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Therapeutic efficacy of environmental enrichment for substance use disorders

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Abstract

Addiction to drug and alcohol is regarded as a major health problem worldwide for which available treatments show limited effectiveness. The biggest challenge remains to enhance the capacities of interventions to reduce craving, prevent relapse and promote long-term recovery. New strategies to meet these challenges are being explored. Findings from preclinical work suggest that environmental enrichment (EE) holds therapeutic potential for the treatment of substance use disorders, as demonstrated in a number of animal models of drug abuse. The EE intervention introduced *after* drug exposure leads to attenuation of compulsive drug taking, attenuation of the rewarding (and reinforcing) effects of drugs, reductions in control of behavior by drug cues, and, very importantly, relapse prevention. Clinical work also suggests that multidimensional EE interventions (involving physical activity, social interaction, vocational training, recreational and community involvement) might produce similar therapeutic effects, if implemented continuously and rigorously. In this review we survey preclinical and clinical studies assessing the efficacy of EE as a behavioral intervention for substance use disorders and address related challenges. We also review work providing empirical evidence for EE-induced neuroplasticity within the mesocorticolimbic system that is believed to contribute to the seemingly therapeutic effects of EE on drug and alcohol-related behaviors.

1. Introduction

Drug addiction is a growing problem in the United States that affects public health as well as social and economic welfare. It is estimated that addiction-related costs to society exceed \$740 billion annually due to crime, loss of productivity and healthcare (NIDA 2016). In 2017 more than 70,000 Americans died from drug overdose, mainly from opioid or opioid-based prescription drugs. The recent increases in drug overdose deaths have been so steep (Rudd et al. 2016; Colon-Berezin et al. 2019; Jannetto et al. 2019) that they contributed to reductions in the country's life expectancy over the last three years, a pattern not seen since World War II, and to the declaration of the national opioid crisis. Despite the enormous toll

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that drug addiction continues to take on our society, there still is no Food and Drug Administration (FDA)-approved medication for the treatment of psychostimulant use disorders and those medications that are available for opioid use disorder (e.g., methadone and buprenorphine) show limited effectiveness in relapse prevention (Kleber 2007; Stotts et al. 2009; Nielsen et al. 2016; Dermody et al. 2018). It is estimated that only 5.3 to 15.3 % of individuals maintain abstinence from alcohol or drugs for more than one year after termination of pharmacotherapy, representing staggering rates of relapse (White 2012; McCabe et al. 2018).

Although pharmacotherapies are often the first line of defense against substance use disorders, behavioral interventions have also been implemented. Those that have been used are often ineffective (e.g., cue-exposure therapy) in preventing relapse (Franken et al. 1999; Marissen et al. 2007) or their effectiveness is short lasting (e.g., contingency management therapy; community reinforcement approach) (Stitzer et al. 1980; Silverman et al. 1996; Roozen et al. 2004; Petry et al. 2005). The lack of effective treatments for the prevention of relapse continues to require considerable efforts and resources to be dedicated to the development of better therapies that will attenuate high relapse rates and help individuals struggling with substance use disorders maintain long-term recovery. A possible problem with these behavioral strategies is that they are focused on specific contingency conditions and appear to work only as long as these conditions are in effect. The result is that when these conditions are stopped (at the end of treatment) the drug taking response typically resumes (relapse) (Troisi 2013; Peck and Ranaldi 2014). As such, in recent years we have investigated alternative behavioral strategies that avoid these pitfalls. One solution might be the use of environmental enrichment (EE), a behavioral strategy that is not dependent on new learning that is effective only under specific (e.g., clinical) contexts and conditions. As a treatment for substance use disorder EE may be useful because (1) it may reduce drug seeking by reducing the reinforcing consequences of the seeking behavior through a behavioral contrast mechanism (Grimm et al. 2008; Ranaldi et al. 2011; Peck and Ranaldi 2014), (2) it modifies neural circuits in regions implicated in compulsive drug seeking (Spires et al. 2004) and drug context learning (Pinaud et al. 2001) and (3) it can reduce stress (Thiel et al. 2012), a known powerful inducer of relapse. EE is a behavioral intervention that has been successfully applied to preclinical and clinical populations producing remarkable changes in neuronal and behavioral functions. The following review summarizes preclinical and clinical studies that examined the efficacy of EE as a *behavioral treatment* for drug-related behaviors. Emphasis is placed on the efficacy of EE in the prevention of relapse and drug seeking. We will also discuss the neuronal effects of EE that might serve as possible neural explanations of changes in drug-related behaviors.

