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Neurobiology of Substance Use in Adolescents and Potential Therapeutic Effects of Exercise for Prevention and Treatment of Substance Use Disorders

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Abstract

Substance (alcohol, marijuana, opioids, cocaine, etc.) use often initiates during adolescence, a critical period of physiological and social development marked by an increase in risk-taking due, in part, to heightened motivation to obtain arousal from rewards. Substance use during adolescence has been associated with a greater risk of substance use disorders (SUD) in adulthood. Although use rates for most substances have remained relatively stable, the frequency of marijuana use and perception that regular marijuana use is not harmful has increased in adolescents. Furthermore, the non-medical use of opioids has increased, particularly in the South, Midwest, and rural low-income communities. Substance use in adolescence has been associated with adverse structural and functional brain changes, and may exacerbate the natural "imbalance" between frontal/regulatory and cortical-subcortical circuits, leading to further heightened impulsive and reward-driven behaviors. Exercise increases growth and brain-derived neurotrophic factors that stimulate endogenous dopaminergic systems that, in turn, enhance general plasticity, learning, and memory. Exercise may help to reinforce the "naïve" or underdeveloped connections between neurological reward and regulatory processes in adolescence from the "bottom up" and "offset" reward seeking from substances, while concomitantly improving cardiovascular health, as well as academic and social achievement. In this review, we provide an overview of the current state of substance use in adolescents and, rationale for the utilization of exercise, particularly 'assisted' exercise, which we have shown increases neural activity in cortical-subcortical regions and may modulate brain dopamine levels during adolescence, a unique window of heightened reward sensitivity and neural plasticity, for the prevention and adjunctive treatment of SUD.

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The authors declare that they have no conflicts of interest to disclose.

Keywords

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Introduction

Substance use disorders (SUD) and related psychopathology are persistent public health problems (Compton et al., 2005), with over 20.3 million adults and 1.3 million children in the U.S. estimated to have a SUD (Substance Abuse and Mental Health Services Administration (SAMHSA), 2014). Worldwide, there are over 3.4 billion illicit drug users, accounting for over 12% of all deaths each year (World Health Organization, 2016). Drug overdose, which has been mostly linked to opioids, is the leading cause of unintentional injury deaths in the U.S. An estimated 2 million Americans, ages 12 and older, have had an opioid use disorder involving prescription opioids, and approximately 600,000 have had an opioid use disorder involving heroin (National Academy of Sciences, 2017). In addition, the number of overdose deaths from illicit opioids (including heroin and synthetic opioids) tripled from 2011 to 2015 in the U.S. (National Academy of Sciences, 2017). Overall, the consequences of substance use costs the U.S. more than $600 billion every year (National Institute on Drug Abuse, National Institutes of Health, U.S. Department of Health and Human Services, 2017; Office of National Drug Control Policy, 2004).

Substance use often initiates during adolescence, and over 80% of drug users began using during adolescence (Lenoue and Riggs, 2016). Unfortunately, only about 11% of individuals ages 12 and older and only about 6% of adolescents 12–17 years old who need treatment for substance misuse, actually receive it (Lipari et al., 2016; SAMHSA, 2014). Furthermore, over half of the adolescents receiving treatment will relapse within one year of treatment (Cornelius et al., 2003; McLellan et al., 2000; Ramo and Brown, 2008), suggesting more accessible and effective programs are needed to prevent and treat substance use in adolescents.

Substance Use Rates in Adolescents

Substance use is often initiated during adolescence, which is a sensitive period of biological and social development marked by an increase in risk taking behavior due, in part, to heightened motivation to obtain arousal from rewards (Eaton et al., 2012; Galvan, 2010; Willoughby et al., 2013). Although use rates for many substances have remained relatively stable or have decreased somewhat in adolescents, the frequency of some substances and the perception that regular use of these substances is not harmful has increased in adolescents. According to the Monitoring the Future (MTF) Survey of drug use and attitudes, self-reported daily use of marijuana in 12^{th} graders increased from 2006 to 2011, and has remained at about 6% as of 2016 in the U.S. (Johnston, 2017; National Institute on Drug Abuse, National Institutes of Health and U.S. Department of Health and Human Services, 2016). Importantly, only 31.1% of 12^{th} graders believe regular marijuana use is harmful, which is 27.2% less than that reported in 2000 (Johnston, 2017; National Institute on Drug Abuse et al., 2016). Data from the National Survey on Drug Use and Health (NSDUH)

indicate 12 to 17 year olds represent 7–13% of all frequent (21 or more days in the past month) marijuana users (Burns et al., 2013; Peiper et al., 2016). Although frequent marijuana use appears to be decreasing in Caucasians, rates in African-Americans and Hispanics are increasing (Burns et al., 2013; Peiper et al., 2016). In 2016, 81% of 12th graders reported marijuana could be obtained “fairly easily” or “very easily” but less accessibility to marijuana was reported among 8th (35%) and 10th (64%) graders (Johnston, 2017). Interestingly, past year use of marijuana in 12th graders was about 5% higher in medical marijuana use states compared to non-medical marijuana use states (38.3% vs. 33.3%) (Johnston, 2017; National Institute on Drug Abuse et al., 2016), and this trend is expected to continue as more states pass medical and non-medical marijuana use laws. Furthermore, the potency of marijuana has been steadily increasing, which may be partially responsible for the increase in marijuana-related emergency room visits (Mehmedic et al., 2010; Zhu and Wu, 2016).

The overall abuse of opioids and deaths attributed to opioid misuse has continued to increase markedly in the U.S. and, among adolescents, the non-medical use of opioids appears to be increasing in the South and Midwest and in rural communities with lower socioeconomic status. According to the 2016 MTF, the prevalence of OxyContin use was 0.9%, 2.1%, and 3.4% in 8th, 10th, and 12th grades, respectively; and, the use of Vicodin was 0.8%, 1.7%, and 2.9% for 8th, 10th, and 12th graders, respectively (Johnston, 2017). Heroin use remains low with only about 1% or less of adolescents reporting use in the past year in the 2016 NTF (Johnston, 2017). Importantly, opioid use before/during high school is associated with a 33% increase in the risk of future opioid misuse after high school (Miech et al., 2015), and is associated with initiation of other illicit drugs as early as age 13 (Becker et al., 2008), suggesting opioids may be providing the “gateway” to the abuse of other substances. Furthermore, nearly 7 out of every 10 non-medical prescription opioid adolescent users reported co-ingestion of marijuana (58.5%), alcohol (52.1%), cocaine (10.6%), tranquilizers (10.3%), and amphetamines (9.5%) in the past year (McCabe et al., 2012). Interestingly, the prevalence of non-medical prescription pain drugs is higher among adolescents than it has ever been, and data suggest the younger adolescents (middle school) may be particularly affected (Miech et al., 2013). Moreover, data from the NSDUH indicate that adolescents ages 12–17 living in rural areas (6.8%) have 35% greater odds of past-year prescription opioid misuse than those living in large urban areas (5.3%) (Monnat et al., 2017). A recent systematic review of 15 studies with nationally representative populations found that low family income, poor mental health, and lack of treatment for mental health issues were positively associated with adolescent prescription opioid misuse (Young et al., 2012). Unfortunately, adolescents in rural regions with lower income who are misusing opioids may be less likely to seek and receive treatment (Oser and Harp, 2015).

