substance-related neurotoxicities can be more reliably detected, and the need to structure prevention efforts in a manner that is developmentally appropriate and perhaps personalized to individual vulnerabilities.

Keywords Executive function · Adolescence · Cannabis · Alcohol · Neurotoxicity

Introduction

Substance abuse represents a major public health problem in the United States and worldwide [1]. Earlier ages of substance use initiation, first intoxication, and binge drinking are associated with elevated risks of developing later substance use disorders (SUD) [2–5]. These patterns suggest that loss of control over use, especially in adolescence, represents a significant vulnerability factor for the development of problematic use patterns.

The ability to control one's behavior is an aspect of executive function (EF), broadly defined as the ability to select, monitor, and control behavior to solve novel problems and adaptively pursue long-range goals [6]. Working memory, updating, inhibitory control, and behavioral flexibility are core executive control functions [7]. These can be further parcellated into attentional, behavioral, and emotional domains [8]. Attentional control involves directing perceptual resources to stimuli that facilitate goal acquisition and disengaging attention from irrelevant or maladaptive stimuli. Behavioral control involves adjusting motor activity levels and momentary actions in response to engaging stimuli. Emotional control is the ability to regulate emotional states and arousal. Thus, adequate control includes the regulation of responses to both internal states and external stimuli [9, 10]. Prudent decision-making that balances immediate motivations with longer-term goals is another marker of adequate control [11].

These various processes are enabled by overlapping neural circuits. The prefrontal cortex (PFC), through dynamic interconnections with other cortical regions, the thalamus, limbic system, and striatum, acts in a supervisory manner to systematically recruit and coordinate neural circuitry in the service of goal-directed action [12]. Under demanding or stressful

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circumstances, the EC system can be overwhelmed [10, 13] such that there are individual differences in the capacity to recruit appropriate control mechanisms but also in what it is that must be managed at any given point in time (e.g., motivational drives; objective stressors; complexity and novelty of the environment). Another factor that influences EC system integrity is its maturity [14–16]. Between infancy and adulthood, the EC system becomes progressively adept at managing increasingly complex states and situations [16], but it is inconsistently recruited during adolescence [17], particularly when emotional stakes are perceived to be high [18].

A developing system is malleable. Through neurochemical and synaptic alterations [19], perturbations, such as substance use, may lead to deviant outcomes [20] including disruptions in capacities for behavioral control. It is imperative to investigate the mechanisms that underlie these dynamics given their implications for prevention efforts. The purpose of this review is to examine the role of control processes in the liability for substance misuse and whether substance use, once initiated, leads to subsequent decrements as proposed by neurotoxicity models of SUD [5].

Executive Control Is Compromised in SUD

Case-control studies have demonstrated relatively worse EC functions in individuals diagnosed with SUDs. Many recent systematic reviews and meta-analyses have synthesized the empirical literature across hundreds of studies [21–37]; Table 1]. When those with SUDs, including alcohol use disorder (AUD), are aggregated and contrasted with controls, deficits are evident in working memory, cognitive flexibility, and decision-making [27]. Deficient levels of behavioral control are typically observed [30], though some analyses suggest that effect sizes are small and perhaps even negligible in cannabis [23] as well as MDMA [28] users. Decisional impulsivity, as measured through temporal discounting and risk-taking tasks [36, 37], is increased in most SUDs, though findings are again inconsistent for cannabis [21, 22, 25]. When adult and adolescent cannabis users are contrasted, EF impairments are more robust in younger and heavier users [24] and in the context of more recent use [29], which might account for inconsistencies across studies. Opiate use is associated with numerous EF, decision-making, and control deficits; effect sizes for group differences appear to be consistent regardless of recency of use [36].

Much of this literature focuses on cognitive and behavioral control. However, individuals with SUDs also exhibit biases in attentional control, such that they are primed to detect substance-related stimuli relative to other cues [38]. Moreover, they may show emotion dysregulation [39] and susceptibility to negative affect under stressful circumstances. Dual diagnoses are common and associated with EF impairments [40]. These patterns are indicative of EC weaknesses when demands intensify.

Reviews of findings from neuroimaging studies cohere in suggesting that frontostriatal, frontolimbic, and frontocerebellar networks are compromised in SUDs, underpinning deficits in cognitive, behavioral, and emotional control [26, 31–35]. Because findings are largely similar for various substances of abuse and when individuals with varied drug preferences are combined and contrasted with non-users, it appears that aberrant patterns of EC are manifested transdiagnostically.

