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Review

Exercise as a novel treatment for drug addiction: A neurobiological and stage-dependent hypothesis

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ABSTRACT

Physical activity, and specifically exercise, has been suggested as a potential treatment for drug addiction. In this review, we discuss clinical and preclinical evidence for the efficacy of exercise at different phases of the addiction process. Potential neurobiological mechanisms are also discussed focusing on interactions with dopaminergic and glutamatergic signaling and chromatin remodeling in the reward pathway. *While exercise generally produces an efficacious response, certain exercise conditions may be either ineffective or lead to detrimental effects depending on the level/type/timing of exercise exposure, the stage of addiction, the drug involved, and the subject population.* During drug use initiation and withdrawal, its efficacy may be related to its ability to facilitate dopaminergic transmission, and once addiction develops, its efficacy may be related to its ability to normalize glutamatergic and dopaminergic signaling and reverse drug-induced changes in chromatin via epigenetic interactions with brain-derived neurotrophic factor (BDNF) in the reward pathway. We conclude with future directions, including the development of exercise-based interventions alone or as an adjunct to other strategies for treating drug addiction.

Contents

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1. Introduction

Drug addiction is the leading cause of preventable death in the United States followed closely by obesity (Mokdad et al., 2004). New and more effective treatments are critically needed, but developing treatments for drug addiction is challenging because its underlying neurobiology varies over time as the disease progresses. During early "non-addicted" stages, such as when drug use is initiated, dopamine signaling in the reward pathway (i.e., nucleus accumbens, NAc; ventral tegmental area, prefrontal cortex, PFC) is believed to be a primary mechanism motivating drug use (for reviews see Gardner, 2011; Kalivas and Volkow, 2005; Koob and Volkow, 2010; Pierce and Kumaresan, 2006; Willuhn et al., 2010). Drugs of abuse, including psychostimulants, alcohol, nicotine, hallucinogens, cannabinoids, and opiates increase dopamine in the NAc (Carboni et al., 1989; Chen et al., 1990; Damsma et al., 1989; Di Chiara and Imperato, 1988; Hernandez and Hoebel, 1988; Maisonneuve et al., 1991; Yoshimoto et al., 1992). Blocking/ablating this pathway can disrupt drug self-administration, particularly psychostimulant self-administration (e.g., Chang et al., 1994; Corrigall et al., 1992; Lyness et al., 1979; Singer et al., 1982; Singer and Wallace, 1984; Robledo et al., 1992; but see Lyness and Smith, 1992 for ethanol self-administration and Gerrits and Van Ree, 1996 for heroin self-administration). Other signaling pathways, such as glutamatergic pathways, also motivate drug use, particularly during later stages of the addiction process (i.e., with recurrent use, once addiction has developed, during relapse; e.g., Allen et al., 2007; Bauer et al., 2013; Ben-Shahar et al., 2009, 2012, 2013; Bossert et al., 2012; Fischer-Smith et al., 2012; Ghasemzadeh et al., 2011; Hao et al., 2010; Kufahl et al., 2011, 2013; Madayag et al., 2007; McCutcheon et al., 2011; Meinhardt et al., 2013; Okvist et al., 2011; Schwendt et al., 2012; Sidhpura et al., 2010; for reviews see Kalivas and Volkow, 2011; Loweth et al., 2013; Van den Oever et al., 2012; Wolf and Tseng, 2012). Brain adaptations caused by chronic exposure to drugs of abuse also leads to mesolimbic hypofunction (Koeltzow and White, 2003; Maisonneuve et al., 1995; Paulson et al., 1991; Schmidt et al., 1996), which in turn, may promote drug use to compensate for its decreased effect on dopamine release and may motivate relapse to drug use during abstinence to reverse dopamine deficits (for review see Melis et al., 2005). Chronic exposure to drugs of abuse also leads to alterations in gene expression through neuronal chromatin remodeling (e.g., Damez-Werno et al., 2012; Gozen et al., 2013; Repunte-Canonigo et al., 2013; Tomasiewicz et al., 2012), and these changes may underlie the persistent vulnerability to relapse after extended periods of abstinence (for reviews see Biliński et al., 2012; Kovatsi et al., 2011; LaPlant and Nestler, 2011; Robison and Nestler, 2011). Together, these results suggest that the efficacy of a potential treatment for drug addiction should be tailored for the stage of the addiction process. This type of approach has been used successfully in the treatment of other diseases (e.g., diabetes, cancer, HIV), but has not been fully considered for addiction treatment.

Physical activity, and specifically exercise, is a potential non-pharmacological treatment for addiction that targets systems implicated in both early and late stages of the addiction process and has secondary health benefits (e.g., prevention of obesity and secondary diseases such as diabetes). Mechanistically, physical activity and exercise activate the same reward pathway as drugs of abuse, through increases in dopamine concentrations and dopamine receptor binding (Greenwood et al., 2011; MacRae et al., 1987). These effects may be particularly beneficial at preventing drug use and reducing initial vulnerability to drug use. Physical activity and exercise also decrease glutamate in the striatum (Guezennec et al., 1998), which may protect against overstimulation of glutamatergic receptors following chronic drug exposure. Exercise may also influence brain plasticity through mechanisms centered on remodeling of chromatin at regions that are implicated in drug addiction (Gomez-Pinilla et al., 2011; Chase and Sharma, 2013; Kumar et al., 2005; Sadri-Vakili et al., 2010; Vassoler et al., 2013; Wan et al., 2011).

Despite promising results, certain exercise conditions may be either ineffective or lead to detrimental effects. Given that exercise is becoming more frequently considered as a potential treatment for addiction and other psychiatric disorders, and given that it is a relatively easily implemented and freely available option, it is critical to identify the conditions that produce beneficial effects, and those that may lead to detrimental effects. In this review, we will discuss evidence for the efficacy of physical activity and exercise at reducing drug use at the different stages of the addiction process including the initiation of use, the transition to addiction, withdrawal, and relapse. Although the main goal is to understand the potential efficacy of exercise as a treatment for addiction, evidence for the effects of both physical activity and exercise are discussed. "Physical activity" is used to describe findings primary from epidemiological studies that are generally self-reported levels of daily activities, including occupational, sports, conditioning, household, or other activities. "Exercise" is used to describe findings primary from the human laboratory and some epidemiological studies, and refers to a subset of physical activity that is structured and repetitive (e.g., treadmill running, walking). *Studies were selected based on Pub Med and Web of Science searches using the key words exercise, physical activity, smoking, nicotine, tobacco, heroin, morphine, opioid, cocaine, methamphetamine, illicit drug use/abuse/dependence, marijuana, and alcohol. In cases where meta-analytical studies were available, these reviews were preferentially discussed over the individual studies.* We also reviewed findings from animal models of exercise, including both forced and voluntary running on a treadmill or a wheel, in order to identify potential mechanisms for its efficacy. To this end, we focused on three signaling pathways/mechanisms critically involved in the development and maintenance of addiction: dopaminergic and glutamatergic signaling and chromatin remodeling in the reward pathway. The potential role of other signaling pathways, including the endogenous opioid pathway, is also briefly discussed. *In addition to the key words used to identify human studies, we included the terms wheel and treadmill running, as well as dopamine, glutamate, chromatin, epigenetic, and Bdnf.* We conclude with future directions including the potential role of exercise as an intervention for drug addiction.

2. Effects of exercise on initiation of drug use

2.1. Initiation of drug use: Results from human studies

In humans, the initiation phase encompasses the transition from initial drug sampling to regular use. Although a causal effect of exercise on rates of initiation of drug use in humans has not been examined, epidemiological data obtained from adolescents, a population believed to be particularly vulnerable to initiate drug use, indicate a negative association of the two. For example, results from school-based, community-based, and national cross-sectional studies show that that highly active teens, teens who exercise regularly, and teens involved in team sports are less likely than less active teens, teens who do not exercise, and teens not involved in team sports to use cigarettes and illicit drugs (e.g., Escobedo et al., 1993; Field et al., 2001; Kirkcaldy et al., 2002; Kulig et al., 2003; Martinsen and Sundgot-Borgen, 2012; Melnick et al., 1997; Pastor et al., 2003; Pate et al., 1996, 2000; Rainey et al., 1996; Ströhle et al., 2007; Terry-McElrath et al., 2011; See Table 1 for representative summary of the studies and findings). Results from longitudinal studies reveal similar findings where high levels of physical activity

Table 1
Evidence from human and animal studies for the effects of exercise on drug use initiation.