2. Early observations of environmental enrichment effects

EE can consist of making available to animals one or more of the following: sensory stimulation, physical activity and social interaction. Although there is no standard implementation of EE, in most instances, animals are provided with bigger housing cages and novel objects (i.e., “toys”). For some, access to physical activity on a treadmill or a running wheel is a key feature of EE, although not the only one. Some laboratories incorporate social interaction as part of enrichment; however social housing in drug self-

administration studies, a focus of this review, can be technically problematic and not often used. What researchers agree on is that EE provides animals with more sensory stimulation and or physical activity in a behaviorally non-contingent manner (i.e., not dependent on the emission of a specific behavior) than what they would receive under standard conditions.

The first evidence of environmental effects on behavior derives from work of Donald O. Hebb, the Canadian neuropsychologist (Hebb 1947), who raised laboratory rats in his home. Hebb noted that his pet rats performed better on a maze than rats reared in standard laboratory conditions (Hebb 1947). In a follow-up study, Hebb demonstrated that pet dogs reared in EE also performed better on problem-solving tasks than dogs reared in simple cages with no view of their surroundings and little contact with humans (Clarke et al. 1951). Although these observations gave us a suggestion of how early experiences influence behavior, more systematic experimental research was initiated by Mark Rosenzweig in the late 1950's. Rosenzweig and his colleagues demonstrated that rats reared in groups in super-sized cages filled with toys, ladders, tunnels and running wheels had greater cortical acetylcholinesterase activity and larger cerebral cortices than rats reared in isolation and standard cages (Krech et al. 1960; Bennett et al. 1964). Until Rosenzweig's work the adult brain was generally thought to be fixed and unable to undergo any degree of neuroplasticity. Since then, a number of studies have shown that the multimodal stimulation from EE promotes neuronal plasticity that includes alterations in the morphology of neurons (Holloway 1966; Greenough et al. 1973; Rosenzweig and Bennett 1996; Kolb et al. 2003a) and glial cells (Viola et al. 2009; Diniz et al. 2010), long term synaptic potentiation and depression (Artola et al. 2006; Hosseiny et al. 2014) and alterations in gene transcription (Greenwood et al. 2011) and neurogenesis (Kempermann et al. 1997; van Praag et al. 2005; Hosseiny et al. 2014). Exposure to EE also modifies the neurochemical parameters of brain-derived neurotrophic factor (BDNF) (Falkenberg et al. 1992; Bakos et al. 2009) and cholinergic (Bennett et al. 1964) and glutamatergic systems (Melendez et al. 2004), both important for learning and memory. Because EE promotes various forms of neuronal plasticity, it has been explored as a treatment for a number of medical conditions, leading to findings that it produces neuroprotective effects in neurodegenerative disorders such as Parkinson's (Jadavji et al. 2006) or Alzheimer disease (Arendash et al. 2004; Prado Lima et al. 2018) and can effectively promote recovery from stroke (Kolb and Gibb 1991) or traumatic brain injuries (Will et al. 2004; Fischer and Peduzzi 2007).

3. The therapeutic potential of environmental enrichment for drug abuse and addiction

Given its effects on neurochemistry and behavior, EE has also been studied in relation to drug abuse. Earlier studies mostly focused on the ability of EE implemented during rearing (before any drug exposure) to subsequently reduce drug effects (Bardo et al. 1995; Bezaud et al. 2003; Solinas et al. 2009). The main objective of these studies was to evaluate preventative applications of EE to reduce vulnerability to drug abuse [for reviews see (Stairs and Bardo 2009; Solinas et al. 2010)]. Soon it became conceivable to investigate the therapeutic potential of EE by introducing it not during rearing but after exposure to drugs and the development of drug-taking habits (Thiel et al. 2010; Ranaldi et al. 2011). A number

of studies investigated whether exposure to EE after the development of drug-related behaviors (e.g., intravenous drug self-administration) would diminish subsequent drug self-administration, motivation to seek drug and the propensity to relapse. We will now highlight major findings from this preclinical work.

3.1. Intravenous drug-self administration

The intravenous drug self-administration paradigm has been used extensively in basic drug addiction research to model the human drug use condition. In this paradigm animals can voluntarily determine if and how much drug they self-administer intravenously. Studies that implemented EE during rearing suggested protective effects of EE against the future acquisition of reliable self-administration of psychostimulants (Bardo et al. 2001; Green et al. 2002, 2010; Puhl et al. 2012), opiates (Hofford et al. 2017) as well as against the escalation of drug intake (believed to mimic “out of control” intake in humans with substance use disorder) in rats (Gipson et al. 2010; Smith et al. 2011). Likewise, EE in the form of physical exercise introduced before drug exposure can decrease the propensity for drug self-administration, again suggesting that it can reduce vulnerability to drug abuse (Smith et al. 2011; Smith and Pitts 2012; Lynch et al. 2017). However, these reports are in sharp contrast to other findings that housing conditions during rearing do not influence propensities to self-administer amphetamine (Schenk et al. 1988; Green et al. 2002), methamphetamine- (Lu et al. 2012; Hofford et al. 2014), heroin (Imperio et al. 2018) or cocaine- (Bozarth et al. 1989; Westenbroek et al. 2013).