Although alcohol remains the most commonly used substance among adolescents, the percentage of students in grades 8, 10, and 12 reporting alcohol use in the past year (17.6%, 38.3%, and 55.6%, respectively, in 2016 MTF), and those reporting binge drinking (5 drinks in a row in the past 2 weeks) continues to decline (Johnston, 2017; National Institute on Drug Abuse et al., 2016). The daily use of cigarettes has also been steadily declining (0.9%, 1.9%, and 4.8% among 8th, 10th, and 12th graders in 2016) (Johnston, 2017). The use of

electronic cigarettes (e-cigarettes) and little cigars has been increasing, but recent data from the 2016 MTF indicate use in adolescents is declining (Johnston, 2017; Peiper et al., 2016).

Overall, the prevalence of past-year substance abuse or dependence of any substance among 12–17 year olds was 5.3% and 5.2% in boys and girls, respectively, in the 2013 NSDUH, which represents a decline since the 2006 NSDUH (8.0% in boys, 8.1% in girls) (Peiper et al., 2016). Furthermore, substance use and concurrent substance use (using two or more substances during the same time period) is associated with a greater risk of SUD and adolescents using alcohol, cigarettes, and marijuana and alcohol and marijuana, compared to alcohol alone, are more strongly associated with development of SUD in adulthood (Green et al., 2016; Moss et al., 2014). This appears to be reflected in the NSDUH data, which show an increase in SUD in young adults 18 to 25 and among those ages 26 and older (Peiper et al., 2016). Therefore, intervening during adolescence is necessary to prevent SUD in emerging and young adulthood.

Adolescence is a Critical Period of Development

Adolescence is an important developmental period between childhood and adulthood, which is marked by many physiological and social changes including, but not limited to, puberty and increased risk-taking and sensation (reward)-seeking behaviors (Crone and Dahl, 2012; Willoughby et al., 2013). The ages used to define adolescence or, more specifically, achieving independence and mature social and personal responsibilities (Cohen et al., 2016), varies with broader definitions, including ages spanning from 10 to 22 years and narrower ranges encompassing ages 12–17 years (as seen above with data on the substance use rates in the U.S.). Thus, age by itself may be a poor proxy for development and maturation to adulthood (Cohn, Westenberg and Cohn, 2004).

Normal brain development during adolescence involves an overall decrease in gray matter volume and a concomitant increase in white matter volume, as well as cortical thinning (Bava et al., 2013; Gogtay et al., 2004; Paus, 2005; Raznahan et al., 2014). The decreases in gray matter are believed to occur to enable greater synaptic pruning (or elimination of unnecessary connections), and the increases in white matter are believed to provide for increased myelination of axons to produce more efficient connections between brain regions (Bava et al., 2013; Paus, 2005; Raznahan et al., 2014). Furthermore, the cortical thinning may occur to help eliminate weak synaptic connections (Gogtay et al., 2004; Paus, 2005). Mesocorticolimbic dopamine systems actively mature during adolescents, with more immature interactions between dopamine D1 and D2 receptors and an overall increase in dopaminergic availability (Dwyer and Leslie, 2016; Wahlstrom et al., 2010). These structural changes during adolescence are believed to help drive normal adaptive changes in cognitive function, working memory, and social cognition (Fuhrmann et al., 2015).

In adolescence, there is a general “imbalance” in functional development across brain regions, with earlier development occurring in posterior regions and anterior regions progressing later, which leads to underdeveloped connections between mid-brain cortico-limbic (reward) and frontal (inhibitory) region circuits (Casey et al., 2008; Ernst, 2014; Gogtay et al., 2004). More specifically, the “dual systems model” suggests an imbalance in

neural maturation between cognitive control systems that regulate thoughts and emotions (prefrontal cortex) and the limbic system that drives affective and reward-related motivation (ventral striatum), such that cortical-subcortical connections precede top-down regulatory control connections (Casey et al., 2008; Casey, 2015; Somerville et al., 2010). This "imbalance" enables heightened risk-taking behavior, particularly when the behavior results in immediate rewards (Defoe et al., 2015; van Duijvenvoorde et al., 2010). However, others argue that this imbalance may not be present in all adolescents and, contextual factors, such as peer presence, may be more influential on the actual undertaking of risky behaviors (Shulman et al., 2016). The "triadic model" Figure 1) builds upon the "dual systems model" by adding a third system responsible for emotional intensity and avoidance (possibly involving the amygdala), which may serve to boost or dampen impulsive decision making (Ernst, 2014; Eldreth et al., 2013). Furthermore, complex interactions between affective-motivational processes, cognitive control, and social cognition likely drive decisions to engage in risky behavior (Kilford et al., 2016).

Neuroimaging studies show a fairly consistent pattern of functional activation connecting subcortical and cortical (ventral striatum, nucleus accumbens, amygdala, insula) and frontal (medial, lateral, ventral medial, and dorsolateral prefrontal cortex (dlPFC) and orbitofrontal cortex (OFC)) brain regions, in response to anticipation and receipt of rewards in adolescents and adults; however, adolescents have exhibited higher levels of activation in subcortical and cortical regions (Liu et al., 2011; Sescousse et al, 2013; Bartra et al, 2013; Silverman et al., 2015; Liu et al., 2011; Sescousse et al., 2013; Bartra et al., 2013). This "reward sensitivity" is regulated, in part, by dopamine levels and the number of dopamine receptors (Buckholtz et al., 2010; Pessiglione et al., 2006; Schultz, 2010; Sevy et al., 2006), and the dopamine response is critical for cognitive function in the prefrontal cortex (Braver and Cohen, 1999). Thus, adolescence provides a vulnerable state for reward-seeking behaviors and the potential misuse of substances (Koob & Zorrilla, 2010; Volkow & Baler, 2015); however, this period of neural plasticity also affords a window of opportunity to invoke and reinforce reward from healthy behaviors such as sport and exercise (Figure 1; discussed further below).