Results from human studies				
Reference	Subjects	Exercise schedule	Study design	Effect of exercise
Escobedo et al. (1993)	Nationally representative sample of high school students ($N = 11,248$)	Number of school sports teams participated in during the last 12 months	Cross-Sectional Survey (Youth Risk Behavior 1990): Smoking patterns, incidence and age of smoking initiation, odds of regular and heavy smoking	Lower prevalence of regular and heavy smoking Inverse relationship between the number of team sports participated in and odds of regular and heavy smoking
Field et al. (2001)	High school seniors ($N = 89$)	Assessed on a likert scale from rarely (1) to daily (5) exercise. Median split to analyze high versus low exercise groups	Questionnaire: Cigarettes, alcohol, and illicit drug use (Likert scale from 1-never to 4-regularly)	Lower levels of substance use as compared to the low exercise group
Kirkcaldy et al. (2002)	German high school students (14–18 years old; N ~ 1000)	Involvement in endurance sport (never, seldom, often, always)	Questionnaire: Cigarettes, beer, and marijuana use (Likert scale from 1-never to 4-regularly), and Addiction Score (Personality)	Lower cigarette and marijuana use in most active No difference for beer drinking Lowest addiction score in most active
Kulig et al. (2003)	Nationally representative sample of high school students ($N = 15,349$)	Regular vigorous physically active versus non-active versus on a sports team versus not on a sports team	Cross-Sectional Survey (Youth Risk Behavior 1999): Cigarette, alcohol, illicit drug use (past 30 days)	Active team males were less likely to use illicit drugs, except marijuana and equally likely to use alcohol Active team females were less likely to be substance users
Martinsen and Sundgot-Borgen (2012)	Norwegian elite sport high school students ($N = 677$ athletes) and age-matched controls ($N = 421$ students)	Elite athletes trained ~15 h/week versus physically active controls (54% reported at least 1 h/day of moderate activity)	Questionnaire: Cigarettes, snus, alcohol, performance-enhancing illicit drug use (no, occasionally, every day)	Lower cigarette, snus, and alcohol, and illicit drug use in elite athletes versus controls Higher drinking among female athletes compared to male athletes
Melnick et al. (1997)	Nationally representative sample of high school students ($N = 16,262$)	Number of in and out of school sports teams participated in during past 12 months versus nonathletes	Cross-Sectional Survey (Youth Risk Behavior 1997): Cigarette, cigars, cigarillos, chewing tobacco or snuff use (past 30 days)	Lower cigarette, equal cigar, and higher smokeless tobacco in athletes Lesser likelihood of ever smoking with greater sports participation, particularly in males
Pastor et al. (2003)	Spanish high school students ($N = 1038$)	Participation in sports, not including in-school athletics (scale of 1–6, where 1 was never and 6 was 6–7 times/week)	Questionnaire: Alcohol and cigarette use (never to regular)	Negative association between level of sports team participation and cigarette and alcohol use
Pate et al. (1996)	Nationally representative sample of high school students ($N = 11,631$)	Low active (fewer than 2 days of light exercise and no hard exercise days in past 2 weeks) versus high active (6 or more days of light and 6 or more days of hard exercise in past 2 weeks)	Cross-Sectional Survey (Youth Risk Behavior 1990): Cigarette, alcohol, marijuana, cocaine use (past 30 days)	High activity was associated with less cigarette and marijuana use High activity in females was associated with more alcohol consumption No association of physical activity and cocaine use
Pate et al. (2000)	Nationally representative sample of high school students ($N = 14,221$)	Sports participation (1 or more sports teams in or out of school during the past year) versus frequent vigorous physical activity (3–7 days in past week)	Cross-Sectional Survey (Youth Risk Behavior 1997): Tobacco, alcohol, illicit drug use (past 30 days)	Sports participants were more likely to engage in frequent vigorous activity Sports participants were less likely to report cigarette and illicit drug use No effect on alcohol use
Rainey et al. (1996)	High school students in South Carolina ($N = 7846$)	Moderate and high active athletes (1 versus 2 or 3 in past year) versus sedentary and high active nonathletes (0 versus 5 or more days of moderate activity in the past week)	Cross-Sectional Survey Youth Risk Behavior (state): Frequency of cigarette, alcohol, smokeless tobacco use	Lesser likelihood of smoking in athletes Higher rates of binge drinking in highly active athletes

Ströhle et al. (2007)	German community cohort (age 14–24; *N* = 2548)	Regular (3+ times a week), nonregular (1–4 times a month) and no exercise (less than once a month)	Alcohol, illicit, and nicotine abuse and dependence (DSM-IV)	Lower substance abuse in regular and non-regular exercise groups as compared to no exercise
Terry-McElrath et al. (2011)	Nationally representative sample of 8th-, 10th-, and 12th-grade students (*N* = 653,211)	Participation in sports, athletics, and exercise (1-never to 5-almost every day) versus athletic team participation (1-not at all to 5 great)	Cross-Sectional Survey (Monitor the Future survey 1991–2009) Alcohol, marijuana, steroid, cigarettes, and smokeless tobacco use	Negative association of levels of exercise and levels of alcohol, marijuana, and cigarette use Negative association of team participation and cigarette and marijuana use, but positive association with smokeless tobacco and alcohol use in high school students
Aaron et al. (1995)	Junior high school students from 2 schools in Pennsylvania and 2 follow-ups up to age 18 (*N* = 1400)	Self-reported past year physical activity (hours/week) and participation in sports	Longitudinal Survey (adapted from Youth Risk Behavior Survey) Likelihood and use of cigarette, alcohol, and marijuana use at baseline, and 1 and 3 years later	Moderate and high active females less likely to start smoking as compared to low physically active females
		Aerobic fitness assessment at baseline		No association of physical activity and alcohol in females In males, no association of physical activity and smoking Highly active males and males participating in sports were more likely to initiate alcohol use
Nelson and Gordon-Larsen (2006)	Nationally representative sample of middle and high school student (*N* = 11,957)	High active (5 or more weekly bouts of moderate to vigorous physical activity)	Longitudinal survey (in school and at home) Likely and frequency of cigarette, alcohol, illicit drug use	Less likely to smoke, get drunk frequently, and use illicit drugs other than marijuana in high active compare to less active
Terry-McElrath and O'Malley (2011)	High school seniors and 4 follow-ups up to age 26 (*N* = 11,741)	Participation in sports, athletics or exercising (1-never to 5-daily exercising or actively participating in sports or athletics)	Longitudinal survey Alcohol, cigarette, illicit drugs (past 30 day use)	At age 18, higher activity was associated with lower cigarette, alcohol, illicit drug use An increase in levels of activity into adulthood with associated with decreased use of cigarettes, alcohol, and illicit drug use School athletic team participation at age 18 was positively associated with alcohol use
Kujala et al. (2007)	Finnish twins beginning at age 16–18 (3 baseline surveys) with follow-ups at age 22–27 (*N* = 4240)	Persistently active (3+ times/week) versus persistently inactive (1–2 times/month) and occasionally active (all others)	Longitudinal survey of daily cigarette smoking	Lower risk for daily smoking at baseline and in adulthood in persistently active as compared to a persistently inactive twin
Korhonen et al. (2009)	Finnish twins beginning at age 16–18 (3 baseline surveys) with follow-ups at age 22–27 (*N* = 4240)	Persistently active (3+ times/week) versus persistently inactive (1–2 times/month) and occasionally active (all others)	Longitudinal survey of frequency and use of alcohol and illicit drug use	Higher baseline activity predicted a decreased risk of later drug use Decreased illicit drug use in persistently active Lower drinking-related problems in persistently active group, particularly women

Table 1 (*continued*)

Results from human studies				
Reference	Subjects	Exercise schedule	Study design	Effect of exercise
Mattila et al. (2012)	Finnish adolescent and young adult men (18–29 years) entering the obligatory military duty ($N = 16,746$)	Highly, moderate, light, and no physical activity in past 6 months (from 0–5+ h/wk) versus participation in sports activities at least once/week	Health survey on the first day of military duty including frequency and use of cigarettes and snus	Less likely to smoke, but more likely to use snus in high active group as compared to no physical activity group Team sports participation was associated with snus use and dual use of snus and cigarettes, but not cigarette use alone
Castrucci et al. (2004)	Nationally representative sample of high school students ($N = 16,357$)	Participants and non-participants in organized sports (past year)	Cross-sectional survey (Robert Wood Johnson Foundations 1996) of cigarette, smokeless tobacco, and cigar use (past 30 day and year)	Sports participants were less likely to smoke, but more likely to use smokeless tobacco Of those who did smoke, sports participants smoked fewer cigarettes and were less likely to be current smokers
Peretti-Watel et al. (2003)	French elite student athletes (ages 16–24; $N = 458$)	Elite athlete (~15+ h/week of practice; individual, team and sliding) versus subsamples of two national surveys of males and females of a similar age and from the same region of France	Cross-sectional survey of alcohol, marijuana, and cigarette use	Among elite athletes, males were more likely to use alcohol and marijuana as compared to females and equally likely to smoke Lower prevalence of alcohol, cigarette and marijuana use in elite athletes as control samples Elite athletes participating in team sports were more likely to use alcohol Sliding sports participation was associated with alcohol use in males and marijuana use in females More weekly training was negatively associated with smoking and alcohol in females but positively associated with smoking in males
Wichstrøm and Wichstrøm (2009)	Norwegian high school students with follow-ups after 2, 7, and 13 years ($N = 3251$)	Current and past participation in organized sports (team versus independent; power sports, endurance sports, versus technical sports; past week)	Longitudinal study of frequency and use of tobacco, marijuana, and alcohol	At baseline, sports participants used tobacco less frequently than the nonparticipants Sports participation was associated with a later reduction in marijuana use Sports participants were more likely to increase alcohol intoxication Team sports participants had lower growth in tobacco and marijuana use but increased growth in alcohol intoxication Endurance sports participants had lower growth in alcohol intoxication, tobacco, and marijuana use

Moore and Werch (2005)	8th graders from 3 schools in Florida ($N = 891$)	In-school versus out of school-sponsored sports/physical activities	Cross-sectional survey of alcohol, marijuana, and cigarette use	For females, out of school dancers, cheerleaders, gymnasts, and surfers were more likely to drink alcohol as compared to the in-school Female skateboards were more likely to drink heavily and smoke cigarettes For males, school-sponsored swimmers were more likely to use alcohol and drink heavily as compared to out of school swimmers Out of school swimmers and wrestlers were more likely to smoke cigarettes School-sponsored football players and swimmers were more likely to use marijuana
Collingwood et al. (2000)	Junior and high school at-risk students in Illinois ($N = 329$)	First Choice Fitness program: 9–12 week program (30–60 min of group physical training: aerobic running, calisthenics, and stretching, 3 days/week plus an individual exercise program). Physical activity was compared to peers using a 7 point scale	A pre- and post-test questionnaire assessing cigarette, smokeless tobacco, and illicit drug use	Program participation tended to increase physical activity and fitness Low levels of drug use at baseline Participants decreased cigarette and alcohol use but no consistent effect on other drugs
Werch et al. (2005)	9th and 12th grade students in suburban high school in Florida with follow-ups at 3 and 12 months ($N = 604$)	Project SPORT (a fitness consultation and accompanying print materials) or control (standard health and fitness print materials). Physical activity was assessed during last 7 days of program as vigorous (at least 20 min with sweating and breathing hard) or moderate (at least 20 min with no sweating or breathing hard)	Longitudinal study of alcohol, cigarette, and marijuana use	Upon study completion at 3 months, project SPORT participants engaged in more moderate physical activity, smoked fewer cigarettes, consumed less alcohol, and were less likely to initiate alcohol use as compared to controls at 3 months At the 12 month follow-up, The SPORT group smoked fewer cigarettes and were less advanced in marijuana initiation, but did not differ from controls on alcohol use initiation

Results from animal studies

Reference	Subjects	Exercise schedule	Drug schedule	Effect of exercise
Miller et al. (2012)	Male rats	Concurrent voluntary wheel running 1-h/day on days 1–7, 8–14, or 15–21	Methamphetamine SA (initiation) 1-h/day, FR1	Decreased SA during acquisition No effect when available after acquisition
Ehringer et al. (2009)	Male and female mice	Concurrent unlimited voluntary wheel running	Alcohol consumption (initiation) 24-h, 2-bottle free choice versus 2-h, drinking-in-the-dark	In males, decreased consumption at lower concentrations In females, decreased consumption at all concentrations No effect on the initiation of consumption under the drinking in the dark model
Smith and Pitts (2011)	Male rats	Unlimited voluntary wheel running prior to training (6 weeks) and prior to and following each SA session	Cocaine SA 2-hr/day, FR1	Decreased rates of acquisition
Smith et al. (2008)	Female rats	Unlimited voluntary wheel running in prior to training (6 weeks) and prior to and following each SA session	Cocaine SA PR	Decreased motivation