Interestingly, when EE (running wheel) is introduced concurrently with the option to self-administer drug, it produces remarkable changes in drug-related behaviors. Six-hours of concurrently available wheel running can suppress cocaine self-administration in rats, with greater suppressant effects in females than males (Cosgrove et al. 2002) and in adolescents than adults (Zlebnik et al. 2012). However, Miller and colleagues showed that in rats well-trained to self-administer methamphetamine, one hour of concurrently available wheel running was not sufficient to reduce methamphetamine intake (Miller et al. 2012). In contrast, brief physical activity, following the establishment of drug self-administration, can be sufficient to alter drug taking. Such brief intervention is especially interesting from a clinical perspective, as poor compliance is common among patients in long and time-consuming interventions. It's been reported that rats with a history of intravenous self-administration of methamphetamine, methylenedioxymethamphetamine (MDMA) or methylone and given 22-h of home cage access to a running wheel showed a reduction in their drug intake in subsequent self-administration sessions (Aarde et al. 2015). Likewise, three brief 4 h EE interventions introduced both immediately after and 24 h after each extinction session to rats previously self-administering cocaine have been shown to effectively reduce the re-acquisition of cocaine self-administration in subsequent sessions (Gauthier et al. 2015). Interestingly, when rats received 4 h of EE either 24 h before an extinction session or immediately after each extinction session, EE had no effect on the re-acquisition of cocaine self-administration under a second order schedule of reinforcement (Gauthier et al. 2015). To our knowledge, the effects of longer periods of exposure to EE or different forms of EE treatment on drug self-administration have not been reported. Overall,

these reports indicate that EE, especially physical exercise, when introduced *concurrently or after* drug exposure, has therapeutic potential for drug abuse and use disorder.

3.2. Conditioned place preference

The conditioned place preference (CPP) paradigm is commonly used to study the rewarding effects of drugs and drug-related stimuli (i.e., conditioned stimuli). After repeated drug-place pairing (conditioning), animals spend more time in the place associated with the drug, suggesting the drug-paired compartment, through learning processes, produces rewarding effects (Mucha et al. 1982; Tzschentke 1998, 2007; Bardo and Bevins 2000). It appears that EE produces differential effects on drug-induced CPP. There is some evidence that EE has preventative potential against drug effects. Rearing with EE has been shown to attenuate the development of opiate (Xu et al. 2007; El Rawas et al. 2009) and cocaine CPP in rodents (Solinas et al. 2009; Zakharova et al. 2009; Nader et al. 2012). However, the Ranaldi lab found that EE in rearing did not prevent the development of cocaine CPP across a range of cocaine doses (Galaj et al. 2017). Similar findings were observed by others when the conditioning drugs were psychostimulants (Schenk et al. 1986; Thiriet et al. 2008; Hofford et al. 2014; Galaj et al. 2017) or opiates (Smith et al. 2005). Also, other studies found that EE (including access to a running wheel), when introduced before conditioning, actually strengthened nicotine (Ewin et al. 2015), morphine (Eisenstein and Holmes 2007) or cocaine CPP (Smith et al. 2008) and delayed the extinction of CPP (Mustroph et al. 2011). A very recent study found no evidence of wheel running during rearing on the development of cocaine CPP in mice (Lespine and Tirelli 2019). Thus, the power of EE as a preventative intervention against the development of CPP remains inconclusive and warrants further studies.

On the other hand, the literature provides compelling evidence that EE introduced *after* conditioning is a powerful behavioral intervention capable of diminishing the expression of drug-induced CPP in rodents (Solinas et al. 2008; Chauvet et al. 2011; Galaj et al. 2017). Thirty days, but not 7, of EE treatment is sufficient to completely abolish cocaine CPP in mice (Solinas et al. 2008). We recently reported that Long Evans rats when exposed to 30 days of enrichment after cocaine or heroin exposure did not show a CPP as compared to non-EE rats (Galaj et al. 2016, 2017). Other forms of enrichment have also been successful at diminishing CPP. For example, mice with one or four weeks of access to running wheels immediately after cocaine conditioning showed reduced CPP as compared to sedentary controls (Mustroph et al. 2016). In addition, treadmill running has been reported to reduce nicotine CPP in mice when introduced after conditioning (Zhou et al. 2018).

Additional evidence for the potential therapeutic effects of EE comes from studies implementing social interaction either concurrently or immediately after drug exposure. When allowed to explore a compartment previously paired with a psychostimulant and one paired with another sex- and age-matched conspecific, rats and mice prefer the compartment paired with another conspecific rodent, suggesting that social interaction can effectively compete with cocaine reward and serve as a therapeutic deterrent against cocaine-related behaviors (Fritz et al. 2011; Yates et al. 2013; Kummer et al. 2014). Interestingly, mice and rats can develop cocaine CPP after a single cocaine exposure but do not re-express their

preference for a cocaine-paired compartment when given four brief episodes of social interaction in the compartment previously paired with cocaine (Fritz et al. 2011; Bregolin et al. 2017). Thus, just four 15 min episodes of social interaction can be sufficient to reduce a preference for drug-paired stimuli over social interaction and to inhibit the subsequent re-expression of psychostimulant CPP [for a review see (Zernig et al. 2013)].