Many extant studies captured case-control differences through single assessments and after SUDs were well-established raising questions about whether deficient EC is caused by substance use. Alternatively, individuals with poor EC may be more likely to experiment with substances due to impulsivity and may initiate use at an early age. They might also experience liabilities such as lack of parental support and academic difficulties [41]. Vulnerability or risk models propose that premorbid differences explain the EC deficits observed in SUD. Distinctions attributable to premorbid vulnerability versus neurotoxicity, which can be discerned through longitudinal modeling, are important to establish, because prevention efforts and their timing will vary depending on which process is targeted.

Poor Executive Control Is a Vulnerability Factor for Substance Misuse

To address this question, EC must be reliably measured across the lifespan. Laboratory measures are not easily or even routinely implemented prior to school age. However, difficulties with attention regulation, inhibitory control, and emotional stability often co-occur within individuals, characterizing what has been termed behavioral disinhibition, undercontrol, or externalizing [42]. Disinhibition, conceptualized as a coherent dimension of behavior, is manifested by high activity levels observed as early as infancy, irritability/aggression, impulsivity, as well as symptoms of attention-deficit hyperactivity disorder (ADHD), oppositional defiant disorder, antisocial behavior, and substance misuse. Whether behavioral disinhibition is fully synonymous with deficient EC as typically measured in the laboratory debated. Evidence is accumulating in support of an overlap in the constructs [43–45].

Across measures, three types of studies support vulnerability models to explain the EC deficits observed with substance misuse: (1) those that follow behaviorally disinhibited children from an early age into the initiation and progression of substance use; (2) family studies indicating that those at high familial risk for SUD have poor EC and/or high levels of behavioral disinhibition prior to SUD onset; (3) longitudinal twin studies that quantitatively model genetic versus

Table 1 Executive control deficits in the context of active substance misuse: reviews from 2016 to 2020

Authors	Year of publication	Type of paper	Focus	Population	Findings
Biernacki, Mclennan, Terrett, Labuschagne, Rendell	2016	Meta-analysis 22 studies	Decision-making in current and past opiate users relative to controls as measured by gambling, discounting, and impulsivity measures	Adults	Current and past users demonstrate decision-making deficits relative to controls
Bloomfield, Hindocha, Green, Wall, Lees et al.	2019	Review	Human neuroimaging studies of cannabis use; acute and chronic effects		Cannabis use can alter neural circuitry, subvert the reward system, and interfere with executive functions; numerous neurochemical systems are involved in these effects including endocannabinoid, dopamine, glutamate, and GABA systems
Broyd, van Hell, Beale, Yucel, Solowij	2016	Systematic review 105 studies	Cognition in acute and chronic cannabis use	All ages	Verbal learning, memory and attention impaired by acute and chronic use; mixed evidence for impaired EF and decision-making
Chen, Yang, Chen, Su, Jiang, Zhao	2020	Meta-analysis and meta-regression 52 studies	Risky decision-making in all classes of SUD	Adolescents and adults	Increased risky decision-making in all SUD except for cannabis and amphetamine-like stimulants; evidence for worse impairment with increasing age
Chye, Christensen, Yucel	2020	Review 43 adolescent studies 20 adult studies	Structural and functional neuroimaging studies of cannabis use in adolescents	Adolescents	Case-control comparisons primarily implicate frontal and parietal regions when inhibitory control, memory, or reward processing was required
Figueiredo. Tolomeo, Steele, Baldacchino	2020	Systematic review and meta-analysis 13 studies	Neurocognition in chronic cannabis use	All ages	Cannabis users show deficits in cognitive flexibility, cognitive impulsivity, attention, short-term memory and long-term memory; no evidence of deficits in motor impulsivity
Gorey, Kuhns, Smaragdi, Kroon, Cousijn	2019	Systematic review 21 studies	Age differences in impacts of cannabis on cognition	Contrast of adolescent vs. adult animals and humans	Executive functions more impaired in adolescent frequent cannabis users vs. adult cannabis users; age effects strongest in heavy dependent users
Lovell, Akhurst, Padgett, Garry, Matthews	2019	Meta-analysis 30 studies	Cognitive outcomes in long-term regular recreational cannabis use	Adults	Cannabis was associated with small-magnitude deficits in executive function, learning and memory, and global cognition; there were moderate deficits in decision-making Non-significant effects were noted for working memory and attention
Mahoney, Bryant, Haut	2019	Review	Cognition, emotional health, and neural findings with abuse of opiates, alcohol, stimulants, cannabis, benzodiazepines, synthetics, or hallucinogens	All ages but primarily studies of adults	Most substances of abuse are associated with frontal impairments; neural structures implicated include the PFC, striatum, and interconnecting pathways
Ramy, Regier	2019	Review	Cognition in SUD with a focus on EF, precognition and social cognition	Adults	EF deficits are consistently observed in SUD and may represent intermediate phenotypes; precognitive and metacognitive processes may anchor these findings
Roberts Jones, Montgomery	2016	Meta-analysis 39 studies	Executive functions in polydrug/MDMA users	Adults	MDMA users demonstrate executive dysfunction when findings aggregated across tasks; deficits are most pronounced for attention, cognitive flexibility, and updating; no deficits in inhibitory control
Scott, Slomiak, Jones, Adon, Rosen, Moore, Gur	2018	Meta-analysis 69 studies	Cognition and cannabis use	Adolescents and young adults	Significant effect sizes for learning, executive function (including inhibitory control), delayed memory, and attention; longer abstinence periods associated with decreased effect sizes; no differences in effect size by age or by age of cannabis use initiation
Stephan, Alhassoon, Allen, Wollman, Hall, et al.	2016	Meta-analysis 77 studies		Adults	