Abnormal Structural and Functional Brain Development May Predict Substance Use during Adolescence

Abnormal structural and functional brain development during childhood may increase the risk of substance misuse in adolescence. Lower frontal gray matter volume, lower cerebellar white matter volume, and lower white matter integrity in frontal and cortico-limbic regions have all been shown to predict alcohol and/or marijuana use in adolescence (Cheetham et al., 2012; Jacobus et al., 2013; Squeglia et al., 2014; Weiland et al., 2014). Interestingly, adolescents with smaller nucleus accumbens (NAc) volumes have been shown to be more likely to initiate substance use (Urosevic et al., 2015). In addition, a dose-dependent decrease in OFC volume has been associated with higher levels of substance use by age 18 (Cheetham et al., 2017). Moreover, thinner cortical thickness in childhood has been associated with marijuana use in adolescence and, a thinner dlPFC in earlier adolescence predicted binge drinking in late adolescence (Brumback et al., 2016; Jacobus et al., 2016).

Longitudinal functional MRI studies in childhood and earlier in adolescence have shown that differential neural activation, in response to inhibitory control and working memory tasks, may predict substance use later in adolescence and emerging adulthood. For example, less frontal (middle frontal gyrus) and parietal (inferior parietal lobe) brain activation in response to a working memory Go/No-Go task predicted heavier alcohol use (Squeglia et al., 2009; Wetherill, Squeglia et al., 2013). In addition, lower baseline ventromedial prefrontal cortex activation in response to a Go/No-Go response inhibition task predicted higher alcohol use later in adolescence (Mahmood et al., 2013). Furthermore, poorer working memory on the N-back task has predicted greater marijuana use (Cousijn et al., 2014).

Studies are emerging suggesting that resting-state cerebral blood flow may also lend insight towards predicting substance use in adolescence. For example, lower neural activation in reward and default mode networks (DMN) in 12–15 year olds has been associated with greater alcohol consumption three years later (Ramage et al.,. In addition, lower connectivity between the amygdala and OFC predicted alcohol use during adolescence (Peters et al., 2017). Interestingly, the presence of parents versus peers may also affect functional connections since, during “safe decision making”, in the presence of mothers, there was greater functional connectivity between the lateral prefrontal cortex and the ventral striatum (Telzer et al., 2015).

Other factors may increase the likelihood of early substance use, including *prenatal* substance exposure as well as other psychosocial and environmental factors, such as distress, depression, family conflict, violence, and exposure from environmental toxins (e.g., air pollution) (Anthony and Petronis, 1995; Behrendtet al., 2009; Buu et al., 2009; Delaney-Black et al., 2011; Frank et al., 2011; Kelly et al., 2011; Kilpatrick et al., 2000; Minnes et al., 2015; Reinherz et al., 2000; Richardson et al, 2002; Tucker et al, 2012). In particular, *prenatal* cocaine exposure is known to disrupt the monoaminergic neurotransmitter system (dopamine, serotonin, norepinephrine) in the prefrontal cortex (Mayes et al., 2007; Thompsonet al., 2009). Therefore, prenatal cocaine exposure may disrupt the developmental programming of an infant’s behavioral regulatory system, potentially resulting in maladaptive behavioral regulation, early substance use (Minnes et al., 2011) and general inhibitory control problems (Lambert and Bauer, 2012; Minnes et al., 2010; Thompson et al., 2009; Richardson et al., 2011). Adolescents with prenatal cocaine exposure, compared to adolescents without prenatal cocaine exposure (matched on several potential confounding factors including head circumference), had thinner cortical thickness, particularly in the dorsolateral prefrontal cortex, which correlated with impulsive behavior (Liu et al., 2013). Fetal alcohol exposure leads to a wide range of birth defects and difficulties in learning and memory, attention, visuospatial skills, language and speech disabilities, and mood disorders that may increase substance use during adolescence (Nguyen et al., 2017). The fetal endogenous cannabinoid signaling system, which is important for modulating neurodevelopment and the regulation of cardiovascular processes, is altered by *prenatal* marijuana exposure, particularly forms with higher delta 9 (D9)-tetrahydro-cannabinol (THC) to non-psychoactive cannabinol (CBD) ratios, providing a “first hit” that may manifest into cognitive impairment and emotional control issues (impulsivity, hyperactivity, externalization) in the presence of other stressors during adolescence (Richardson et al., 2016). In addition, human fetuses exposed to marijuana have lower dopamine receptor 2

(D2) mRNA expression in the ventral striatum, and this leads to increased substance-seeking behavior in animals (DiNieri et al., 2011; DiNieri & Hurd, 2012).

Structural Brain Effects from Substance Use during Adolescence

Because alcohol is and has been the most commonly used substance followed by marijuana during adolescence, most structural and functional neuroimaging studies have focused on the effects of these substances. Larger striatum and cerebellum and smaller prefrontal cortex and amygdala volumes have been observed in chronic marijuana users (Lorenzetti et al., 2016). In heavy drinkers, the decreases in gray matter volume occurring normally during adolescence are accelerated in frontal regions, potentially leading to non-beneficial pruning, and the normal increases in white matter volume are attenuated, particularly in the hippocampal region (Squeglia et al., 2015). Lower gray matter volume in the prefrontal cortex, amygdala, and striatum have been observed in heavy chronic marijuana users (Battistella et al., 2014). Preclinical studies suggest adolescent cocaine exposure impairs hippocampal cell genesis (proliferation and survival) (Garcia-Fuster et al., 2017), and adult hippocampal neurogenesis plays a role in cocaine addiction (Castilla-Ortega et al., 2016). Further, substantia nigra hyperechogenicity was observed in young adults with a history of illicit stimulant use (cocaine, methamphetamine) who were currently abstinent and, such morphological changes in the substantia nigra, which may alter dopamine levels, are associated with developing Parkinson's disease later in life (Todd et al., 2013). In addition, greater cortical thickness, particularly in frontal and parietal lobes, has been observed in adolescent marijuana users and some, but not all, studies suggest the adverse effects may not be reversible (Jacobus et al., 2014; Jacobus et al., 2015; Ganzer et al.,, 2016). Furthermore, poorer white matter integrity has been observed in adolescents with exposure to alcohol and/or marijuana (Bava et al., 2013; Jacobus et al., 2013; Jacobus et al., 2013). In addition, the THC in marijuana exposure during adolescence affects cannabinoid receptor (CB1) density and has other adverse effects on the cannabinoid system, which is vital for neurodevelopmental processes including neuronal genesis, neuronal migration, glial formation, and axonal elongation (Fuhrmann et al., 2015).