Table 1 (*continued*)

Results from animal studies				
Reference	Subjects	Exercise schedule	Drug schedule	Effect of exercise
Smith and Pitts (2012)	Male rats	Unlimited voluntary wheel running prior to training (6 weeks) and prior to and following each SA session.	Heroin SA 2 h/day, FR1	Decreased maintenance SA
Smith and Witte (2012)	Female rats	Unlimited voluntary wheel prior to training (6 weeks) with or without continued exposure prior to and following each SA session	Cocaine SA PR schedule	Decreased motivation when available prior to each PR session No additional effect of pre-training
Lett et al. (2002)	Male rats	Voluntary wheel running prior to training 2 h/day, 8 days	Morphine CPP	Prevents the development of a CPP
Rozeske et al. (2011)	Male rats	Unlimited voluntary wheel running prior to training for 6 weeks	Stress-potentiated morphine CPP	Blocks the development of CPP
El-Rawas et al. (2009)	Male mice	Voluntary wheel running as part of enriched environment beginning at least 2 months prior to conditioning.	Heroin CPP	Attenuated the development of a CPP
Solinas et al. (2008)	Males mice	Voluntary wheel running as part of enriched environment beginning at least 2 months prior to conditioning	Cocaine CPP	Attenuated the development of a CPP
Chen et al. (2008)	Male mice	Forced treadmill running prior to training ~60 min/day for 4, 8, and 12 weeks	MDMA CPP	"Session-number" dependently prevents the development of a CPP
Fontes-Ribeiro et al. (2011)	Male rats	Forced treadmill running prior to training ~50 min/day for 8 weeks	Amphetamine CPP	Prevents the development of a CPP
Hosseini et al. (2009)	Male rats	Forced treadmill running prior to each SA session with and without pre-training ~90 min/day	Morphine SA 2-h/day, FR1	Decreased maintenance intake No additional effect of pre-training
Thanos et al. (2010)	Male and female rats	Forced treadmill running prior to training ~60 min/day for 6 weeks	Cocaine CPP	Prevents the development of a CPP in males Attenuates CPP in females
Eisenstein and Holmes (2007)	Male rats	Three weeks of unlimited voluntary wheel running prior to conditioning	Morphine CPP	Increased CPP
Mustroph et al. (2011)	Male mice	Unlimited voluntary wheel running (3 weeks) prior to or after conditioning	Cocaine CPP	Attenuated CPP when available after conditioning Increased CPP when available prior to conditioning
Smith et al. (2008)	Female rats	Unlimited voluntary wheel running prior to training (6 weeks) and prior to and following each conditioning/test session	Cocaine CPP	Enhanced the development of a CPP
Engelmann et al. (2013)	Male rats	Unlimited voluntary wheel running prior to training (6 weeks) with or without continued exposure prior to and following each SA session	Methamphetamine SA (initiation) 1-h/day, FR1, 10 days	Attenuated acquisition when available prior to each SA session Enhanced acquisition when access was discontinued prior to SA training

predict lower levels of cigarette and illicit drug use during both adolescence and early adulthood (Aaron et al., 1995; Nelson and Gordon-Larsen, 2006; Terry-McElrath and O'Malley, 2011). These studies also show that an increase in levels of exercise participation from adolescence to adulthood predicts a decrease in rates of smoking and use of marijuana and other illicit drugs during adulthood (Terry-McElrath and O'Malley, 2011). Similarly, twin studies, which provide better control of environmental factors, have shown that within pairs of adolescent twins discordant for levels of exercise, the more active twin has a decreased risk of later smoking and illicit drug use during adulthood as compared to the less active twin (Kujala et al., 2007; Korhonen et al., 2009).

However, not all research reports have found a negative association between levels of physical activity and alcohol and drug use. For example, numerous studies have reported that participation in team sports, which is presumed to indicate a higher level of physical activity, can have both risk and protective effects on adolescent alcohol and drug use. For example, although rates of smoking and illicit drug use are typically lower in adolescents who participate in team sports (e.g., Escobedo et al., 1993; Pastor et al., 2003; Pate et al., 2000; Martinsen and Sundgot-Borgen, 2012; Melnick et al., 1997), these individuals also often report similar or even higher rates of alcohol and smokeless tobacco use (e.g., Pate et al., 2000; Terry-McElrath et al., 2011; Mattila et al., 2012; Castrucci et al., 2004; Kirkcaldy et al., 2002; for review see Lisha and Sussman, 2010). The relationship between sports participation and rates of alcohol and drug use varies by type of sport and between males and females (Martinsen and Sundgot-Borgen, 2012; Pate et al., 1996; Peretti-Watel et al., 2003). For example, higher rates of alcohol use have been reported in female athletes involved in out-of-school, mixed-gender sports, such as skateboarding, gymnastics, and dance, and in male athletes involved in in-school, male-dominated sports such as football and wrestling (Moore and Werch, 2005; Rainey et al., 1996; Aaron et al., 1995). These findings indicate that the type of exercise and/or psychosocial interactions associated with certain forms of exercise/sports may also influence initiation of drug use. The level of physical activity by team participation may also influence this relationship. In fact, levels of physical activity can be highly variable between sports and between individuals with results from one study showing that nearly a quarter of individuals participating in a team sport were not vigorously active (Kulig et al., 2003) suggesting that team sport participation may not be a useful measure for level of physical activity or exercise. Several studies have attempted to dissociate the contribution of physical activity versus team participation on adolescent substance use (Rainey et al., 1996; Kulig et al., 2003; Terry-McElrath et al., 2011). For example, Terry-McElrath et al. (2011) examined the association between levels of cigarette, smokeless tobacco, alcohol, and marijuana use and levels of self-reported exercise versus athletic team sports participation and found that although high levels of exercise were associated with lower levels of substance use, sports team participation yield mixed results with higher rates of both alcohol and smokeless tobacco use. The authors suggested that exercise may help suppress the positive relationship between team participation and alcohol use, while working synergistically with team participation to reduce smoking and illicit drug use. This idea is further supported by results from elite adolescent athletes who report lower rates of alcohol, tobacco, and illicit drug use as compared to other adolescents (Peretti-Watel et al., 2003; Martinsen and Sundgot-Borgen, 2012) and by findings showing that drug prevention programs that include physical activity and/or exercise components effectively reduce both rates of initiation and use of alcohol, tobacco and illicit drugs (Collingwood et al., 2000; Werch et al., 2005).

Together, these data suggest that exercise may protect against drug use initiation, particularly cigarette and illicit drug use (see Table 1), but future studies that directly examine the effects of exercise and control for type (group or individual), intensity, and duration of exercise are needed to better understand the exercise conditions that produce beneficial versus harmful effects (particularly with regard to alcohol use). Although these results suggest a beneficial effect of exercise on rates of initiation of drug use it is not yet possible to determine a causal effect. Animal studies, which can control for psychosocial factors as well as the type and duration of exercise, may be valuable in this regard.

2.2. Initiation of drug use: Results from animal studies

Animal models of the initiation phase have been developed and they may be useful for not only determining whether there is a causal effect of exercise on vulnerability to drug use initiation, but also for determining the biological basis for its efficacy. A simple method of evaluating initiation is to give an animal access to a drug during a daily experimental session with deliveries available contingent upon an operant response (i.e., lever press), and then measuring the number of sessions needed to reach a criterion level of intake as well as subsequent levels of daily intake. Several studies have examined the effects of voluntary running in a wheel, a proposed animal model of aerobic exercise that is reinforcing in rodents (Iversen, 1993), on rates of initiation of drug self-administration (see Table 1) and the results are consistent with the human data. For example, rats given concurrent access to a running wheel and methamphetamine self-administer less drug during the initiation phase as compared sedentary rats (Miller et al., 2012). Concurrent access to a running wheel has also been reported to decrease the initiation of alcohol consumption under 2-bottle free access conditions (Ehringer et al., 2009). These results suggest that exercise may function as an alternative non-drug reinforcer that competes with the drug and reduces vulnerability. Similar findings have been reported for cocaine self-administration where wheel running reduced rates of acquisition under non-concurrent conditions (i.e., wheel running sessions occurred prior to and after the daily self-administration sessions; Smith and Pitts, 2011), suggesting that exercise may have protective effects that go beyond its ability to function as an alternative non-drug reward. This idea is further supported by results showing that non-concurrent daily wheel running reduces levels of cocaine and heroin self-administration under short access conditions (Smith et al., 2008; Smith and Pitts, 2012; Smith and Witte, 2012), and by findings showing that a history of wheel running can prevent the development of a preference for a drug-associated environment (Lett et al., 2002; Rozeske et al., 2011), which has also been used as a marker of initial vulnerability to addiction. Similar findings have been reported for the effects of wheel running in the context of an enriched environment where a history of housing under these conditions blocked the subsequent development of a preference for both a cocaine- and heroin-paired environment (El-Rawas et al., 2009; Solinas et al., 2008). Interestingly, forced running on a treadmill also attenuates drug self-administration and the development of a preference for a drug-associated environment (Chen et al., 2008; Fontes-Ribeiro et al., 2011; Hosseini et al., 2009; Thanos et al., 2010), suggesting that the ability of exercise to reduce the reinforcing effects of drugs of abuse may not depend its reinforcing effects (but see Section 3.2). Taken together, these studies suggest that exercise, whether concurrently available or available prior to drug exposure and whether forced or voluntary, has the potential to reduce the reinforcing effects of drugs of abuse and thus reduce the probability of the transition from initial to regular use.