Table 1 (continued)

Authors	Year of publication	Type of paper	Focus	Population	Findings
			Clinical neuropsychological findings of executive dysfunction in alcohol use disorder		Planning, problem-solving, and inhibitory control are significantly impacted by AUD; effect sizes were strongest for decisional and cognitive impulsivity
Sullivan, Pfefferbaum	2019	Review	Effects of aging and comorbidities on deficits observed in alcohol use disorder (AUD)	Adults	Frontostriatal, frontocerebellar, and frontolimbic network functions are compromised in AUD; executive functions and motivation are impacted
Tervo-Clemmens, Quach, Calabro, Foran, Luna	2020	Meta-analysis and review 22 studies	Functional neuroimaging studies relevant to adolescent substance use	Adolescence	The reviewed studies were most relevant to SUD vulnerability and showed activation differences in the striatum, versus PFC, in high-risk youth
Verdejo-Garcia	2017	Review	Executive function in all classes of chronic substance use	All ages	EF deficits observed in all classes of SUD but to varying degrees; deficits in decision-making are common
Zilverstand, Huang, Alia-Klein, Goldstein	2018	Systematic review 105 studies	Neuroimaging evidence of impaired response inhibition and salience attribution in drug addiction	Adolescents and adults	Six brain networks were implicated in SUD across tasks: the reward, habit, salience, and executive networks as well as two additional networks devoted to self-directed behavior and memory, respectively

environmental sources of variation in the covariance among behavioral disinhibition, executive control, and substance use.

Behavioral Disinhibition and Substance Use Involvement

Individuals with high childhood levels of impulsivity/disinhibition are more likely to initiate substance use and to experience problematic use [46]. Data from epidemiologically informed samples followed from early childhood into adulthood cohere in suggesting that preschoolers with low levels of behavioral control have earlier substance use initiation and more problematic use by early adulthood [47, 48]. Recently, Meier et al. [49] analyzed data from a representative cohort of 1037 individuals born in Dunedin, New Zealand, and followed prospectively to age 38. A set of nine pre-adulthood risk factors were used to predict persistent substance dependence in adulthood with high accuracy. Childhood conduct disorder symptoms were among the strongest early life predictors of later disorder. Similarly, children diagnosed with ADHD, studied as part of the International Multicenter ADHD Genetics study, were more likely to develop adult SUD [50]. Zellers et al. [51•] incorporated a biometric latent growth model of marijuana use frequency across five assessment waves in two samples of twins spanning ages 14 to 30. Adolescent externalizing psychopathology was genetically associated with young adult increases in marijuana use and with maintenance of use over time. Furthermore, a recent longitudinal study of over 800 US high school students studied between ages 16 and 30 found that externalizing but not internalizing symptomatology predicted adult AUD [52].