Functional Brain Effects from Substance Use during Adolescence

Substance exposure during adolescence may adversely affect cognitive functioning, as measured by neuropsychological tests and functional neuroimaging tasks. Adolescent alcohol and marijuana users have poorer performance on working memory, verbal learning and memory, visuospatial functioning and psychometric motor speed tasks, and poorer performance has been observed with higher doses and an earlier age-of-onset (Ganzer et al., 2016; Hanson et al.,, Medina et al., 2011; Nguyen-Louie et al., 2015). Moreover, marijuana users appear to suffer additional attentional deficits (Randolph et al., 2013), and the cognitive deficits may be sustained in chronic users (Ganzer et al., 2016; Renard et al., 2014).

Heavy alcohol users have shown decreased brain activation in frontal and parietal regions, in response to inhibition and working memory tasks (Wetherill et al., 2013; Squeglia et al., 2012) and decreased activity in the cerebellum in response to a reward processing task

(Wheel of Fortune) (Cservenka et al., 2015). In addition, when winning money, higher activity in the ventral striatum was associated with higher amounts of alcohol consumption in adolescents (Braams et al., 2016). Higher activation in the anterior cingulate cortex (ACC) and cerebellum has been observed in response to alcohol cues in alcohol abusers (Brumback et al., 2015). These responses are supported by preclinical studies that show alcohol use disrupts inputs to the dopamine system and, the use of alcohol during adolescence alters risk-based decision making by modulating incentive learning (Kruse et al., 2017).

Greater activation in the dorsolateral prefrontal cortex has been observed in response to cannabis images, and these effects predicted greater cannabis use and cravings in cannabis users (Cousijn et al., 2013). Furthermore, heavy cannabis users compared with controls showed higher activation during “wins” from Iowa gambling task in core areas associated with decision making, and win-related activity and activity anticipating loss outcomes in executive function areas predicted a change in cannabis use after 6 months (Cousijn et al., 2013).

Gaps in Understanding Effects of Substance Use on the Brain

The majority of prior studies have focused on alcohol and marijuana, the two substances most commonly used during adolescence; however, additional studies are needed to evaluate potential adverse effects of other substances, including the non-medical use of prescription opioids, which is becoming particularly problematic in the South, Midwest, and low-income rural areas (Young et al., 2012). Furthermore, many studies have not evaluated the potential synergistic effects of concurrent use of two or more substances within the same time-period (Lorenzetti et al., 2016), marijuana potency (THC content), which has been increasing over time, and co-occurring psychological disorders. In addition, many prior studies have had small sample sizes and prospective studies have had relatively short amounts of follow-up time. Moreover, very few studies have integrated physiological (e.g., puberty) and social maturity as well as contextual influences into their evaluations. Importantly, however, there are several large multi-site trials underway, which will undoubtedly help to better understand the neurobiology of substance exposure and concurrent substance use in childhood and adolescence, including the IMAGEN (Schumann et al., 2010), National Consortium on Alcohol and Neuro-Development in Adolescence (NCANDA) (Brown et al., 2015) and Adolescent Brain Cognitive Development (ABCD) (Bjork et al., 2017; Volkow et al., 2017) studies. The IMAGEN study has been following 2,000 youth from Europe for over eight years, and the NCANDA study will be following over 800 youth at five sites in the U.S. for at least 10 years (Brown et al., 2015; Schumann et al., 2010; Dwyer and Leslie, 2016; Wahlstrom et al., 2010). The ABCD study, initiated recently, will be following 11,500 youth at 21 sites across the U.S. for at least 10 years. By utilizing common instruments, neuropsychological tests, and neuroimaging tasks (Kwako, Momenan et al., 2016), these ongoing large cohort studies will be able to establish more comprehensive normative data and understand the effects of substance use in more diverse ethnic samples (as most prior studies have predominantly evaluated Caucasians). These large studies will also be poised to better estimate substance dose and causal dose-response effects using biomarkers, smart-phone, and ecological momentary assessment (EMA) techniques, and to evaluate potential

mediating and moderating effects by gender, family history of substance use and genetic variation.

Treatment Programs for Substance Use Disorders

Earlier initiation of substance use in adolescence is associated not only with an increased risk of SUDs but, also with antisocial behavior and impairments of adaptive functioning, including legal and relationship difficulties, incarceration, academic failure, unemployment, and mental health issues (Anthony & Petronis, 1995; Behrendt et al., 2009; DuRant et al., 1999; Fergusson and Horwood, 1997; Gordon et al., 2004; Guttmannova et al., 2012; Slade et al., 2008). Emerging studies also suggest that adolescents with obesity are at higher risk of engaging in substance misuse (Lanza et al., 2015). Furthermore, prevention of substance use is a “Healthy People 2020” initiative with the goal “to reduce substance abuse to protect the health, safety, and quality of life for all, especially children” (U.S. Department of Health and Human Services).

A variety of treatment modalities are typically utilized in current programs, including behavioral therapy (cognitive behavioral therapy, CBT), family-based therapy, 12-step programs (e.g., Alcoholics Anonymous), motivational interviewing, contingency management, and combinations of these components (Schuckit, 2009; Brewer et al., 2017). However, most of these programs were initially developed for adults and have been modified for adolescents. Nevertheless, most trials have shown the importance of multiple component programs and including parents to effectively reduce and/or prevent substance use during adolescence (Brewer et al., 2017; Newton et al., 2017). Furthermore, web- and smartphone-based programs as well as gamified Cognitive Bias Modification (CBM) treatments are emerging, and have shown some promise in preventing and treating substance misuse (Boendermaker et al., 2015).