3.3. Animal abstinence models

The conflict-based abstinence paradigm is an appropriate animal model that mimics the human experience of abstinence. Drug users, who nearly always have access to their drug of choice and are motivated to abstain in order to avoid the negative consequences (i.e., medical, social, financial and legal stressors) of continued drug use, often face the conflict situation of choosing to continue drug use or abstaining. In the “animal conflict model” (Cooper et al. 2007), animals can self-administer the drug but doing so necessitates enduring stressful consequences (i.e., crossing a grid floor that is electrified by a current). Typically, the electric current is increased after each day of continued drug taking until the animal ceases lever pressing for a defined number of IVSA sessions and reaches abstinence. The Ranaldi group found that EE facilitates abstinence from cocaine or heroin self-administration in the conflict model. Rats that completed cocaine or heroin self-administration training were transferred to EE (sensory stimulation with novel objects and running wheels) or non-EE cages and allowed to continue to self-administer the drug in daily 30-min sessions during which the floor area near the levers was electrified. EE rats achieved abstinence (defined as zero lever presses for 3 consecutive sessions) in fewer numbers of sessions and at lower electric barrier currents than non-EE rats (Peck et al. 2015; Ewing and Ranaldi 2018). These results support the idea that EE introduced *after* the acquisition of a drug self-administration behavior might be an effective behavioral intervention that facilitates abstinence from cocaine and heroin use.

In basic drug addiction research, extinction of drug seeking or preference for drug-related stimuli has been extensively used to study abstinence. The extinction paradigm involves the reduction of drug-related responding upon the removal of reinforcers (drug) or conditioned stimuli (e.g., light/tone) associated with the drug. However, it is important to note that extinction is different from abstinence because under extinction conditions, animals cannot self-administer the drug as it is not available nor does the animal face negative consequences of continued drug use. Nevertheless, there is evidence that EE can facilitate extinction of drug seeking. In rats that acquired self-administration of cocaine, 30 days of EE significantly reduced lever pressing during daily extinction sessions (Thiel et al. 2009, 2010; Chauvet et al. 2009; Ranaldi et al. 2011; Zlebnik and Carroll 2015). EE intervention introduced during forced abstinence (where animals are not exposed to drug self-administration chambers) is also effective at reducing nicotine and methamphetamine seeking (Sanchez et al. 2013; Sobieraj et al. 2016; Sikora et al. 2018). However, the Ranaldi group reported that 30 days of EE introduced after heroin self-administration had no effects on extinction of heroin seeking (Galaj et al. 2016). Perhaps longer exposure to or more intense EE is needed to facilitate extinction of heroin seeking. Clearly more studies are needed to address this issue.

Interestingly, when rats who previously self-administered cocaine received 4 h of EE both 24 h before and immediately after each extinction session, EE rats showed a significant reduction in cocaine seeking as compared to non-EE rats (Gauthier et al. 2015), suggesting that even brief EE interventions can be effective at reducing cocaine seeking. Similarly, daily 2-h wheel running episodes introduced during the extinction phase can reduce cocaine (Lynch et al. 2010; Peterson et al. 2014b) or nicotine seeking (Lynch et al. 2019). Notably, the most robust effects of EE (especially of wheel running) on drug seeking occur when EE is introduced during early extinction sessions and these effects can persist even when access to the running wheel is terminated. In contrast, wheel running introduced during late stages of extinction is not as effective at reducing cocaine seeking (Beiter et al. 2016; Abel et al. 2019). In support of the idea that EE has therapeutic value to combat drug-related effects are findings that EE introduced after conditioning can facilitate the extinction of CPP induced by cocaine [(Mustroph et al. 2011) but see (Solinas et al. 2008; Robison et al. 2018a)], methamphetamine (Huang et al. 2016) but not alcohol (Li et al. 2015a). Overall, these studies suggest that EE as a behavioral intervention may decrease incentive motivation to seek drug and perhaps limit the experience of craving that often precedes relapse.