Lab measures of EC yield similar findings. In a cross-sectional survey of over 1500 9-year-olds, low levels of self-reported EF were associated with higher levels of lifetime substance use [53], despite substance use being relatively rare in this age group. Similar associations in relation to working memory performance are evident [54•]. Peeters and colleagues [55] examined two EF domains, working memory and inhibitory control, in a high-risk sample of over 500 12–15-year-olds in the Netherlands and found through a survival analysis that relatively weak working memory, measured by a self-ordered pointing task, predicted both the initiation of the first alcoholic drink and the first binge drinking episode, above and beyond the effect of response inhibition, which also predicted drinking initiation. Recent cross-sectional examinations of participants ($n = 817$; ages 12 through 21) in the National Consortium on Alcohol and Neurodevelopment in Adolescence (NCANDA) study found that executive dysfunction, including performance on a delay discounting measure of cognitive impulsivity,

was significantly related to both risky alcohol and cannabis use [56, 57]. Finally, Jones et al. [58] followed substance-naive adolescents ($n = 249$) into the adult initiation of substance use, reporting that trait measures of impulsivity as well as laboratory behavioral control tasks predicted later drinking behavior (maximum drinks in a day, heavy episodic drinking, alcohol-related problems).

Interactions between EC vulnerabilities and motivational tone appear likely: using a longitudinal design, Peeters et al. [59] found that adolescent drinkers with poor inhibitory control showed stronger approach tendencies and attentional biases toward alcohol cues compared to those with better inhibitory skills. They also demonstrated greater alcohol use over a 6-month follow-up period. More recently, Kim-Spoon et al. [60] demonstrated that high levels of self-reported behavioral activation (e.g., reward sensitivity) predicted an earlier onset of substance use among adolescents with low, but not high, inhibitory control. Strickhouser et al. [61] reported that among a large nationally representative sample of Australian children, high sociability levels in early childhood predicted adolescent substance use initiation, while trait levels of persistence were protective. Accordingly, those with strong motivational drives as well as low capacities for control, which combine to challenge the EC system, are particularly vulnerable to impulsivity and substance misuse.

In support of these behavioral findings, an increasing number of neuroimaging studies indicate that the neural circuitry underpinning EC is compromised prior to substance use initiation. Blunted patterns of neural activation in regions such as the middle frontal gyrus, striatum, and inferior parietal cortex, which mediate inhibitory control, have been observed [62, 63]. These findings cohere with findings of similar deviations in individuals with severe SUD [64]. Variations in striatal activation were implicated in a recent meta-analytic study of adolescents vulnerable to SUD on the basis of externalizing tendencies and positive family histories [45]. In addition to deviations within cognitive control circuitry, recent work also suggests heightened reward system activation in individuals vulnerable to later substance misuse [63], although prospective work involving substance-naive individuals is needed.

In summary, youth with higher trait levels of disinhibitory behaviors as well as relatively poor executive control as measured by behavioral and imaging probes are more likely to engage in substance use at an early age (when the brain is still developing), to use heavily, and to later experience fully syndromic patterns of SUD. Predictive associations are inconsistent or negligible for other forms of behavioral dysregulation, such as internalizing tendencies [52].

Family Studies

A parallel line of work has focused on children, adolescents, and young adults at high risk for SUD based on positive family histories [65]. AUD has been a typical focus of such studies. Its prevalence is higher in those with positive parental histories, a pattern that may be mediated, in part, by genetically transmitted trait levels of disinhibition and, hence, low levels of EC [66]. Individuals with positive family histories of SUD demonstrate increased sensation seeking, impulsivity, and other disinhibitory traits [39, 66–68], as well as relatively low scores on EF measures in childhood and adolescence, even prior to the onset of substance use [68]. They are more likely to initiate substance use at an early age and are more likely to show associations between baseline EF and subsequent substance use. These associations may be mediated by temperamental traits or adverse life events [68].