Pharmacological agents may also be used in the treatment of SUD in adolescents. The Food and Drug Administration (FDA) has approved nicotine replacement therapy, sustained-release bupropion, and varenicline for tobacco use disorders, benzodiazepines, disulfiram, naltrexone, and acamprosate for alcohol use disorders and, methadone, naltrexone, and buprenorphine/naloxone for opioid use disorders (Hammond, 2016). No medications are currently FDA indicated for cannabis use disorder (Hammond, 2016), but the efficacy of N-acetylcysteine (NAC) compared to placebo has been shown in one trial of cannabis dependent adolescents (Gray et al., 2012). However, interestingly, NAC did not significantly reduce cannabis use in a subsequent trial of adults with cannabis dependence (Gray et al., 2017). Recently, the American Academy of Pediatrics recommended medication-assisted treatment for adolescents with severe opioid use disorders, however, only 0.4% (95% CI: 0.2%–0.7%) of adolescents in treatment for prescription opioids actually received medication, compared to 12.0% (95% CI: 11.7%–12.2%) of adults (Feder et al., 2017). Furthermore, the pharmacokinetic and pharmacodynamics responses to many of these agents and their potential side effects when taken during adolescence, a sensitive period of development, are not fully understood (Hammond, 2016).

Although exercise is not typically a component of current treatment programs, individuals with SUDs are interested in engaging in exercise as part of their treatment to help reduce substance cravings and boredom, and improve their overall physical and mental health (Abrantes et al., 2011; Gimenez-Meseguer et al., 2015; Neale, Nettleton and Pickering, 2012). Many patients with SUDs have expressed the preference to begin an exercise program early in their recovery (within the first 3 months) (Abrantes et al., 2011; Neale et al., 2012). Interestingly, some patients have reported that exercising was actively discouraged during treatment (Neale et al., 2012). Unfortunately, very little is currently known about the specific exercise preferences, motivators and barriers of adolescents with SUDs.

Overall, regardless of the type of treatment program offered, most individuals with SUDs do not take advantage of available treatment programs, as only about 6–7% of U.S. adolescents who need treatment actually receive it (Lipari et al., 2016; SAMHSA, 2014). Furthermore, unfortunately, over 50–60% of adolescents with SUDs are likely to relapse within one year of treatment (McLellan et al., 2000; Ramo and Brown, 2008; Cornelius et al., 2003). Thus, there is clearly a need for more accessible and improved treatment approaches for substance misuse and co-occurring psychiatric disorders in adolescents.

Rationale for Therapeutic Effects of Exercise in Substance Use Disorders

As mentioned above, substance misuse causes cognitive impairments in the same brain regions that are necessary to be engaged to initiate and maintain behavior change. Therefore, treatments to overcome these cognitive deficits are needed in conjunction with, or perhaps *before*, conventional behavioral therapies are initiated to help “prime” and/or repair structural and functional brain deficits induced by substance abuse.

Exercise has been shown to improve memory, inhibitory control, and attention in adults with mild cognitive impairments (Cammisuli et al., 2017), but statistically significant improvements in motor function, cognitive speed, and auditory and visual attention have been somewhat inconsistent in healthy adults (Angevaren et al., 2008; Young et al., 2015). There have been substantially fewer randomized trials in healthy children and adolescents, but several studies have shown improvements in attention, cognitive flexibility, and executive function with structured physical activity and exercise (Ardoy et al., 2014; Berse et al., 2015; Budde et al., 2008; Lambrick et al., 2016; Landry and Driscoll, 2012; Mahar, 2011; Song et al. 2016; Donnelly et al., 2016). Furthermore, cognitive improvements may be dose dependent, as children engaging in a 40-minute compared to a 20-minute daily exercise program were shown to have better performance on mathematic and anti-saccade eye tracking tasks (Davis et al., 2011).

Exercise induces structural and functional changes in the brain, including neurogenesis, angiogenesis, and improved neuronal health (Mueller, 2007), which may, in turn, affect overall brain health and function. Exercise is known to improve overall cardiovascular function, which increases cerebral blood flow and restores homeostasis to the neuronal microenvironment (Baek, 2016; Tarumi and Zhang, 2017). Animal studies have shown that exercise stimulates an interactive cascade of peripheral signaling molecules (insulin growth

factor (IGF)-1) that cross the blood-brain barrier to increase neurotrophic factors (brain-derived neurotrophic factor, BDNF) in the hippocampus (a brain region central to learning and memory) potentiating synaptic transmission and plasticity (Cotman and Berchtold, 2002). A meta-analysis of 29 human studies has found BDNF levels increase with a single bout of exercise and even higher BDNF levels have been observed with chronic exercise (Szuhany et al., 2015). Recent data are also emerging that show levels of the neuropeptide, orexin-A, increase with exercise in humans and may enhance hippocampal neurogenesis and function (Chieffi et al., 2017). Exercise has also been shown to increase circulating and hippocampal levels of IGF-1, but data in human studies are somewhat inconsistent (Reinhardt and Bondy, 1994; Rojas, 2010; Griffin et al., 2011; Patterson, 2013). Vascular endothelial-derived growth factor (VEGF) is also upregulated with exercise, leading to blood vessel growth in the hippocampus as well as in the cortex and cerebellum (Fabel et al., 2003; van et al., 2005; Ding et al., 2006; Black et al., 1990). Furthermore, larger hippocampal volume and greater caudate and putamen volumes (two structures in the basal ganglia) have been observed in higher fit compared to less fit adolescents (Chaddock et al., 2010; Chaddock et al., 2010).

Exercise may exert neuroprotective effects and/or may help restore damage from substance use exposure. For example, exercise has been shown to restore hippocampal function following neurotoxicity from alcohol binging in rats (Leasure and Grider, 2010; Maynard and Leasure, 2013). Exercise has also been shown to increase gliogenesis in the prefrontal cortex and may help counteract the executive function impairments associated with an increased chance of relapse from methamphetamines and other substances (Mandyam et al., 2007). Chronic inflammation, which can arise from obesity and potentially SUDs, may impair IGF-1 and BDNF signaling, leading to “neurotrophin resistance” via upregulation of pro-inflammatory cytokines, such as IL-β (Tong et al., 2008; Cotman et al., 2007).

Exercise is known to evoke neurotransmitters and endogenous opioids in the brain (Greenwood and Fleshner, 2011) that are similar to those induced by substances of abuse. For example, exercise increases the levels of dopamine, epinephrine, norepinephrine, and β-endorphins, which are the same neurotransmitters activated by drugs and alcohol, and may be attributed to the “runners high” or neural reward received from higher intensity exercise in some individuals (Volkow et al., 2010; Volkow et al., 2010; Volkow et al., 2012; Volkow et al., 2012; Herrera et al., 2016; Boecker et al., 2008; Heitkamp, 1993; Bortz et al., 1981). The increase in these neurotransmitters may also contribute to the improvement in positive affect and mood reported with exercise (Matta Mello et al., 2013). In addition, exercise may help to normalize the glutamatergic system, which has been shown to be dysregulated, particularly during substance withdrawal periods, in preclinical studies (Lynch et al., 2013).