3.4. Reinstatement (animal relapse) models

A hallmark of addiction is recurring relapse, which is thought to be driven by both incentive motivation for drug and avoidance of negative affective states (Wise and Koob 2014). The repeating cycle of abstinence and relapse has been primarily studied using the reinstatement model (Carroll and Comer 1996; Shaham and Miczek 2003) in which extinguished responding for a drug is reinstated by acute exposure to drug cues, stress or drug. A growing body of literature provides supporting evidence for a therapeutic potential of EE to reduce relapse. In rats with a history of cocaine, methamphetamine, heroin or nicotine self-administration EE intervention can diminish cue-induced reinstatement of drug seeking (Thiel et al. 2009, 2010; Chauvet et al. 2009; Thanos et al. 2013; Sobieraj et al. 2016; Galaj et al. 2016). Using a within-session extinction/reinstatement procedure, Lynch's group demonstrated that daily 2 h access to a running wheel during 10–15 days of forced abstinence from nicotine self-administration was sufficient to reduce nicotine seeking during the extinction phase but not cue-induced reinstatement of nicotine seeking in rats (Sanchez et al. 2013, 2014). As mentioned above, the therapeutic effectiveness of EE (e.g., wheel running) depends on the duration of intervention, with extended EE exposure producing more robust effects (Peterson et al. 2014a, b).

Another powerful trigger of relapse is re-exposure to drug itself. There are reports that EE (including a running wheel) either fails to reduce (Thiel et al. 2009; Chauvet et al. 2009) or, in some cases, can enhance reinstatement of responding after cocaine priming in adult rats (Thanos et al. 2013). However, when EE exposure is increased to 60 days during forced abstinence with additional days of extinction, EE can reduce cue-induced and cocaine-primed reinstatement of drug seeking in adolescent, but not adult, rats (Li and Frantz 2017). Key findings of this study are noteworthy. First, the therapeutic benefits of EE are correlated with the duration of EE exposure suggesting that prolonged behavioral interventions might be necessary to prevent drug-primed relapse. Second, adolescent rats are more responsive to the seemingly therapeutic effects of EE than adult rats, suggesting that EE's therapeutic

benefits might be partially attributable to propensity for neuroplasticity (presumably greater in adolescents than in adults; see the discussion below).

In addition, EE as a behavioral intervention has been shown to effectively reduce stress-induced reinstatement of drug seeking in rats [(Chauvet et al. 2009; Zlebnik et al. 2010) but see (Ogbonmwan et al. 2015)]. In female Sprague Dawley rats with already-established cocaine CPP, six weeks of 1-h daily treadmill running can reduce stress-induced reinstatement of cocaine CPP (Robison et al. 2018a). EE, when introduced after the development of CPP, can also prevent drug-induced reinstatement of cocaine (Solinas et al. 2008), or alcohol CPP (Li et al. 2015a). These findings suggest that EE may reduce the propensity to relapse, adding to a growing body of evidence supporting the therapeutic use of EE to combat substance use disorders.

Relapse to drug use in humans can occur even after prolonged abstinence (Hunt et al. 1971) and is often preceded by drug craving (O'Brien et al. 1992). This phenomenon was also identified in laboratory animals based on the observation that rats with a history of cocaine (Shalev et al. 2001; Grimm et al. 2001; Freeman et al. 2008), heroin, nicotine (Abdolahi et al. 2010), methamphetamine (Shepard et al. 2004), or alcohol (Bienkowski et al. 2004) self-administration show increases in responding in the absence of the drug (aka drug seeking) over time. In this “incubation of drug craving” model, animals, after acquiring the drug self-administration behavior, are not given the opportunity to seek the drug during “forced abstinence” and later are exposed to drug cues or drug priming to elicit drug seeking. It has been reported that 30-day access to a running wheel or 60-day EE exposure (group housing with wheel and toys) during forced abstinence diminishes time-dependent increases in cocaine seeking (incubation of craving) (Chauvet et al. 2012; Zlebnik and Carroll 2015). However, when EE was discontinued, its seemingly therapeutic effects on incubation of drug craving disappeared (Chauvet et al. 2012), suggesting that prolonged, rather than brief, exposure to EE might be a more effective approach in the prevention of relapse

4. Applicability of EE to the human population struggling with substance use disorder

Undoubtedly, the therapeutic potential of EE for the treatment of substance use disorder has been demonstrated in a number of preclinical models of addiction. However, major concerns and challenges arise in regards to translating the therapeutic benefits of EE to a clinical population struggling with substance use disorders. Some of these concerns derive from the misconception that EE in humans equates to a luxurious lifestyle filled with expensive adventures and commodities. This approach, for obvious reasons, lacks practicality and feasibility within clinical settings. But what clinical EE intervention might consist of is making available to individuals with SUDs non-contingent multidimensional enrichment that might be (and often is in sufferers of SUDs) normally lacking in their everyday lives. Furthermore, a therapeutic strategy might include the identification of *feasible* rewarding stimuli/activities for an individual and designing schedules that regularly include these enrichments in that individual's routine. A growing body of literature has shown that intervention strategies involving enhanced cognitive stimulation, social interaction, and

physical activity (aka EE) are highly effective in the treatment of neurological and psychological disorders (Pang et al. 2013; Morres et al. 2019; Cugusi et al. 2019), including addiction (Eddie et al. 2019). The most consistent and noteworthy are the findings that exercise as a form of enrichment can impede drug-related behaviors.