Brain mechanisms that contribute to these effects have been described [69–74]. A meta-analysis focused on the electrophysiologically derived P300 waveform, a potential endophenotypic marker of liability to disinhibition, indicated significant reductions in SUD, particularly in males with positive family histories [72]. Using brain MRI techniques, DeVito and colleagues [69] contrasted family history–positive and family history–negative adults in fMRI go/no-go task performance, impulsivity, and alcohol use. Family history–positive individuals showed greater activation in the left anterior insula and inferior frontal gyrus during successful inhibitions, an effect that was found primarily in males. Another study [70] used diffusion-weighted imaging and voxel-wise multilevel modeling to assess white matter microstructural development in 45 substance-naive adolescents, who subsequently engaged in binge drinking, and 68 adolescents, who remained largely abstinent, all with varying degrees of familial AUD. Deviations in frontostriatal white matter microstructure were evident early in adolescence, prior to alcohol use, as a function of both future binge drinking and family history. Numerous other neuroimaging studies demonstrate similar structural and functional neural deviations in family history–positive individuals [71, 73]. A recent large-scale study of 6898 youth enrolled in the Adolescent Brain Cognitive Development (ABCD) Consortium study examined neural activation during the Stop Signal Task, which demands response inhibition, in substance-naive youth aged 9 to 10 years with and without parental AUD histories. Greater levels of neural activation in frontostriatal and cerebellar networks were observed in family history–positive youth [74•].

In summary, behavioral studies of family history–positive individuals support that relative impairments in executive control represent a liability for early substance use initiation and later substance use problems. Across MRI studies, the direction of effects (e.g., higher versus lower levels of BOLD activations and structural anomalies) varies, perhaps due to developmental timing, task variations, or other individual difference factors.

Longitudinal Twin Studies

Behavior genetic studies provide a unique opportunity to use quantitative modeling of genetic similarities to assess covariance between executive function and substance use and whether shared variance between the two is due to genetic similarity or to environmental influences. Twin and family study paradigms have consistently affirmed that SUDs are highly heritable [75]. Using structural equation modeling, it has been demonstrated across laboratories that the latent factor of behavioral disinhibition is also heritable [76] as are individual variations in a common executive function factor [77] and specific EF measures, such as delay discounting [78]. In a recent study, Gustavson et al. [79] analyzed data from 850 twins enrolled in the Colorado Twin Registry, examining associations between numerous facets of executive control, including a common factor, and substance use characteristics in adolescents studied longitudinally at age 17 and again at age 23. Higher EF levels in adolescence, but not adulthood, were associated with lower substance use frequencies and lower numbers of substances ever used. Twin analyses indicated that these associations were genetic in origin.

In summary, there is compelling highly replicated evidence from a variety of paradigms that a low level of executive control, whether reflected through behavioral disinhibition, decreased performance on discrete EF tasks, or altered patterns of relevant neural structure and function, represents a premorbid genetically influenced vulnerability for later substance use problems.

Neurotoxicity: Does EF Decline After Substance Use Initiation?

These patterns raise the question of whether executive control further declines from premorbid levels after substance use initiation onset and as symptoms of SUD emerge. At theoretical, preclinical, and anecdotal levels, there is ample reason to expect a decline. Many substances, particularly alcohol, methamphetamine, and MDMA, are neurotoxic: neuronal integrity and the functional connectivity of neural circuitry are compromised with heavy use [31, 80, 81]. SUD is, by definition, characterized by a loss of behavioral and emotional control [82]. Due to neuroplastic changes in neurochemical systems that mediate responses to positive reinforcers, sensitivity to rewards other than the substance itself is diminished. Use becomes increasingly compulsive as neural processing is altered in favor of habit-based systems, mediated by dorsal striatal circuitry. Allostatic changes are observed in striatal and limbic circuits as addiction progresses from the initial binging stage, to loss of control over use, to maintenance of use by negative reinforcement. These changes are well-documented in animals [19, 83].

Because executive control is already compromised prior to SUD in at-risk individuals, it is challenging in the midst of addiction to further achieve control over increasingly strong impulses to continue use. This difficulty is exacerbated by withdrawal symptoms and the accompanying negative affect that emerges with acute and longer-term abstinence. These conditions create ongoing demands for emotional regulation [83].

However, beyond this loss of control over substance-seeking behavior, relatively few studies have demonstrated addiction-related decrements in discrete laboratory-measured EFs. Animal studies provide evidence of allostatic changes in prefrontal neurochemistry, particularly within glutamatergic systems and following psychostimulant administration [84, 85]. There are covarying declines in working memory function limited to high load conditions [84]. Yet, a recent critical review of the human literature found limited evidence of working memory decrements following cocaine administration [86].