Similar to human studies, results from animal studies suggest that not all exercise conditions decrease initial vulnerability to drugs. For example, Miller et al. (2012) found that although wheel running reduced methamphetamine self-administration when it was concurrently available during the acquisition period, it was

not effective at decreasing self-administration when it occurred after acquisition occurred, indicating that its efficacy may vary with level of exposure or stage of the addiction process (also see Section 3.2). Similar effects have been observed for alcohol where wheel running decreased consumption under 24-h free-choice conditions, but not consumption under a drinking-in-the-dark model that induces higher levels of consumption (Ehringer et al., 2009). There is also preliminary evidence to suggest that the efficacy of exercise at reducing initial vulnerability may vary between individuals and depend on the drug. For example, running is more effective at decreasing the initiation of alcohol consumption in females (Ehringer et al., 2009), but is more effective at preventing the development of a preference for a cocaine-associated environment in males (Thanos et al., 2010). The persistence of these effects are unclear, with results from some studies suggesting that a history of exercise can protect against later vulnerability (Chen et al., 2008; Lett et al., 2002; Rozeske et al., 2011; Fontes-Ribeiro et al., 2011; Thanos et al., 2010), but results from other studies suggesting that its efficacy depends on its availability immediately prior to the testing session (Smith and Witte, 2012; Hosseini et al., 2009). Similar to results obtained in humans, studies using the conditioned-placed preference (CPP) paradigm suggest that under certain conditions exercise may increase rather than decrease subsequent vulnerability. For example, results from several studies have shown that chronic unlimited access to a running wheel prior to conditioning enhanced rather than diminished subsequent drug-induced place preference (Eisenstein and Holmes, 2007; Mustroph et al., 2011; Smith et al., 2008). There is also recent evidence showing that although access to a wheel prior to each self-administration session decreased the acquisition of methamphetamine self-administration, a history of unlimited access to a wheel without continued availability enhanced rather than attenuated subsequent acquisition (Engelmann et al., 2013). Thus, although exercise generally decreases the positive reinforcing effects of drugs of abuse, under certain conditions, such as a history of chronic unlimited access to exercise, it enhances these effects of drugs of abuse.

Taken together, these data suggest that exercise decreases the positive reinforcing effects of many different classes of drugs, but that its efficacy varies with level of drug exposure and across individuals and drug classes (see Table 1). Additionally, while a history of modest exercise may protect against later drug use, a history of chronic high level exercise may enhance later vulnerability (but see Rozeske et al., 2011). The similarities between the findings in humans and animals suggest a biological basis for the effects of exercise on initial vulnerability to addiction. Future research is needed to understand the conditions that produce an efficacious response and the time-course for these effects, and to determine the conditions that are ineffective or that produce a detrimental response.

2.3. Initiation of drug use: Neurobiological basis for the efficacy of exercise

As mentioned above, exercise may function as an alternative non-drug reward that competes with the drug and decreases the likelihood of its use. The effects of exercise on dopaminergic signaling in the reward pathway as a mechanism for its efficacy is an obvious possibility given the critical role that dopamine plays at this stage of the addiction process. Indeed, the ability of exercise to function as a reinforcer is believed to occur through a similar process (for review see Knab and Lightfoot, 2010). Acute bouts of forced running on a treadmill increase serum levels of calcium that are transported into the brain where they then activate the synthesis of dopamine (Sutoo and Akiyama, 1996). Chronic voluntary and forced running increase levels of tyrosine hydroxylase, the rate limiting enzyme in dopamine synthesis, as well as dopamine in several areas of the brain including the reward pathway (Droste et al., 2006; Greenwood et al., 2011; for review see Dishman, 1997; Foley and Fleshner, 2008; Sutoo and Akiyama, 2003). Voluntary wheel running in rats is also associated with burst activation of dopamine neurons in the VTA (Wang and Tsien, 2011). Animals selectively bred for high levels of wheel running have higher basal and exercise-induced concentrations of dopamine in the NAc as compared to controls (Mathes et al., 2010). Collectively, these data show that exercise can affect dopaminergic signaling at many different levels, which may underlie its ability to modify vulnerability during drug use initiation.

Exercise also produces neuroadaptations that may influence an individual's vulnerability to initiate drug use. Consistent with this idea, chronic moderate levels of forced treadmill running blocks not only subsequent methamphetamine-induced conditioned place preference, but also stimulant-induced increases in dopamine release in the NAc (Chen et al., 2008) and striatum (Marques et al., 2008). Like the behavioral effects of exercise, the neurobiological effects of exercise also differ with access conditions. For example, the ability of voluntary wheel running in the context of an enriched environment to prevent the development of a heroin- and cocaine-induced place preference is not mediated via dopamine signaling in the NAc (El-Rawas et al., 2009). In contrast, Greenwood et al. (2011) showed that chronic high levels of voluntary running produced neuroadaptive changes in the reward pathway that were similar to the effects observed following chronic exposure to drugs of abuse. Specifically, 6 weeks of voluntary wheel running increased levels of ΔFosB and tyrosine hydroxylase mRNA in the NAc, and decreased the number of dopamine D2-receptors, a neuro-adaptive effect that is associated with an enhanced vulnerability to drugs of abuse (Dalley et al., 2007; Martinez et al., 2004, 2012; Morgan et al., 2002; Nader and Czoty, 2005; Voisey et al., 2012; Volkow et al., 1999). Chronic high levels of exercise may also lead to an upregulation of dopamine D1 receptor-signaling, another marker of enhanced vulnerability to addiction (e.g., Lynch et al., 2007; Worsley et al., 2000; Zhang et al., 2006), with recent findings showing that direct manipulation of D1 receptors in the NAc attenuates wheel running in high, but not low runners (Roberts et al., 2012a). These findings are important because they suggest that although moderate levels of exercise produce changes in the reward pathway that may protect against later drug use, chronic high levels of exercise, like chronic exposure to drugs of abuse, may sensitize the reward pathway. Support for this idea is provided by findings showing that a history of unlimited access to a running wheel enhances subsequent vulnerability to acquire methamphetamine self-administration and to develop a preference for a drug-associated environment (Eisenstein and Holmes, 2007; Mustroph et al., 2011; Smith et al., 2008; Engelmann et al., 2013). There is also a growing literature in humans on exercise addiction with evidence to suggest that it produces many of the same behavioral and neurochemical changes in the brain as chronic exposure to drugs of abuse (for review see Berczik et al., 2012).

Exercise also produces structural adaptations in the brain at the chromatin level that may alter an individual's susceptibility to drug use. In this sense, gene expression changes can occur in the absence of altering the underlying DNA sequence through epigenetic regulation, which can either activate or repress gene transcription through chromatin modifications. These include post-translational histone modifications and covalent modifications of genomic DNA (for review see Takizawa and Meshorer, 2008). Such epigenetic effects, and the role these changes play in addiction, have only recently been explored, but it is becoming apparent that such adaptations may mediate long-lasting changes in vulnerability (e.g., Botia et al., 2012; Damez-Werno et al., 2012; Freeman et al., 2008; Gozen et al., 2013; Pascual et al., 2012; Schwarz et al.,

2011; Repunte-Canonigo et al., 2013; Tomasiewicz et al., 2012; for review see Feng and Nestler, 2013; Nielsen et al., 2012). In particular, emerging evidence implicates brain-derived neurotrophic factor (BDNF) and epigenetic regulation of the *BDNF* gene, a gene critically involved in synaptic plasticity, as associated with both initial and later vulnerability to addiction (Chase and Sharma, 2013; Im et al., 2010; Jia et al., 2011; Kumar et al., 2005; McGough et al., 2004; Meng et al., 2012; Greenwald et al., 2012; Sadri-Vakili et al., 2010; Schmidt et al., 2012; Vassoler et al., 2013; Wan et al., 2011; for review see Schmidt et al., 2013; McGinty et al., 2010). For example, recent results show that male rats with a history of cocaine self-administration passed on a cocaine-resistant phenotype to their male offspring that was characterized by low rates of acquisition of cocaine self-administration and increased H3 histone acetylation of *Bdnf exon IV* in the PFC (Vassoler et al., 2013). Exercise increases BDNF in both humans and animal models (for review see Zoladz and Pilc, 2010), and recent work suggests that it promotes stable changes in gene expression through epigenetic regulation of chromatin containing the *BDNF* gene at the same exon region that is associated with vulnerability to addiction (exon IV). Specifically, Gomez-Pinilla et al. (2011) found that chronic voluntary wheel running increased histone H3 acetylation and decreased DNA methylation of the promoter IV region, thereby increasing the expression of *Bdnf exon IV* mRNA. Together, these findings suggest that exercise may serve as a substitute for drugs of abuse by increasing dopaminergic signaling and may alter vulnerability by producing persistent adaptations in dopaminergic signaling and chromatin remodeling. However, more work is needed to determine the causal effects of these proposed mechanisms of exercise on the initial vulnerability to addiction.

3. Effects of exercise on the progression from use to addiction

3.1. Progression from use to addiction: Results from human studies

A number of factors predict a vulnerability to becoming addicted once drug use initiation occurs. Although not directly examined, there are hints in the literature to suggest that exercise may protect against the transition from initial use to addiction (see Table 2). For example, Kenford et al. (2005) examined health factors, including beliefs about the importance and regularity of exercise, on the progression to regular smoking in a cohort of occasional smokers. They found that over a 4-year period, 20% progressed to become daily smokers, whereas 35% remained occasional smokers, and 45% became non-smokers, with results showing a modest negative association between beliefs about the importance of exercise and these transitions. Additionally, numerous studies have examined rates of drug use among adult athletes and nonathletes, and like results from adolescent populations, rates of illicit drug use, abuse, and dependence are generally lower in adult athletes compared to adult nonathletes (e.g., Terry-McElrath and O'Malley, 2011; Peretti-Watel et al., 2003; Wichstrøm and Wichstrøm, 2009, for review see Lisha and Sussman, 2010). However, as with rates of drug use among adolescence, there are some notable exceptions, such as equal or higher rates of alcohol use within athletes as compared to nonathletes, particularly for males (Terry-McElrath and O'Malley, 2011; Peretti-Watel et al., 2003; Wichstrøm and Wichstrøm, 2009; for review see Martens et al., 2006). As with adolescent sport team participation, it is possible that social factors negate the effects of physical activity on alcohol consumption, and results from a controlled intervention study among college alcohol misusers supports this idea. Specifically, Correia et al. (2005) found that individuals instructed to increase their levels of physical activity/exercise as well as creative activities over a 4-week period reported lower levels of alcohol and illicit drug use at follow-up as compared to individuals not instructed to do so.