In nicotine smokers, physical exercise reduces acute cravings (Williams et al. 2011; Elibero et al. 2011; Prapavessis et al. 2014; Kurti and Dallery 2014; Fong et al. 2014) and leads to temporary cessation of smoking (Prapavessis et al. 2016) and withdrawal symptoms (Taylor et al. 2007; Janse Van Rensburg et al. 2009; Kurti and Dallery 2014). While exercise exerts acute effects on smoking cessation, these effects are often short-lasting and most smokers relapse within a year (Prapavessis et al. 2016; Patten et al. 2017). Thus, it has been suggested that physical exercise can be an effective behavioral intervention for nicotine use disorder, if engaged in frequently and consistently over time.

Nicotine use disorder is not the only SUD for which physical exercise can derive therapeutic benefits. Light, but not heavy, methamphetamine users who underwent an eight-week exercise program reported using less methamphetamine and had a lower percentage of drug positive urine, as measured 1, 3 and 6 months post-intervention, (Rawson et al. 2015). Another study reported that acute exercise eliminated craving for methamphetamine during, immediately following, and 50 min post-intervention (Wang et al. 2015). Though not statistically significant, exercise also decreased cocaine, but not nicotine, use in the last 24 h in individuals with concurrent cocaine and nicotine use disorders (De La Garza et al. 2016). Physical exercise has also shown promise for alcohol use disorder as heavy drinkers during prolonged (6–12 month) (Jensen et al. 2019) or 8-week supervised exercise program reduced their alcohol consumption (Georgakouli et al. 2017). It is worth noting that these types of interventions likely produce additional physiological and psychological benefits, including improved cardiovascular function and mood, the latter being critical in the treatment of SUDs. It has been well documented that the high prevalence of depression and suicidality among individuals struggling with SUDs, contributes to relapse and continuation of drug use (Bradizza et al. 2006; Milby et al. 2015; Volkow et al. 2019). Thus, one may argue that by alleviating depression, exercise can improve the individual's quality of life and provide incentive motivation to dramatically change their life.

Exercise can reduce stress, anxiety and depression, all states associated with heroin withdrawal, suggesting it might help maintain abstinence by heroin-addicted individuals. In the area of sensory stimulation Bennett et al. (1998) indicated that one weekend camping trip – adventure therapy – resulted in reduced relapse in alcohol users compared to a similar control group without the camping trip. Also, Cutter et al. (2014) found that video-game playing decreased substance use, suggesting that engaging in non-concurrent and non-contingent video game playing might be useful as a drug addiction treatment. Similarly, body motion-engaged video games can contribute to a decline in craving in young individuals struggling with opioid-related problems as well as in longer participation in this outpatient treatment program (Abroms et al. 2015). There is evidence that engagement in interactive videogames stimulates the mesocorticolimbic system (Cole et al. 2012), improves optimism, reduces stress and depression (key triggers of relapse) and promotes sustained exercise that provides additional health benefits (Cutter et al. 2014; Fish et al. 2014; Bock et

al. 2019). It is also important to note that in these studies participants did not choose between drug and enrichment but simply engaged in the enrichment activities and experienced a benefit from doing so. This is similar to our rat model that does not make available a choice between drug and enrichment. These EE procedures (in humans and in rats) do not involve, nor do they need to involve, contingency management or choice principles for them to be effective.

4.1. Other forms of enrichment

Employment has been viewed as an essential part of recovery that significantly improves the recovering individual's quality of life. However, recovering addicted individuals often face challenges in returning to the job market and in maintaining their employment. Some of them are uncertain about their work abilities and vocational choices while others experience anxiety associated with finding, applying for and being accepted for employment. Vocational training can provide intellectual stimulation, incentive motivation for change and opportunities to develop skills necessary for employment. Vocational training can also contribute to a reduction in drug and alcohol use (Hammer et al. 1985; Gómez et al. 2014). Those who complete vocational training tend to have better employment and recovery outcomes (Hammer et al. 1985; Platt 1995). However, too often, vocational training requires abstinence contingency. Koffarnus and colleagues found that alcoholics who had received paid vocational training (contingent upon abstinence) consumed less alcohol and had fewer alcohol positive breathe samples during monthly assessments than individuals who received either unpaid or abstinence contingent vocational training (Koffarnus et al. 2011). Likewise, homeless substance users receiving an enhanced day treatment program with vocational training and housing contingently upon drug-free urine samples showed a greater abstinence rate than individuals receiving weekly individual and group counseling (Milby et al. 1996, 2000). Although contingency management therapy, like the one described here, produces positive short-term outcomes, its efficacy diminishes over time (Silverman et al. 1996; Higgins et al. 2000; Rawson et al. 2002; Koffarnus et al. 2011; Barnett et al. 2017). Because of a lack of clinical studies with prolonged follow-up assessments it remains unknown whether abstinence-non-contingent stimulation (aka EE intervention) can produce better long-term outcomes. However, some studies report promising trends emerging with longer EE exposure. Higher abstinence rates are observed with 4 week non-contingent interventions as compared to one-week interventions (Barnett et al. 2017). Given the highly promising results obtained with EE interventions in a pre-clinical setting, it is reasonable to suggest that prolonged multidimensional EE interventions (involving physical activity, social interaction, vocational training, recreational and community involvement) might produce therapeutic effects for individuals with SUDs. Clearly, this issue warrants thoughtful consideration and future study.