Furthermore, exercise provides many other physical and mental health benefits. Exercise improves cardiovascular health (Penedo et al., 2004; Wilson et al., 2016), which may be compromised in SUDs even after abstinence (Degenhardt et al., 2014; Huang et al., 2016; Karila et al., 2014; Maisch, 2016; Thylstrup et al., 2015). Exercise has also been shown to reduce depression, distress, and anxiety in adolescents (Schuch et al., 2016; Schuch et al., 2016; Nabkasorn et al., 2006; Blumenthal et al., 1999; Salmon, 2001), all of which may be more prevalent in adolescents with SUDs (Kelly et al., 2015; Rhew et al., 2017). Exercise

improves self-efficacy (Parschau et al., 2013; McAuley and Blissmer, 2000), which may enhance adherence and overall effectiveness of behavioral treatment programs (Selzler et al., 2016). Physical activity also reduces the risk of several cancers (e.g., breast, liver, colon) (Courneya and Friedenreich, 2011; Moore et al., 2016) where risk may be elevated from the exposure to substances such as cigarettes, alcohol, and/or opioids (Afsharimani et al., 2011; Joshi et al., 2016; Liang et al., 2009; Moussas and Papadopoulou, 2017; Wang et al.,, 2016).

Evidence for Exercise to Prevent and Reduce Substance Misuse

Epidemiological studies suggest that higher levels of physical activity may decrease the use of substance misuse, although the results for alcohol are somewhat inconsistent. For example, cross-sectional studies have shown that higher levels of physical activity and participation in sports is inversely associated with smoking among adolescents (Rodriguez and Audrain-McGovern, 2004; Verkooijen et al., 2008). Further, data from the MTF study found that participation in physical activity in adolescence was associated with a lower use of cigarettes and marijuana into early adulthood, but there was an increased use of alcohol in those participating in school athletics (Terry-McElrath and O'Malley, 2011). The International Health Behavior in School-aged Children study of Polish adolescents found that boys who engaged in moderate physical activity for at least one hour, four days per week had a lower use of marijuana (Tabak et al., 2015). In addition, a study of Norwegian adolescents found that sports training, but not other hobbies, conducted one or more times per week, significantly decreased the risk of lifetime cannabis use among those exposed to cannabis use opportunities (OR=0.68; 95% CI: 0.50–0.92) (Burdzovic and Bretteville-Jensen, 2017). Thus, engaging in physical activity can decrease the use of substances in those with substance use opportunities, and this effect appears to be attributable to more than just the time occupied by the activities.

Acute exercise has been shown to reduce cigarette cravings and attentional bias to smoking images in adults (Haasova et al., 2013; Van Rensburg et al., 2009; Roberts et al., 2012). In particular, acute exercise (10 minutes of moderate intensity cycling) decreased activation in reward (caudate nucleus), motivation (orbitofrontal cortex), and visuo-spatial attention (parietal lobe, parahippocampal, fusiform gyrus) brain regions, in response to smoking versus neutral images (Van Rensburg et al., 2009). In addition, acute exercise significantly reduced anxiety in smokers following quit attempts (Abrantes et al., 2017). Furthermore, a 2-week aerobic exercise program (10, 30-minute moderate intensity treadmill bouts) reduced marijuana cravings in non-treatment seeking cannabis-dependent adults (Buchowski et al., 2011). Trials evaluating the acute effects of exercise on cravings and attentional bias in adolescents are needed.

Several randomized trials of chronic exercise, predominantly aerobic (cardiovascular) types, as an adjunctive treatment have been conducted in adults with SUDs, but trials in adolescents with SUDs are scant. Most trials in adults have shown better abstinence rates in the exercise versus control (education) arms in patients with alcohol and illicit drug use disorders (Linke and Ussher, 2015; Zschucke et al., 2012; Giesen et al., 2015). A meta-analysis of three trials found that exercise decreased the number of drinks per week in adults with alcohol use disorders (Hallgren et al., 2017). A review including 20 randomized trials

conducted by the Cochrane Tobacco Addiction Group concluded that only two trials provided evidence that exercise improved long-term smoking cessation, and the other trials were too small or were not of sufficient quality to reliably include (Ussher et al., 2014). A subsequent randomized trial revealed that the beneficial effects of vigorous intensity exercise on point prevalence and prolonged abstinence may be limited to those with high anxiety at baseline (Smits et al., 2016). The Stimulant Reduction Intervention using Dosed Exercise (STRIDE) trial, which was conducted in 9 residential addiction treatment programs across the U.S., found that adult participants in the exercise arm had a 4.8% higher abstinence rate (78.7%) compared to those in the health education arm (73.9%), when controlling for treatment adherence and baseline stimulant use (Trivedi et al., 2017). Exercise has also been shown to improve secondary physiological (e.g., fitness, strength) and psychosocial (depression, anxiety) outcomes in these adult exercise trials (Linke and Ussher, 2015; Zschucke et al., 2012; Giesen et al., 2015).

Potential Therapeutic Effects of 'Assisted' Exercise for Substance Use Prevention and Treatment

Although studies presented above suggest that the "imbalance" between the development of subcortical-cortical and frontal/regulatory circuitry during adolescence may increase risky-behavior and substance abuse, following Telzer (Telzer, 2016), this period of heightened reward (ventral striatum) sensitivity may also provide a unique window of opportunity to promote positive health behaviors. Telzer suggested using "prosocial rewards to offset the rewarding nature of engaging in risky behaviors" (Telzer, 2016); however, we propose that exercise be utilized to promote adaptive (positive, healthy) behaviors and offset (suppress) maladaptive substance use and other adverse (negative, unhealthy) reward-seeking behaviors (Figure 1).