Results on the effects of exercise in the human laboratory among drug-dependent individuals have also been examined. For example, Taylor et al. (2007) reviewed the effects of acute exercise on smoking behavior and found a positive effect of exercise in each of the 4 studies that included a comparison between exercise and a passive condition. Two recent pilot studies found positive effects of exercise training (2 weeks–6 months) for *reducing current illicit drug use* among drug-dependent individuals. Specifically, Roessler (2010) showed that of 38 illicit drug-dependent individuals that enrolled in the exercise trial, 20 completed the program and 15 of the 20 had at least reduced their drug intake. The other study examined the effects of exercise training in cannabis-dependent individuals and showed a 50% reduction in cannabis use that persisted throughout the exercise component of the study (Buchowski et al., 2011). *Although the findings indicate the efficacy of exercise at reducing drug intake in drug-dependent individuals, more research is needed to determine its effects in drug abusers who have not yet transition to addiction.*

3.2. Progression from use to addiction: Results from animal studies

Two of the fundamental features of drug addiction in humans, loss of control over use and the resulting excessive/compulsive use of the drug, can be reliably recapitulated in animals that are given extended access to the drug (6-h or more; e.g., Ahmed, 2012; Cohen et al., 2012; Rogers et al., 2008; Vendruscolo et al., 2011). Importantly, increased motivation for the drug and increased drug-seeking, additional key features of addiction in humans, occur after extended access drug self-administration when examined after an abstinence period (Cohen et al., 2012; Grimm et al., 2001; Lynch and Taylor, 2004; Ramôa et al., 2013; Roberts et al., 2007). The possibility that exercise may prevent the development of these characteristics or "an addicted phenotype" has been examined in several recent studies (see Table 2). For example, Smith et al. (2011) examined the effects of chronic voluntary wheel running on cocaine self-administration under extended access conditions and found that exercising rats self-administered less cocaine and showed less escalation of intake over time as compared to sedentary rats. Similar effects of wheel running have also been reported for methamphetamine self-administration under extended access conditions (Engelmann et al., 2013) and for alcohol consumption under conditions that induce high levels of consumption (e.g., 24-h access free-choice conditions, drinking-in-the-dark procedures; Brager and Hammer, 2012; Hammer et al., 2010; Pichard et al., 2009). Several recent studies have also examined the possibility that exercise during abstinence from chronic drug exposure may prevent the development of an addicted phenotype characterized by high levels of drug-seeking. For example, Lynch et al. (2010) examined the effects of 2 h/day access to a running wheel during a 14-day abstinence period on subsequent cocaine-seeking (as assessed under a reinstatement paradigm) with results showing that exercising versus sedentary rats exhibited less cocaine-seeking behavior. Similar findings have been reported for the effects of wheel running on nicotine-seeking (Sanchez et al., 2013). The effects of exercise are also session length-dependent with findings showing that although 1 h/day of access to a running wheel during abstinence did not affect subsequent cocaine-seeking, 2 h/day was effective, and 6 h/day almost completely suppressed subsequent cocaine-seeking (Peterson et al., 2013). These findings suggest that exercise may "magnitude"-dependently prevent the development of an addicted phenotype possibly by blocking/reversing behavioral

Table 2
Evidence from human and animal studies for the effects of exercise on the progression from use to addiction.

Results from human studies

Reference	Subjects	Exercise schedule	Study design	Effect of exercise
Kenford et al. (2005)	Low-level/occasional smokers ($N = 321$) College students	Health and Activity Questionnaire to assess beliefs about the importance and regularity of exercise	Prospective analysis of beliefs about exercise and risk of transitioning to regular smoking	Negatively, but modestly, associated with the transition from occasional to regular smoking
Correia et al. (2005)	Alcohol and illicit drug users ($N = 133$) College students	Assigned to an exercise/physical activity and creative/artistic activity group and instructed to increase both activities by 50% of baseline	Daily self-reported alcohol and illicit drug use at baseline and 28 days later	Decreased alcohol and illicit drug use from baseline
Roessler (2010)	Illicit drug-dependent ($N = 38$)	Combination of aerobic exercise (e.g., spinning) and team sport activities (e.g., volleyball, badminton)	Assessed measures of drug and alcohol use at intake and upon study completion using the European Addiction Severity Index	Completion rate of 52%
	Outpatient treatment program in Denmark	2 h/day, 3 times/week, 2–6 months		Reduced alcohol and drug use Reduced urge to use alcohol and drugs Increased ability to control drug use
Buchowski et al. (2011)	Non-treatment seeking marijuana-dependent individuals ($N = 12$)	10 daily 30 min treadmill sessions at 60% of maximal aerobic capacity	Self-reported drug use assessed 1-week before, during, and 2-weeks after the exercise intervention	Decreased marijuana use within the exercise period and at follow-up as compared to baseline Decreased craving following exercise.

Results from animal studies

Reference	Subjects	Exercise schedule	Drug schedule	Effect of exercise
Smith et al. (2011)	Male and female rats	Unlimited voluntary wheel running prior to training (6 weeks) and prior to and following each SA session	Cocaine SA 23-h/day, FR5, every 4 days or 6-h/day, FR1, 14 days	Decreased SA under both extended access conditions Decreased escalation of intake over time Similar effect in both males and females
Engelmann et al. (2013)	Male rats	Unlimited voluntary wheel running prior to training (6 weeks) with or without continued exposure prior to and following each SA session	Methamphetamine SA 6 h/day, FR1, 22 sessions, then PR schedule	Decreased escalation and motivation when available prior to each SA session Prior wheel running without continued access did not reduce escalation or motivation
Brager and Hammer (2012)	Aging male hamsters	Concurrent unlimited voluntary wheel running (30 days) following initiation of alcohol consumption	Alcohol consumption (24-h access) 2-bottle free choice	Decreased consumption and preference and these effects persisted for up to 10 days after running wheels were locked
Hammer et al. (2010)	Male hamsters	Concurrent unlimited voluntary wheel running (4 weeks) following initiation of alcohol consumption.	Alcohol consumption (24-h access) 2-bottle free choice	Decreased consumption and this effect persisted beyond the wheel running phase
Pichard et al. (2009)	Male mice with a high (C57BL/6J) versus a low (DBA/2J) alcohol preference	Concurrent unlimited voluntary wheel running (1 week) following initiation of alcohol consumption and then 3 weeks of either continued unlimited voluntary wheel or forced wheel (2, 45-min sessions/day)	Alcohol consumption (24-h access) 2-bottle free choice	Decreased consumption in high alcohol preferring mice when running was voluntary, but returned to baseline levels during the forced period of running No effect of voluntary or forced running on the low levels of alcohol consumption in low preferring mice

Table 2 (*continued*)

Results from animal studies				
Reference	Subjects	Exercise schedule	Drug schedule	Effect of exercise
Lynch et al. (2010)	Male rats	Voluntary wheel running (2 hr/day) during 14 day abstinence period.	Cue-induced cocaine-seeking (assessed using a within-session design following extended access cocaine SA and a 14 day abstinence period).	-Decreased cocaine-seeking under both extinction and reinstatement conditions.
Sanchez et al., 2013	Adolescent-onset male rats	Voluntary wheel running (2 h/day) during 14 day abstinence period	Cue-induced nicotine-seeking (assessed using a within-session design following extended access nicotine SA and a 14 day abstinence period)	Decreased cocaine-seeking under both extinction and reinstatement conditions
Peterson et al. (2013)	Male rats	Voluntary wheel running (1, 2, or 6 h/day) during 14 day abstinence period	Cue-induced cocaine-seeking (assessed using a within-session design following extended access cocaine SA and a 14 day abstinence period)	"Session-length"-dependently decreased cocaine-seeking under reinstatement conditions
Cosgrove et al. (2002)	Male and female rats	Concurrent voluntary wheel running (5 days) following acquisition of cocaine SA followed by a cocaine only phase (5 days)	Cocaine SA 6-h/day, FR1, 15 days	Decreased SA in females, but not males Intake returned to baseline when wheel access was no longer available
Zlebnik et al. (2012)	Adolescent and adult female	Voluntary wheel running (6 h/day, 3 days) prior to cocaine SA training and then concurrent access following acquisition and maintenance of cocaine SA (16 days). This was following by a cocaine only phase (10 days) in the wheel groups versus a concurrent phase for the locked wheel groups	Cocaine SA 6-h/day, FR1, 26 days	Decrease SA and escalation in adolescent but not adult rats irrespective of whether the locked or unlocked condition came first Among adolescents, cocaine SA increased when the wheel was locked after having being first unlocked Concurrent access was necessary for decreased consumption
Werme et al. (2002)	Male rats	Unlimited voluntary wheel running (2 weeks) prior to alcohol and then again following initiation and maintenance of alcohol consumption (5 weeks) during a 1, 2, or 4 week abstinence period with continued access during the alcohol resumption test	Alcohol deprivation effect (assessed following 24-h free choice access and abstinence)	Increased alcohol consumption and preference in groups given 1 or 2, but not 4 weeks access during abstinence
Leasure and Nixon (2010)	Female rats	Unlimited voluntary wheel running (2 weeks) prior to binge alcohol exposure	Forced binge alcohol exposure (8 h/day)	Less behaviorally intoxicated

and neuro-adaptive changes that develop during and following extended access to the drug.

Similar to reports for the effects of exercise on levels of drug intake following acquisition, there is some controversy for the effects of exercise on both drug intake under extended access conditions and on the subsequent development of an addicted phenotype. For example, Cosgrove et al. (2002) found that although concurrent access to wheel running during the extended access session reduced cocaine self-administration, this effect was significant for females, but not males, suggesting that the efficacy of exercise may vary by sex. That these findings contrast with findings under non-concurrent conditions where wheel running was shown to decrease cocaine self-administration in both males and females suggests that when exercise is available as an alternative non-drug reinforcer its efficacy may be more pronounced in females compared to males. This idea is supported by findings showing that concurrent access to saccharin, a non-drug reinforcer, is more effective at reducing drug self-administration in females than males (Cosgrove and Carroll, 2003). Adolescents may also be more sensitive than adults to the effects of exercise as an alternative to drug with recent findings showing that concurrent voluntary wheel access reduced cocaine self-administration and escalation of intake under extended access conditions in adolescent but not adult rats (Zlebnik et al., 2012). This study also showed that a history of wheel running was not effective at reducing subsequent consumption. However, as discussed above, wheel running produces persistent beneficial effects when available following chronic drug exposure during abstinence (Lynch et al., 2010; Peterson et al., 2013; Sanchez et al., 2013), indicating that the timing of exercise availability is critical in determining its efficacy. Persistent beneficial effects have also been observed in some studies with alcohol consumption (Brager and Hammer, 2012; Hammer et al., 2010). The efficacy of exercise may also depend on the contingency of the response and the drug self-administered. For example, Pichard et al. (2009) reported that although voluntary running decreased alcohol consumption, levels of consumption returned to baseline levels when animals were subsequently forced to run. Additionally, Werme et al. (2002) found that 24-h access to a running wheel during abstinence not only failed to block the enhanced alcohol consumption typically seen following abstinence (e.g., the alcohol deprivation effect), it increased the likelihood of its occurrence, with higher consumption in the wheel running group as compared to sedentary controls. These results with alcohol are in contrast to the effects described above for cocaine and nicotine as well as to recent results with alcohol showing that wheel running can reduce ethanol consumption and behavioral sensitivity to ethanol intoxication during binge exposure (Brager and Hammer, 2012; Hammer et al., 2010; Leasure and Nixon, 2010; Pichard et al., 2009). Although these contrasting effects may be explained by procedural differences across the various studies, such as access to exercise (i.e., limited versus continuous, forced versus voluntary; timing of its availability; for review see Leasure and Jones, 2008), additional research will be needed before conclusions can be made about the potential efficacy of exercise in alcohol-abusing populations, particularly in light of mixed findings from both human and animal studies.