4.2. Social support networks as a form of EE

A corollary component of EE intervention for SUDs is the strengthening of social support networks around drug-addicted individuals. Non-drug using family members, friends, colleagues, 12-Step program groups, or program sponsors can play a critical role in the recovery process. Social networks that support recovery lead to longer participation in treatment programs, positive outcomes and prolonged abstinence from drugs and alcohol

(Havassy et al. 1991; Bassuk et al. 2016; Lookatch et al. 2019). Thus, support from others in Alcoholics Anonymous (AA) programs is a significant predictor of lower alcohol consumption and contributor to abstinence 1 or 3 years after the treatment (Kaskutas et al. 2002; Bond et al. 2003). Other recovering addicted individuals often have greater impact on recovery than non-AA members as they are thought to be able to relate to problems the individual is facing and teach the skills necessary to overcome cravings (Kaskutas et al. 2002; Bond et al. 2003). The reports concerning social support for recovery suggest that choosing social support networks carefully is imperative to successful recovery as just any type of friend will not suffice, and in some cases, the “wrong friends” may negatively impact treatment outcome.

The relationship that most recovering addicts describe as helpful for initiating abstinence is peer support (Lookatch et al. 2019). One 12-month follow-up study revealed that brief interaction with a physician followed by a visit with a recovering alcoholic (peer intervention) is sufficient to motivate patients with alcohol problems to seek professional help and to work towards improvement of their life (Blondell et al. 2001). There is some evidence that a recovering addicted individual benefits most from peer support when the peer is highly involved in their recovery (e.g., by arranging meetings between the patient and local AA or Narcotics Anonymous groups, attending meetings together, etc.) (Timko et al. 2006; Timko and DeBenedetti 2007).

More recently, O’Connell and colleagues demonstrated that individuals with alcohol and mental health problems who received skills training in a peer-led social engagement program that included social interaction in inpatient and outpatient settings, twice-weekly mutual meetings, and recreational outings, showed reductions in alcohol use at 3- and 9-month follow-ups (O’Connell et al. 2017). Though brief social interactions are effective for AUD, they may not be sufficient for cocaine or heroin use disorder (Bernstein et al. 2005; Day et al. 2018). Continuous social interaction that includes peer-run groups, coaching, workshops, seminars, social and recreational activities and community events might be more appropriate.

5. EE causes brain plasticity

The growing literature demonstrating the therapeutic benefits of EE as a behavioral intervention for SUDs has lead to an expansion of our current knowledge of the neural mechanisms by which EE exerts these effects. By providing sensorimotor stimulation, social interaction and physical activity, EE is thought to mold the whole brain, inducing experience-based neuroplasticity in brain regions critical for reward, habits, emotional regulation, decision-making and impulse control. These findings are quite pertinent because the same brain regions involved in these psychological phenomena have been implicated in a number of drug-related behaviors and are believed to be “hijacked” by repeated drug use (Koob and Le Moal 1997; Robinson and Kolb 2004; Kalivas et al. 2005).

There is evidence that novel environmental stimuli (typical components of EE) can activate the mesolimbic system (Bardo et al. 1990; Bunzeck and Düzel 2006) which includes the dopamine (DA) cells originating in the ventral tegmental area (VTA). By triggering the

release of DA into the prefrontal cortex (PFC) (Feenstra and Botterblom 1996; Beaufour et al. 2001) and nucleus accumbens (NAc) (Jones et al. 1996; Rebec et al. 1997b, a; Legault and Wise 1999), novel stimuli promote exploratory behavior, increase reward processing, regulate motivation and enhance learning. In support of this premise are the findings that lesions in PFC (Burns et al. 1996) or blockade of DA neurotransmission in NAc (Hooks and Kalivas 1995) impedes novelty exploration in rats. The phasic elevation of DA neurotransmission by novel environmental stimuli depends on glutamatergic transmission in the VTA (Legault and Wise 1999) and activation of the PFC, a brain region critical for the detection of novelty (Burns et al. 1996; Rebec et al. 1997b) and for responding to unexpected stimuli (Knight and Grabowecy 1995). In addition, other mesolimbic regions such as the basolateral amygdala (BLA) and ventral hippocampus have been implicated in novelty-related and investigatory behaviors (Wu and Brudzynski 1995; Burns et al. 1996; Wittmann et al. 2007) and are known to undergo neuroadaptation after EE exposure.