'Assisted' exercise compared to voluntary rate exercise may be able to provide even greater effects in suppressing reward from substance use, due to potentially larger increases in neurotransmitters (e.g., dopamine) and neurotrophic factors (e.g., BDNF), which may be particularly beneficial in adolescents with SUD having a "dopamine deficit" due to genetic variation and/or lower levels of striatal dopamine receptors (D2/D3) during substance abstinence (Volkow et al., 2001; Volkow et al., 2013; Volkow and Baler, 2014). We have previously shown that 'assisted' exercise, which provides mechanical assistance to pedal up to 35% faster than voluntary rates, provides global improvements in motor function and increased activity in cortical and subcortical regions consistent with neural activation patterns, after applying a dopamine agonist in Parkinson's disease (PD) patients, suggesting 'assisted' exercise may be modulating dopamine levels in the brain (Ridgel et al., 2009; Alberts et al., 2011; Alberts et al., 2016). More specifically, 'assisted' cycling resulted in altered patterns of activation in the primary motor cortex, supplementary motor area, thalamus, globus pallidus, and putamen in individuals with PD, similar to activation patterns seen after levodopa administration (Alberts et al., 2011; Alberts et al., 2016). These human data are consistent with animal studies that show wheel running in rodents has strong rewarding and reinforcing properties, which are modulated through the activity of dopamine in the striatum (de et al., 2005). Further, the higher exercise rates that are afforded by

'assisted' or forced exercise may elicit greater BDNF levels, which may be due to increased dopamine in the dorsal striatum (Alomari et al., 2013; de et al., 2005; Herrera et al., 2016; Petzinger et al., 2010) (Figure 2). Interestingly, in animals, chronic forced exercise during adolescence has been shown to attenuate cocaine use (Thanos et al., 2010). We are currently evaluating the effects of 'assisted' compared to voluntary cycling exercise on food-related neural reward in obese endometrial cancer survivors, and hypothesize that 'assisted' exercise will further enhance the reward received from exercise providing increased (intrinsic) motivation to exercise and lead to greater sustained weight loss (Nock et al., 2014).

Although no trials have yet to evaluate the effects of 'assisted' exercise in humans with substance use disorders, a recent trial has shown an increase in striatal D2/D3 availability (non-displaceable binding potential) after an 8-week exercise program, compared to an education control condition in adult methamphetamine users (Robertson et al., 2016). Therefore, if 'assisted' exercise can further enhance dopamine, BDNF, and striatal dopamine receptor availability, it may provide additional benefits beyond voluntary rate exercise, particularly in patients with dopamine and/or dopamine receptor deficits. Furthermore, given the data from preclinical studies, we propose that the exercise be initiated during early abstinence (Beiter et al., 2016) and started before integrating other cognitive behavioral treatment components, to help "prime" the brain and/or repair structural and functional brain deficits induced by substance abuse (Figure 3). Exercise may help to enhance adaptive (vs. maladaptive) decision making by reinforcing the circuitry connecting frontal and cortical-subcortical regions. Furthermore, treatment programs incorporating exercise should be offered as a preventative measure to adolescents at high risk for substance abuse, based on mental health, family history, genetic profiles, neurocognitive profiles, and other factors.

Summary

Substance abuse is an important public health issue, particularly during adolescence, a critical period of neurobiological and social development. Incorporating exercise into SUD treatment programs during early abstinence may provide additional therapeutic benefit in improving relapse rates and could help to prevent substance abuse in adolescents. If integrated during adolescence, a window of heightened reward sensitivity and neural plasticity, exercise may help to reinforce "naïve" or underdeveloped connections between neurological reward and regulatory processes from the "bottom up" and, in turn, help offset or dampen reward seeking from substances while concomitantly improving cardiovascular health, as well as academic and social achievement. 'Assisted' exercise can potentially further enhance dopamine, BDNF, and striatal dopamine receptor availability, and may provide additional benefits beyond voluntary rate exercise, particularly in patients with dopamine and/or dopamine receptor deficits. Improving healthy behaviors during adolescents may not only dampen desire for other reward-seeking behaviors, but may enhance the likelihood healthy behaviors are sustained into adulthood. Given the dearth of randomized trials in adolescents, additional studies are clearly needed to determine what dose (frequency, intensity, duration, length), type (aerobic, resistance), and format ('assisted', voluntary) of exercise can improve relapse rates and potentially prevent substance misuse during adolescence and emerging adulthood.

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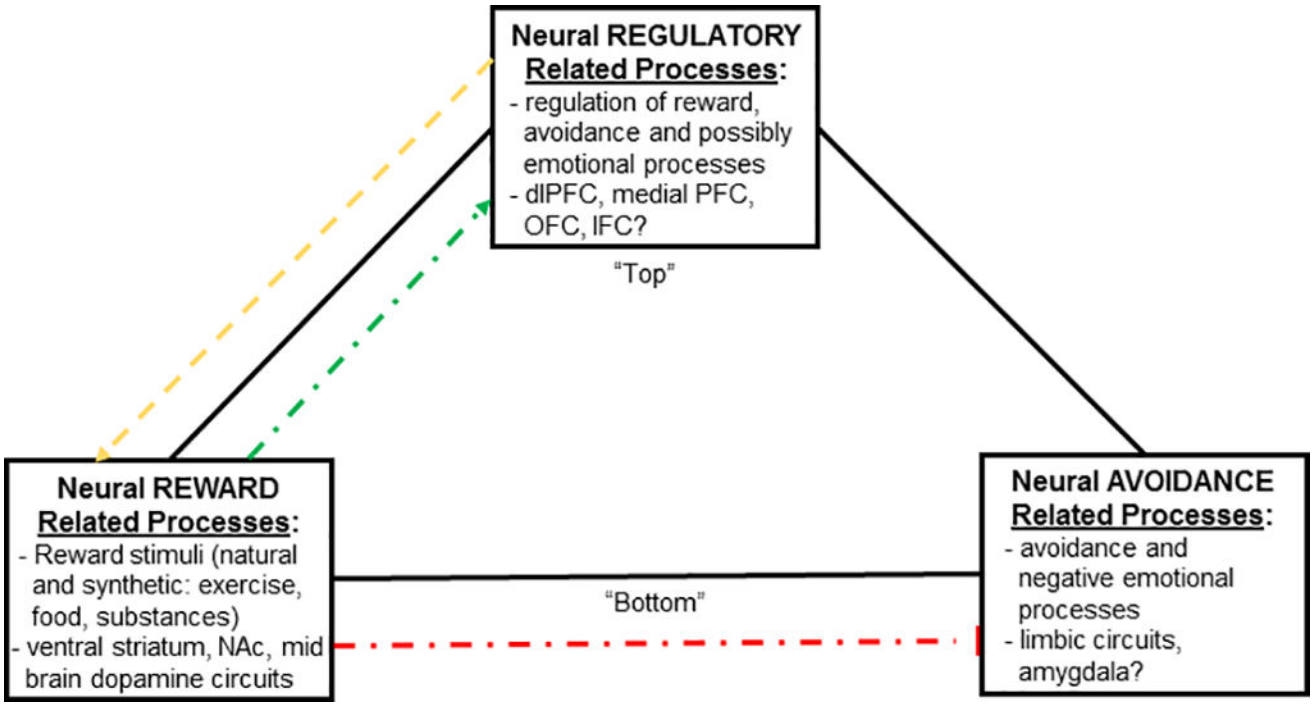

Figure 1.