3.3. Progression from use to addiction: Neurobiological basis for the efficacy of exercise

Exercise affects both dopaminergic and glutamatergic signaling—neurotransmitter signaling pathways implicated in excessive drug intake and the development of addiction. Specifically, chronic exposure to drugs of abuse leads to mesolimbic hypofunction, which may promote drug use to compensate for its decreased effect on dopamine release (Koeltzow and White, 2003; Maisonneuve et al., 1995; Paulson et al., 1991; Schmidt et al., 1996; for review see Melis et al., 2005), with results showing that escalation of cocaine self-administration can be augmented by further suppression of dopaminergic signaling (Ahmed and Koob, 2004). The ability of exercise to increase dopaminergic signaling, particularly in the reward pathway, may protect against excessive drug use. However, as mentioned earlier, it is also possible that chronic high levels of exercise may mimic the effects of chronic drug exposure and increase vulnerability to developing an addicted phenotype. Escalation of drug self-administration and the development of an addicted phenotype is also associated with a dysregulation of glutamatergic signaling in the reward pathway (Allen et al., 2007; Ben-Shahar et al., 2009, 2012, 2013; Fischer-Smith et al., 2012; Ghasemzadeh et al., 2011; Hao et al., 2010; Lu et al., 2007; Madayag et al., 2007; McCutcheon et al., 2011; for review see Pickens et al., 2011; Loweth et al., 2013; Wolf and Tseng, 2012). Although most of the evidence in this regard has been observed for cocaine, similar findings have also been observed for other drugs of abuse including methamphetamine, heroin, and alcohol (Bauer et al., 2013; Bossert et al., 2012; Kufahl et al., 2011, 2013; Meinhardt et al., 2013; Okvist et al., 2011; Schwendt et al., 2012; Sidhpura et al., 2010). Most of the results on the effects of exercise on glutamatergic signaling have been obtained from animal models of cerebral ischemia, which results in the excessive release of glutamate and overstimulation of its receptors, and these findings show that forced running on treadmill for 2 weeks prior to the ischemia can normalize glutamate levels and improve functioning (Jia et al., 2009; Yang et al., 2012; Zhang et al., 2010). These results are important because they suggest that exercise may protect against overstimulation of glutamate receptors, which also occurs following chronic drug exposure. In “normal” animals, forced and voluntary running decrease glutamate concentrations in the striatum (Guezennec et al., 1998) and hippocampus (Biedermann et al., 2012). There is also evidence suggesting that exercise promotes plastic changes in glutamate receptors with results showing that forced treadmill running increases striatal mGluR2/3 expression, which dampens glutamatergic signaling (Real et al., 2010). Forced running also increases striatal fos expression, a marker of functional activity, and this effect can be blocked by concurrent activation of glutamate NMDA and dopamine D1 receptors (Liste et al., 1997), raising the possibility that the effects of exercise on excessive drug self-administration and the development of addiction may require modulation of both dopaminergic and glutamatergic signaling. Recent work has also shown that the length of training on a treadmill (3 versus 30 days) differentially affects glutamate receptor plasticity (Real et al., 2010), raising the possibility that the amount of exercise training may also determine its efficacy for reducing vulnerability during the transition from regular use to addiction.

4. Effects of exercise during drug withdrawal

4.1. Drug withdrawal: Results from human studies

During withdrawal from drugs of abuse, humans report symptoms including anhedonia, negative affect, and craving, and relief from these symptoms is believed to be a major factor that motivates drug use. Exercise has been proposed as a treatment for drug addiction that may acutely assuage withdrawal symptoms and reduce the likelihood of relapse (Bock et al., 1999; Taylor et al., 2007; see Table 3). A growing number of laboratory studies have shown benefits of acute bouts of exercise on withdrawal symptoms in smokers. For example, Taylor et al. (2007) reviewed the effects of acute bouts of exercise on cigarette craving, withdrawal symptoms, and negative affect and found that there were positive effects in each of the

Table 3
Evidence from human and animal studies for the effects of exercise on drug withdrawal.

Results from human studies

Reference	Subjects	Exercise schedule	Study design	Effect of exercise
Bock et al. (1999)	Adult treatment-seeking female smokers ($N = 62$)	Exercise (45- to 60 min of supervised at 60–85% of function capacity, 3× per week for 12 weeks) versus no exercise control	Assessed affect, nicotine withdrawal, and cigarette craving	Decrease in negative affect, nicotine withdrawal, and cigarette craving during the exercise treatment phase but these effects did not persist post-treatment

Results from animal studies

Reference	Subjects	Exercise schedule	Drug schedule	Effect of exercise
Devaud et al. (2012)	Male and female rats	Unlimited voluntary wheel running throughout study beginning 10 days prior to alcohol	Seizure thresholds at 1 or 3 days following alcohol (liquid diet, 14 days)	Attenuated withdrawal-induced seizure susceptibility in both males and females
McCulley et al. (2012)	Male rats	Unlimited voluntary wheel running throughout study beginning 10 days prior to alcohol	Seizure thresholds at 1 or 3 days following alcohol (liquid diet, 14 days)	Attenuated withdrawal-induced seizure susceptibility
Miladi-Gorji et al. (2012)	Male rats	Unlimited voluntary wheel running during morphine conditioning	Anxiety behaviors (elevated plus and light/dark box) in morphine-dependent (2 non-contingent treatments/day) and withdrawn rats (naloxone-precipitated)	Decreased anxious behavior in both morphine-dependent and withdrawn rats Reduced withdrawal signs
Balter and Dykstra (2012)	Male mice	Unlimited voluntary wheel running as part of enriched social (single or group) environment	Thermal sensitivity in morphine-dependent (2 non-contingent treatments/day) mice during withdrawal (at 8, 24, 32, and 48 h)	Decreased thermal sensitivity, particularly in singly housed groups
Brocardo et al. (2012)	Male and female rats	Group paired unlimited voluntary access to running wheel following alcohol treatment beginning 12 days prior to assessment of anxiety- and depressive-like behaviors	Anxiety (elevated plus, open field) and depression-like behaviors (forced swim) following gestational and early postnatal life alcohol exposure (non-contingent)	Reversed the depressive-like behaviors in alcohol-exposed males, but not in alcohol-exposed females

12 studies that compared exercise with a passive condition. Roberts et al. (2012b) recently performed a systematic review update and meta-analysis of studies published in this area from 2006 to 2011. They identified 15 new studies, and of these, 12 found a positive effect of exercise on cigarette craving. Similar results were also observed for the effects of light-moderate exercise on measures of withdrawal symptoms and negative affect, although vigorous exercise generally produced increases in these measures. Very little is known regarding the efficacy of exercise during withdrawal from other drugs of abuse, although results show that it decreases measures of stress, anxiety, and depression (Barbour et al., 2007; Landers and Arent, 2007; Lavie et al., 2011), supporting its potential efficacy.

4.2. Drug withdrawal: Results from animal studies

Very few studies have examined the effects of exercise on signs of withdrawal in animal models. The available results, however, are consistent with the human data and suggest a beneficial effect (see Table 3). For example, recent findings show that voluntary wheel running in male and female rats during withdrawal from alcohol protects against seizures (Devaud et al., 2012; McCulley et al., 2012), a marker that is indicative of the increased neuronal hyperexcitability that occurs during alcohol withdrawal. Voluntary wheel running also reduces anxiety-like behaviors in both morphine-dependent and morphine-withdrawn rats (Miladi-Gorji et al., 2012), and reduces the increase in thermal sensitivity (i.e., hyperalgesia) observed in mice during spontaneous morphine withdrawal (Balter and Dykstra, 2012). Like studies in humans, studies in animals show that voluntary wheel running decreases measures of stress, anxiety, and depression (Brocardo et al., 2012; Duman et al., 2008; Greenwood et al., 2007; for review see Greenwood and Fleshner, 2008) further supporting its potential utility. Additionally, a recent study showed that voluntary wheel running attenuates measures of depression and anxiety in adult rats that were prenatally exposed to ethanol (Brocardo et al., 2012). However, in contrast to findings for its effects on seizure susceptibility during alcohol withdrawal, its effects on measures of depression and anxiety were observed in males, but not females, suggesting that some of the effects of exercise during drug withdrawal may be sex-dependent.

4.3. Drug withdrawal: Neurobiological basis for the efficacy of exercise

During an early withdrawal period there is decreased dopaminergic activity throughout the reward pathway, and withdrawal symptoms including anhedonia, negative affect, and craving have been linked to this decreased activity (Orsini et al., 2001; Rossetti et al., 1992; Weiss et al., 1992, 1996; for review see Hatzigiakoumis et al., 2011; Koob and Volkow, 2010; Melis et al., 2005). In addition to the ability of forced and voluntary running to increase dopaminergic signaling in normal animals, it can also increase abnormally low levels that are characteristic of certain disease models (e.g., hypertension and epilepsy; for review see Sutoo and Akiyama, 2003). These findings are important because they suggest that exercise may normalize the hypofunctioning in the mesolimbic system that occurs following chronic drug exposure during early withdrawal. This idea is further supported by recent findings showing that voluntary wheel running attenuates methamphetamine-induced damage to dopamine and serotonin terminals in the striatum (O'Dell et al., 2011). Its efficacy may also be related to its ability to normalize overall neuronal activity in the reward pathway, and these effects may depend on the drug self-administered. For example, withdrawal from chronic ethanol exposure is associated with upregulation of glutamatergic excitatory neurotransmission (Bauer et al., 2013; Rossetti et al., 1999). Given the ability of exercise to normalize high levels of glutamate in other disease models, and upregulate mGluR2/3 expression in normal animals, it is possible that its efficacy at reducing ethanol withdrawal symptoms is through a similar mechanism. Although withdrawal from other drugs of abuse including psychostimulants and opioids is also associated with an upregulation in glutamatergic signaling, these effects are typically observed following protracted abstinence (Fischer-Smith et al., 2012; Ghasemzadeh et al., 2011; Hao et al., 2010; Lu et al., 2007; Bossert et al., 2012; Kufahl et al., 2011; Schwendt et al., 2012; Sidhpura et al., 2010), with the opposite occurring during early withdrawal periods (Baker et al., 2003; Ben-Shahar et al., 2012; Hotsenpiller et al., 2001; Pierce et al., 1996; for review see Schmidt and Pierce, 2010). Thus, it is possible that exercise will produce different effects during early versus later stages of withdrawal from psychostimulants and opioids. Taken together, these results suggest that exercise may potentially serve as an intervention during withdrawal due its ability to upregulate dopaminergic signaling and normalize glutamatergic signaling (perhaps particularly for alcohol).