In contrast, Paige and Colder [87] assessed a community sample of 387 adolescents who completed nine annual assessments starting at ages 11–12. Attentional and inhibitory control were assessed with temperament inventories. Structural equation modeling indicated that those who engaged in heavy marijuana use at ages 12–14 had low levels of attentional control at ages 18–21, above and beyond baseline levels. In support of this finding, a recent review of longitudinal neuropsychological studies [88] concluded that cannabis use is associated with neuropsychological declines. However, these associations were modest in size, raising questions about clinical significance. Functional declines were most evident in those with the heaviest cannabis use and were often dramatically attenuated after controlling for confounding variables. Despite this trend, some longitudinal studies of heavy users have failed to observe behavioral decrements over time in the context of continued use [89, 90]. For instance, Becker et al. [89] followed daily cannabis users across a 2-year period finding that while verbal learning and memory were persistently impaired over time in users relative to controls, no new deficits emerged.

Similarly, longitudinal twin studies have failed to observe cannabis-related declines in cognitive functions, including EC. Ross et al. [91••], leveraging data from the Colorado Twin Study, used a quasi-experimental co-twin control design to test the impacts of cannabis use on executive functions, finding little evidence in support of cannabis-induced decrements. Only one association among 70 that were examined—an association between cannabis use frequency at age 17 and worse performance on a metric representing common executive function at age 23—was observed.

Recently, Khurana et al. [92••] assessed a community sample of 387 adolescents annually over five consecutive years on a behavioral battery that included working memory tests,

delay discounting, and impulsivity measures. Baseline weaknesses in working memory, in association with a measure of acting without thinking, was a significant predictor of later SUD. Working memory predicted SUD both independent of early drug use and as mediated by early drug use progression, consistent with vulnerability models. Variations in substance use over time were not associated with worsening of working memory. Concordantly, using data from the Tracking Adolescents' Individual Lives Survey (TRAILS) [93], the maturation of executive functioning was assessed in a cohort of 2230 Dutch adolescents within four domains (inhibition, working memory, and shift- and sustained attention) between ages 11 and 19. There were no differences in cognitive maturation in relation to levels of alcohol use involvement, including chronic heavy drinking behavior.

Some studies have been more suggestive regarding post-substance-use alterations in EC functions and indeed have suggested distinct ways in which such effects might manifest themselves. Wilson et al. [54•] examined developmental trajectories of multiple indicators of behavioral inhibition in 1512 twins from the Minnesota Center for Twin Research who were studied at ages 11, 14, 17, 20, and 24. Those who developed SUDs were characterized by low premorbid levels of visuospatial attention and working memory and stable high levels of behavioral disinhibition indexed by questionnaire measures, consistent with other reports. Deviant developmental trajectories were also observed for a lab-based measure of inhibitory control, suggesting that in adolescents, a "decline" in EC functions may be observed as a failure to reach expected developmental levels.

Developmental delays are difficult to assess, because age-scaled norms do not exist for EC measures commonly utilized in laboratory settings, individual variation is high, and sample sizes are often small, limiting the ability to detect developmental differences. More generally, human studies have not been optimized to assess the impacts of premorbid executive dysfunction as well as the effect of substances on the same cognitive measures pre- and post-use. Inconsistencies across studies could also be driven by individual differences in cognitive reserve, the extent to which compensatory processes can be recruited, in the context of some prior insult, to achieve task success. A related construct, brain reserve, refers to compensatory flexibility within neural circuits [94]. Reserve is thought to be relatively high in youth. It may be that behavioral function is largely intact early in the course of substance misuse while brain reserve is diminished. Condordantly, several studies have reported deviations from expected patterns of neurodevelopment in youth who transition from being substance-naive into moderate-to-heavy substance use [c.f., [95–97, 98•].

A recent longitudinal analysis focused on a large number of adolescent participants in the NCANDA Consortium study found that youth who initiated heavy drinking exhibited an accelerated rate of frontal lobe gray matter decline [96] as well as deviations in cerebellar growth over time [97]. Alcohol-dependent adults also show anomalies in the cerebellum as well as regions associated with executive control. They exhibit EF deficits that resemble patterns observed with accelerated aging [31]. Thus, it may be that in younger individuals, neuroplastic alterations that deviate from expected neurodevelopmental changes can be detected early in the course of substance use. These alterations may serve to maintain normative levels of behavior.

These findings must be interpreted with caution given that Robert et al. [98•] using recent longitudinal data from adolescents enrolled in the IMAGEN Consortium found that longitudinal increases in drunkenness frequency were associated with accelerated gray matter atrophy in the left posterior temporal cortex, right posterior temporal cortex, and left prefrontal cortex. However, causal Bayesian network analyses suggested that these patterns were driven by premorbid liabilities.