Proposed effects of exercise on the "triad model", which relates reward (positive, affective stimuli), avoidance (negative, adversive stimuli) and regulatory related neural processes. Connections less developed (weaker) during adolescence (yellow) and connections that could be reinforced with exercise (green). 'Assisted' exercise may induce greater exercise-related reward and motivation, while concomitantly dampening reward-seeking from substances and, may inhibit avoidance/negative emotions (red) while enhancing overall "bottom up" inhibitory control. Adapted from Ernst (Ernst, 2014) and Eldreth et al. (Eldreth et al., 2013).

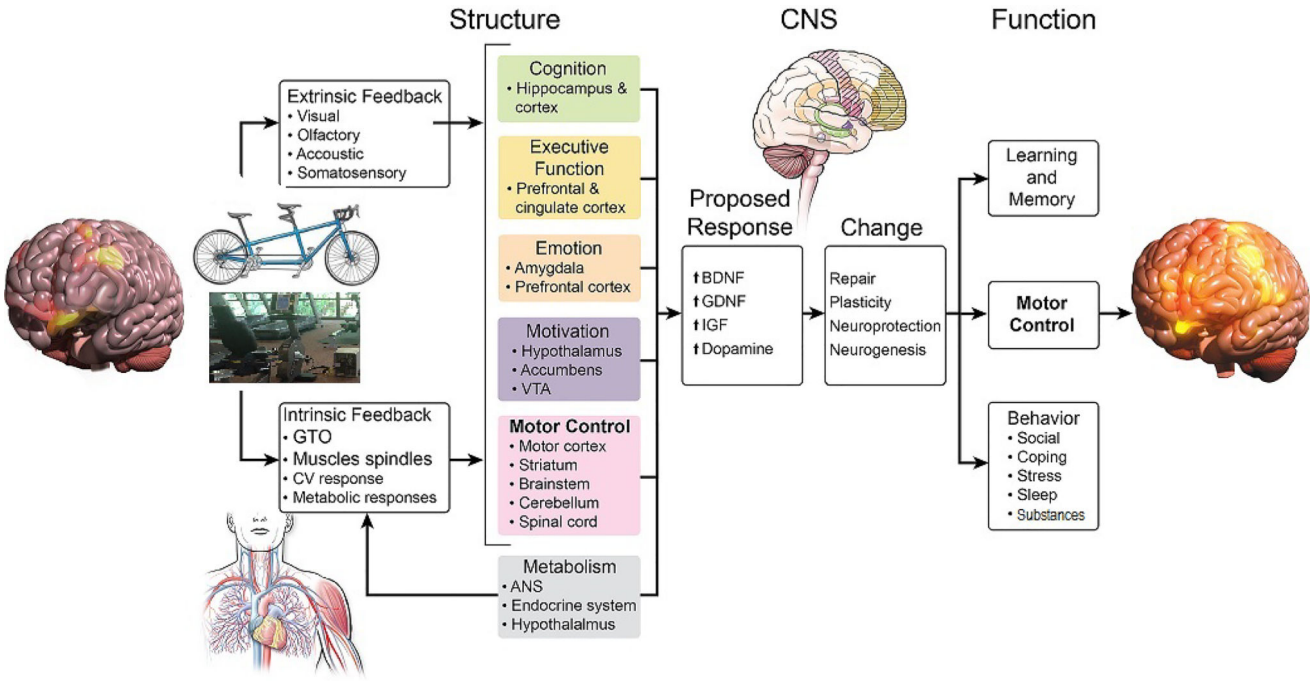

Figure 2.

Hypothesized effects of ‘assisted’ exercise on the brain. Higher rates of pedaling, afforded by ‘assisted’ exercise (on tandem bicycles or ‘smart’ motor-driven cycles) may provide enhanced intrinsic neuromuscular feedback leading to higher levels of neurotrophic factors (BDNF, brain-derived neurotrophic factor; GDNF, glial-derived neurotrophic factor; IGF-1/3, insulin-like growth factor) and neurotransmitters (dopamine), as well as increased striatal dopamine receptor availability providing increased neural activation in cortical-subcortical brain regions (see text). These effects may help to “dampen” reward-seeking from substances, particularly in individuals with a dopamine or neurotrophic deficit, during adolescence, a window of heightened reward sensitivity and neural plasticity and, improve overall cardiovascular, cognitive and psychosocial health. Adapted from Alberts et al. (Alberts et al., 2011).

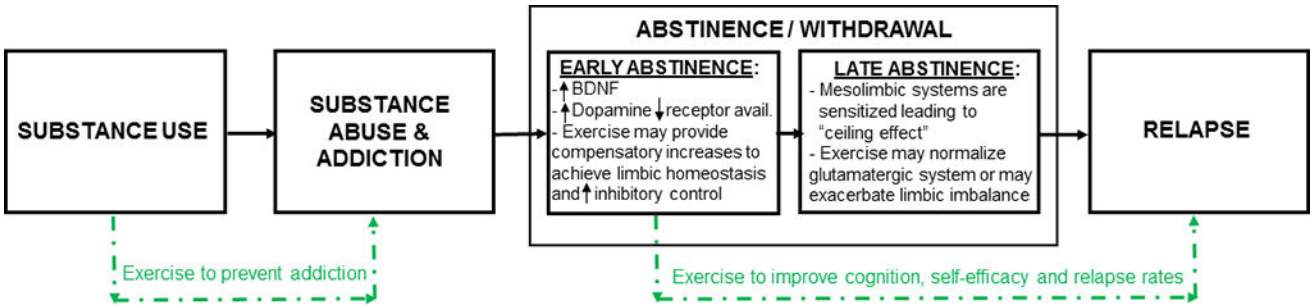

Figure 3.

Proposed utilization of exercise as an adjunctive treatment in adolescents using and addicted to substances. Preclinical models indicate intervening with exercise during early but not late abstinence may provide improvements in relapse rates (Beiter et al., 2016). Taken together with data showing exercise can improve executive function, cognitive flexibility and attention (Davis et al., 2011; Donnelly et al., 2016; Landry and Driscoll, 2012), which are processes needed for behavior change, we propose that exercise be integrated into treatment programs during early abstinence and before cognitive behavioral therapies are initiated to help "prime" the brain and/or repair structural and functional brain deficits induced by substance abuse.