5. Effects of exercise on relapse to drug use

5.1. Relapse to drug use: Results from human studies

Exercise has been proposed as a treatment for drug addiction that may reduce drug craving and risk of relapse. Although few clinical studies have investigated the efficacy of exercise for preventing relapse, the few studies that have been conducted generally report a reduction in drug craving and better treatment outcomes (see Table 4). For example, brief bouts of exercise reduce desire to smoke and nicotine craving during acute withdrawal (for meta-analytic reviews see Taylor et al., 2007; Roberts et al., 2012b; Haasova et al., 2013) as well as urge to drink in alcohol-detoxified patients (Ussher et al., 2004). Longer periods of exercise lead to reduced levels of craving among cannabis dependent-individuals (Buchowski et al., 2011), with evidence to suggest that even modest levels protect against heavy smoking and relapse to smoking (Berg et al., 2012). Exercise also improves treatment outcomes among alcohol- and illicit drug-dependent individuals when used as a supplement to other interventions (Brown et al., 2010). While similar results have been suggested to occur in combination with contingency management treatment (Weinstock et al., 2008), because exercise-related activities were not dissociated from actual exercise, conclusions for its efficacy under these conditions are not yet clear. Although the aforementioned studies were conducted in adults, exercise supplemented with a tobacco cessation program also induced higher nicotine quit rates in high school youths, particularly in boys (Horn et al., 2011), suggesting an extension of protection to younger populations. Conversely, a review of randomized clinical trials investigating the efficacy of exercise alone or as an adjunctive intervention to traditional smoking cessation treatment, found mostly null effect of exercise on long-term smoking cessation with only one of 15 trials showing a benefit at 1 year follow-up (Ussher et al., 2012). However, as noted by the author, as well as in a recent review of this literature (Zschucke et al., 2012), most of the available studies were underpowered and poorly controlled, and thus further work is needed before conclusions can be made regarding the long-term beneficial effects of exercise during relapse. It is also possible that the acute effects of exercise are too short lived to translate into long-term reductions in craving and relapse, particularly when exercise is insufficiently intense and compliance is sporadic during treatment trials. Nonetheless, these studies suggest the efficacy of exercise as a sole or adjunctive treatment for nicotine, alcohol, and illicit drug addiction, although

Table 4
Evidence from human and animal studies for the effects of exercise on relapse to drug use.

Results from human studies

Reference	Subjects	Exercise schedule	Study design	Effect of exercise
Ussher et al. (2004)	Adults within a hospital-based alcohol rehabilitation clinic ($N = 20$)	Stationary cycling for 10-min of moderate intensity (40–60% heart rate reserve) versus another session of light intensity (5–20% heart rate reserve)	Alcohol urge and mood (immediately before exercise, during, immediately and 5 and 10 min following exercise	Decreased urge to drink alcohol during but not following exercise following moderate as compared to the light intensity exercise
Buchowski et al. (2011)	Non-treatment seeking cannabis dependent adults ($N = 12$)	10 daily 30 min treadmill sessions (60% of maximal aerobic capacity)	Cannabis craving was assessed in responses to cues before and after exercise	Cannabis craving was reduced immediately following exercise
Berg et al. (2012)	African American light smokers ($N = 539$)	Self-reported walking for exercise	Smoking reduction and cessation	Participants that quit or reduced their cigarette use were more likely to report walking for exercise
Brown et al. (2010)	Treatment-seeking drug dependent individuals ($N = 16$)	Aerobic group exercise for 20–40 min at moderate intensity (55–69% of maximal heart rate) and self-reported independent daily exercise in conjunction with group behavioral training	Alcohol, cocaine, marijuana, opiates, sedatives were reported being used in the last 3 months prior to intervention	During the 12-week training, at the end of training, and at 3 month follow-up there was an increase in percent days abstinent from alcohol and drugs as compared to baseline
Weinstock et al. (2008)	Drug-dependent individuals undergoing outpatient treatment with contingency management ($N = 187$)	Self-reported completion of at least one exercise activity[a] (exercisers) versus completion of no exercise activities (non-exercisers) during 12-week treatment period	Duration of abstinence during treatment	Exercisers had the longer duration of abstinence as compared to non-exercisers
Horn et al. (2011)	High school students who smoked more than 1 cigarette in the last 30 days ($N = 233$)	Physical activity group (daily pedometer steps and other minutes of activity plus a school based cessation program once/week for 10 weeks) versus groups that had either only the cessation program or a single 10–15 min behavioral intervention session at baseline	Self-classified, 7-day point prevalence quit rates (3 and 6 months after baseline), and carbon monoxide validation (3-month follow-up)	Higher cessation rates at 6 months post intervention in the combined physical activity plus cessation program as compared to the other groups, particularly for males

Results from animal studies

Reference	Subjects	Exercise schedule	Drug schedule	Effect of exercise
Zlebnik et al. (2010)	Female rats	Voluntary wheel running (6 h/day, 8 days) prior to cocaine SA training and then concurrent access following extended access cocaine SA (10 days) during the extinction and/or reinstatement testing sessions	Extinction and cocaine-primed reinstatement (assessed using a between-session design following extended access cocaine SA)	Decreased extinction when available concurrently Decreased reinstatement, but only when available concurrently, and 1 concurrent session was sufficient to induce this decrease
Smith et al. (2012)	Male and Female rats	Unlimited voluntary wheel running prior to training (6 weeks) and prior to and following each session	Extinction and cocaine-primed versus cue-induced reinstatement (assessed using a between-session design following short access cocaine SA)	Decreased extinction, cocaine-primed, and cue-induced reinstatement in both males and females
Thanos et al. (2013)	Male rats	Forced running on a treadmill under low (1 h/day) versus high (2 h/day) conditions during a 6 week abstinence period	Cocaine-primed versus cue-induced reinstatement (assessed using a within-session design following extended access cocaine SA and a 6 week abstinence period)	Decreased cue-induced reinstatement following both low and high running Increased cocaine-primed reinstatement following high running

SA, self-administration.

[a] Included self-reported measures of both direct (e.g., playing basketball, swimming, jogging), and indirect (e.g., buying sneakers, planning a workout routine) exercise-related activities.

more research is needed to determine the conditions that produce a sustained beneficial response.

5.2. Relapse to drug use: Results from animal studies

Animal models of relapse employ a reinstatement procedure wherein the ability of various stimuli to reinstate drug-seeking is determined under conditions of non-reinforcement (that is, responses are no longer reinforced by drug). Although multiple variables provoke drug-seeking in both humans and animals, to date the effects of exercise on drug-seeking in animal models have been examined only in response to cues formerly associated with the drug and in response to priming injections of the drug itself (see Table 4). Results from a study in females show that when wheel running was concurrently available it effectively reduced both extinction and drug-primed reinstatement (Zlebnik et al., 2010). That study also showed that only one acute session was sufficient to induce this decrease, but exercise had to be concurrently available (i.e., access on the day that preceded testing was not effective). Smith et al. (2012) showed that wheel running prior to but not concurrent with reinstatement testing effectively reduced cocaine-seeking during extinction, as well as cocaine-primed and cue-induced reinstatement in both female and male rats. These results suggest that although the beneficial effects of exercise on drug-seeking may persist beyond the period of its availability, they may dissipate fairly rapidly (i.e., within 24-h). As discussed earlier, persistent beneficial effects have also been observed when wheel running is available during abstinence with results showing that even modest levels of running at this time can decrease subsequent nicotine- and cocaine-seeking (where the last wheel running session occurred 24-h prior; Lynch et al., 2010; Peterson et al., 2013; Sanchez et al., 2013; but see Werme et al., 2002). There is also recent work showing that forced running on treadmill reduces subsequent cocaine-seeking in males under cued conditions; however, the same treatment had either no effect (i.e., short exercise conditions, 1 h/day) or increased cocaine-seeking in response to cocaine priming injections (i.e., long exercise conditions, 2 h/day; Thanos et al., 2013), suggesting that forced exercise, particularly at a high level, may enhance drug-seeking in response to drug. Together, these data suggest that exercise has immediate as well as persistent protective effects against relapse, but that it's efficacy may vary by drug self-administered, cues used to trigger drug craving, and with the intensity, timing, and contingency of the exercise conditions.

5.3. Relapse to drug use: Neurobiological basis for the efficacy of exercise

Exercise may modulate drug-induced neuroadaptations in dopaminergic and glutamatergic signaling that are implicated in relapse to drug use. Evidence from studies primarily with cocaine show that chronic exposure produces neuroadaptations in the dopamine system, such as an upregulation of D1 receptors and a downregulation of D2 receptors, with evidence to suggest that dopamine signaling in the reward pathway may become sensitized over extended periods of abstinence (Casanova et al., 2013; Henry et al., 1998; Puig et al., 2012; Unterwald et al., 1994). Thus, it is also possible that exercise beginning later during abstinence may lead to further increases in dopaminergic signaling and enhance rather than attenuate drug-seeking. An upregulation in glutamatergic signaling in the reward pathway also develops following repeated drug exposure and abstinence which may be critical for the enduring drive to seek drugs of abuse (e.g., Bauer et al., 2013; Bossert et al., 2012; Fischer-Smith et al., 2012; Hotsenpiller et al., 2001; Kufahl et al., 2011, 2013; McFarland et al., 2003; Meinhardt et al., 2013; Okvist et al., 2011; Schwendt et al., 2012; Sidhpura et al., 2010). As mentioned earlier, forced running on a treadmill decreases glutamate in the striatum (Guezennec et al., 1998) and thus may protect against this enhanced vulnerability by blocking enhanced glutamatergic signaling following prolonged abstinence. Additionally, as with excessive drug use, the development of a subsequent addicted phenotype and relapse vulnerability may require the activation of both dopaminergic and glutamatergic signaling. Drug-induced neuroadaptations that initially suppress drug-seeking during early withdrawal dissipate over prolonged abstinence, and are associated with time-dependent increases, or "incubation", in drug-seeking (Pickens et al., 2011). Presentation of drug-associated cues increases PFC extracellular regulated kinase (ERK) signaling, which requires coincident activation of dopamine and glutamate NMDA receptor signaling, following 30 days, but not 1 day, of withdrawal. Lynch et al. (2010) showed that wheel running beginning during early abstinence not only prevents an increase in cocaine-seeking in response to drug-associated cues, but also prevents an increase in ERK signaling within the PFC. Thus, exercise may ablate preservation of drug-seeking and reduce vulnerability to relapse following extended abstinence through interactions with both dopaminergic and glutamatergic signaling by attenuating time-dependent increases in ERK activity. These results also suggest that the timing of exercise availability is also critical. Specifically, exercise that begins during protracted abstinence, as opposed to during early abstinence, may produce a different pattern of changes and result in either a non-efficacious or detrimental response.