Some cross-sectional studies and a select number of longitudinal studies have reported dose-outcome effects, which broadly support neuroplastic effects. Earlier ages of substance use onset have been inconsistently associated with worse EF and/or deviant patterns of neurodevelopment perhaps indicating that substance use is more detrimental to brain development when the substance is introduced earlier in the adolescent neurodevelopmental sequence. However, as noted in several recent reviews [29, 46, 99], associations between substance use patterns (age of onset, duration of use, and other proxies for dose effects) and behavioral disinhibition are not reliably observed.

Conclusions, Future Directions, and Implications for Prevention Efforts

Evidence strongly suggests that deficient EC is a premorbid individual difference factor that is genetically transmitted and renders some individuals particularly vulnerable to early experimentation with substances. Yet, despite evidence of allostatic changes associated with drugs of abuse as well as ample evidence of loss of control over responses to the abused substance in addiction, longitudinal impacts on cognition, as measured by laboratory-based executive control tasks, have not been consistently demonstrated. This limitation is attributable, in part, to the relative lack of studies that have followed sufficient numbers of youth from pre-initiation into the development of the addiction syndrome and limitations imposed by typical measurement strategies.

In contrast, an increasing number of developmental imaging studies support the idea that neural structure, structural connectivity, and functional activation within regions and circuits that underpin executive control show deviations in expected developmental trajectories within 1–2 years following

alcohol use initiation that persist after cessation of use [99]. Findings are mixed for cannabis use. This area of inquiry will benefit from studies such as NCANDA [100], ABCD [101], and the planned Healthy Brain and Child Development (hBCD) study, https://heal.nih.gov/research/infants-and-children/healthy-brain, which are large-scale longitudinal developmental neuroimaging investigations supported by the National Institutes of Health, poised to disentangle premorbid influences on substance use initiation from substance-related effects. Thousands of children from demographically diverse backgrounds, including twins, are being followed from substance-naive periods of childhood, through adolescence and into young adulthood.

To the extent that these studies can be methodologically harmonized with epidemiological investigations underway worldwide [98, 102], cross-cultural norms can be gathered for measures of executive control. Such measures are rarely harmonized across studies and laboratories, although there is some consistency regarding which specific tasks tend to yield significant effects, e.g., self-ordered pointing assessments of working memory [55, 92] and temporal discounting measures [37, 56, 68]. Similarly, the field lacks comprehensive norms for metrics such as regional brain volumes as well as the magnitudes and timing of neurodevelopmental shifts. Not all statistical deviations are clinically significant, and normative data would provide a means of mapping individual performance variations onto typical developmental trajectories.

A thesis of this review is that adolescents and young adults are sensitive to increasing information processing loads (e.g., conditions that demand the simultaneous recruitment of attentional, emotional, and cognitive control processes) as executive control processes reach maturity [16, 83]. Sensitive behavioral measures, administered under conditions of experimentally induced high demand, are not routinely utilized but may be needed to detect post-initiation impacts of substance use on executive control.

Prevention efforts remain vital to safeguard vulnerable individuals from later SUD and to circumvent brain-based alterations that may provoke a cascade of behavioral effects that manifest at later points in time. Executive control is increasingly conceptualized as a malleable aspect of behavior, amenable to training, and heavily influenced by context [103]. Consistent with other frameworks [104], this review emphasizes that not all adolescents are at equivalent risk for substance misuse. Because disinhibited children can be identified early relative to their peers, personalized prevention efforts can be instituted in early childhood and at intervals thereafter, perhaps corresponding to ages when expected accelerations in executive function occur. Except in the most impaired individuals, executive control is readily achieved when task demands are low and more challenging under conditions where cognitive load is high, perceived stress is extreme, and emotions are salient. Thus, interventions might focus on ways to diminish demanding internal and environmental sources of burden, for instance, by encouraging increased deliberation in the context of momentary decision-making, stress reduction techniques, and attempts to direct reward strivings in adaptive versus maladaptive ways. If transitions from experimentation to addiction can be examined in a more fine-grained manner through frequent longitudinal assessments, other developmentally appropriate prevention strategies that leverage both individual strengths and also weaknesses in executive control may become evident.

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Papers of particular interest, published recently, have been highlighted as:
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- •• Of major importance

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