Exercise also affects epigenetic mechanisms, and these effects may provide long-term protection during relapse. As discussed earlier, both wheel running and drugs of abuse modify chromatin containing the *BDNF* gene. BDNF is one of the few markers that positively associates with the incubation of drug-seeking over abstinence, and although most of evidence in this regard has focused on animal models of cocaine relapse (Grimm et al., 2003; Li et al., 2013; Sadri-Vakili et al., 2010; Schmidt et al., 2012; for review see Pickens et al., 2011), similar findings have also been observed in humans and for other drugs including alcohol and methamphetamine (Corominas-Roso et al., 2012; Costa et al., 2011; Hilburn et al., 2011; D'sa et al., 2011; but see Theberge et al., 2012 for heroin). Results from these studies show that during early abstinence, when levels of drug-seeking are low, markers of BDNF, including the activity of its intracellular pathways (e.g., ERK), are decreased in several brain regions including the PFC and NAc (Angelucci et al., 2007; Chen et al., 2013; Whitfield et al., 2011; Grimm et al., 2003; for review see McGinty et al., 2010). As abstinence increases, BDNF protein and phosphorylated ERK levels increase progressively and are thought to sensitize the excitatory synapses in these regions and contribute to the incubation effect (Lu et al., 2010). Several studies have also shown that infusion of BDNF into the VTA, NAc, or PFC profoundly affects drug-seeking (Berglind et al., 2007, 2009; Lu et al., 2004; Whitfield et al., 2011). For example, infusion of BDNF into the PFC immediately following cocaine self-administration, but not following protracted abstinence, attenuates subsequent cue-induced cocaine-seeking and normalizes ERK and glutamatergic signaling in the PFC and NAc (Berglind et al., 2007, 2009; Whitfield et al., 2011). Voluntary wheel running independently elevates BDNF gene expression through acetylation of histone 3 and reduction of DNA methylation in the BDNF promoter IV region (Gomez-Pinilla et al., 2011). It is therefore possible that exercise, if available during early withdrawal, may offset the initial decrease in BDNF expression thereby preventing the subsequent increase in BDNF expression that occurs following protracted withdrawal. As such, exercise may lead to chromatin modifications that suppress drug-seeking. In support of this idea, recent data show that wheel running beginning during early abstinence session length-dependently reduced cocaine-seeking and attenuated *BDNF* promoter IV mRNA expression in the PFC (Peterson et al., 2013). In

conjunction, D'sa et al. (2011) reported that elevated BDNF serum levels predicted shorter subsequent time to relapse and higher total cocaine use in recovering cocaine dependent individuals. Taken together, these data suggest that the potential benefits of exercise during relapse, particularly for relapse to psychostimulants, may be mediated via chromatin remodeling and possibly lead to greater treatment outcomes. These effects may vary with the timing of exercise availability, by drug self-administrated, and with type of exercise (e.g., level of intensity, forced versus voluntary).

6. Summary and integration: An neurobiological hypothesis for the efficacy of exercise as a function of stage of the addiction process

The data reviewed from both human and animal studies support the potential utility of exercise at each stage of the addiction process. However, there was also evidence to suggest that its efficacy may vary across individuals (i.e., by age and sex), drug classes (i.e., alcohol versus nicotine and cocaine), stage of the addiction process, and may depend on the exercise conditions tested. For example, although available evidence supports an efficacious response under both voluntary and forced exercise conditions during drug use initiation, voluntary exercise may be necessary to produce an efficacious response during the transition to addiction and during relapse, with evidence to suggest that forced exercise at a high intensity may produce a detrimental response during these stages. Based on these differential effects, we propose that the effects of exercise depend on the underlying neurobiology, which varies with the stage of the addiction process. This idea is based upon a sequential model for the development of addiction/dependence (Koob and Volkow, 2010; Volkow et al., 2011; Kalivas and Volkow, 2011). Specifically, we propose that during drug use initiation, exercise's ability to facilitate dopaminergic transmission may prevent drug use by serving as an alternative reinforcer. It also produces persistent adaptations in dopaminergic signaling, as well as specific changes in chromatin structure, and these effects may alter an individual's vulnerability to subsequent drug use. Where moderate levels of exercise may be protective, high and intense levels may mimic the effects of drugs of abuse and enhance vulnerability. Also, through interactions with dopamine, exercise may prevent the development of addiction by normalizing changes in dopamine that occur with repeated exposure and during drug withdrawal. Exercise may also normalize the dysregulated glutamatergic and dopaminergic signaling that has been observed in the reward pathway following protracted abstinence and thus reduce relapse vulnerability. Exercise may also block drug-induced changes in chromatin via epigenetic regulation of *BDNF*. Although not directly examined, based on the neurobiological data, it is possible that timing of exercise's availability may be critical in determining an efficacious response during these latter stages. Specifically, when available during early abstinence, exercise would be expected to normalize changes and reduce subsequent vulnerability, but during later abstinence, it could potentially mimic/augment the effects of drug exposure and enhance vulnerability. Each of these proposed effects of exercise are likely to depend on the timing and intensity of the exercise and to differ across drug classes and individuals.

We emphasize that both short-term and long-term exercise lead to changes within many neurotransmitter systems, and that changes within these systems can modify the effects described in the current model. For instance, forced and voluntary running alters concentrations of norepinephrine, serotonin, GABA, and the endocannabinoids (Brown et al., 1979; Dunn et al., 1996; Jia et al., 2009; Raichlen et al., 2012) – all of which play important roles in the initiation and development of addiction. To take an illustrative example, both forced and voluntary running reliably increases concentrations of endogenous opioid peptides, including the mu- and delta-receptor ligands, beta-endorphin, leu-enkephalin, and met-enkephalin (Art et al., 1994; Debruille et al., 1999; Chen et al., 2007), as well as the kappa-receptor ligand, dynorphin (Aravich et al., 1993; Fontana et al., 1994). The positive affective states produced by voluntary wheel running are blocked by the opioid antagonist naloxone (Lett et al., 2002), indicating that these effects are mediated by opioid receptors. Chronic running produces changes in opioid receptor availability (Houghten et al., 1986; de Oliveira et al., 2010), and decreases sensitivity to opioid receptor agonists (Kanarek et al., 1998; Mathes and Kanarek, 2001; Smith and Yancey, 2003; Smith and Lyle, 2006). These changes within the opioid receptor system may also play a role in the protective effects of exercise on measures of drug-seeking during all transitional stages of the addiction process. For instance, acquisition of drug self-administration is heavily dependent on dose, with higher doses engendering higher rates of acquisition (Carroll and Lac, 1997). By decreasing sensitivity of exogenously administered opioids, exercise functionally lowers the dose of these drugs, thus decreasing the likelihood that stable patterns of self-administration will develop. The endogenous opioid system also plays an important modulatory role in the reinforcing effects of cocaine (Herz, 1998; Mello and Negus, 2000) and alcohol (Roberts et al., 2000, 2001; Walker et al., 2011). Notably, the kappa opioid receptor system is critically involved in the escalation of cocaine intake under extended-access conditions (Wee and Koob, 2010), and exercise may serve to normalize this system during periods of excessive drug intake. Wheel running also decreases the behavioral manifestations of morphine withdrawal (Balter and Dykstra, 2012), presumably through the release of endogenous opioid peptides. Finally, levels of beta-endorphin remain elevated up to 48 h after a single bout of wheel running in well-trained subjects (Hoffmann et al., 1990). It is thus possible that endogenous opioid peptides released by exercise may "substitute" for a drug to prevent relapse, in much the same way that methadone and other agonist-substitution therapies reduce drug use in pharmacological maintenance programs. All of these effects would serve to modify those described in the current model.

7. Conclusions and future directions

Although few studies have directly examined the efficacy of exercise as a prevention or intervention strategy for addiction, the concept that it may be effective is not new. In fact, as reviewed above, epidemiological studies have long reported negative associations between levels of physical activity and drug use. There are also many anecdotal reports suggesting that people in recovery turn to exercise as either a replacement for drug use or to help maintain abstinence. Prospective studies, and ideally, randomized clinical trials, are ultimately needed to determine whether exercise decreases the likelihood of developing addiction, as well as increases the likelihood of maintaining abstinence once addiction has developed. In the meantime, preclinical research will be necessary to determine the causal effects of exercise on vulnerability to addiction, and to identify the important parameters that influence this relationship. For example, individual differences in preference for exercise may determine the likelihood of engaging in the activity and its subsequent beneficial effects. Levels of exercise are highly variable in humans and can produce positive affective states in some individuals, but negative affective states in others, depending on exercise intensity and context (Ekkekakis et al., 2011). An efficacious response may depend on its ability to engage epigenetics processes that induce positive subjective effects, presumably through interactions with dopamine, as well as negate craving, presumably through interactions with glutamate. Future work is needed to determine the conditions that produce the most

beneficial effects, particularly given that exercise can sensitize the reward pathway and possibly increase the individual's vulnerability to drug addiction under certain conditions. Exercise itself can also become addictive for some individuals, which is not surprising given that it activates many of the same circuits as drugs of abuse. Such evidence underscores the importance of developing a complete understanding of the exercise parameters that produce a beneficial response. Future studies are also needed to characterize the neurobiological mechanisms by which exercise, alone or in combination with other treatments, exerts its efficacy as a function of stage of the addiction process. For example, the beneficial effects of exercise may be augmented during withdrawal if combined with a low dose of a dopamine agonist (i.e., to reduce the likelihood of adverse side effects), and following prolonged abstinence when combined with a glutamate receptor antagonist (i.e., to further block glutamatergic signaling that is heightened at this time). Such a neurobiological-behavioral response pattern or "finger-print" would enable us to identify conditions that produce the most efficacious response, as well as enable us to understand which of its properties can be harnessed to develop even more efficacious treatments.

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