Social interaction (play behavior), another important component of EE, is rewarding in its own right (Calcagnetti and Schechter 1992) presumably because it is associated with DA neurotransmission (Corbett et al. 1993; Kagaya et al. 1996; Willuhn et al. 2014) and activation of limbic regions (Fritz et al. 2011; Dölen et al. 2013; Felix-Ortiz and Tye 2014). Preclinical studies have shown that social interaction can reduce the expression of p 38 mitogen-activated protein kinase in the NAc, which plays a role in stress and anxiety and is typically elevated after drug exposure (Salti et al. 2015), can enhance cortical synaptic function, dendritic spine density and the complexity of neuronal networks (Himmeler et al. 2013; Bureson et al. 2016; Liang et al. 2019). Other neuroplastic changes within the mesocorticolimbic system include presynaptic alterations in DA, glutamate, opioid or serotonin neurotransmission and often postsynaptic alterations in receptor expression and binding (Vanderschuren et al. 1995; Hall et al. 1998; Wood et al. 2005; Han et al. 2012; Araki et al. 2014;). These enduring changes are in stark contrast to neuroplastic changes caused by social isolation. Social isolation-dependent brain pathology in PFC, NAc and BLA include: hyperexcitability of NAc neurons (Zhang et al. 2019), augmented DA and glutamate neurotransmission in response to rewarding and aversive stimuli (Hall et al. 1998; Karkhanis et al. 2015, 2019), enhanced expression of AMPA, NMDA, DA D2 receptors (Wood et al. 2005; Turnock-Jones et al. 2009; Han et al. 2012; Araki et al. 2014) and morphological changes within these regions (Wang et al. 2012). These neuroplastic changes are associated with propensity for drug abuse and can be prevented or reversed by EE exposure.

Likewise, physical activity is a strong natural reward (Belke and Wagner 2005; Brené et al. 2007) and is often incorporated into EE regimens. Physical activity can activate DA neurons and is associated with neuroplasticity within the mesolimbic system. Cfos transcription is a measure of cellular activity and often used to quantify drug-induced activation of reward-processing neurons. It's been reported that rats with a prior history of wheel running have lower cocaine-induced cfos expression in the NAc, dorsal striatum and PFC compared to sedentary rats, suggesting that wheel running, in addition to reducing cocaine-related behaviors, also reduces reward neuron responsivity to drugs of abuse (Zlebnik et al. 2014). Repeated wheel running is associated with greater levels of tyrosine hydroxylase (TH) mRNA in the VTA, delta opioid receptor (DOR) mRNA levels in the NAc shell, and reduced

levels of DA D2 mRNA in the NAc core (Greenwood et al. 2011). Autoradiography studies have shown that exercise reduces DA D1 receptor-like binding within the olfactory tubercle and NAc shell (ventral striatum) but increases DA D2 receptor-like binding in dorsal and ventral striatum (Robison et al. 2018b). It is tempting to speculate that these neuronal changes might be partially responsible for the seemingly therapeutic effects of exercise on drug taking and seeking. Consistent with these findings are reports that reductions in DA-related transporters mRNA level (e.g., DA transporter, DAT and vesicular monoamine transporter, VMAT2) occur in rodent PFC and NAc after chronic exercise or multidimensional EE exposure (Bezard et al. 2003; Zhu et al. 2004, 2005, 2013; Zakharova et al. 2009). However, no EE-induced changes in DAT or VMAT2 expression or function were found in the striatum (Zhu et al. 2004; Hofford et al. 2014).

Multidimensional EE treatment produces beneficial changes in drug-related behaviors that are correlated with reductions in the expression of early immune genes, Zif268 in NAc, VTA and amygdala and reduction in fosB expression in the NAc, all brain regions known to play pivotal roles in drug reward and drug seeking (Fritz et al. 2011; El Rawas et al. 2012). We will now review the neuroplastic changes occurring within the mesocorticolimbic regions that might partially explain the therapeutic effects of EE intervention.

5.1 Effects of EE on the prefrontal cortex

Though EE does not lead to persistent alterations in dendritic morphology of PFC neurons (Kolb et al. 2003b), it produces long-lasting alterations in DA, serotonin and glutamate transmission in the PFC (Zhu et al. 2004; Brenes et al. 2008; Darna et al. 2015) and is associated with an increase in the number of parvalbumin (PV) GABA interneurons in this region (Sampedro-Piquero et al. 2016). The extracellular signal-regulated kinase ERK signaling in the PFC that appears to be critically involved in incubation of drug craving (Koya et al. 2009) can be diminished by wheel running, suggesting that this might constitute a contributing factor in the observation of reduced reinstatement of cocaine seeking (Lynch et al. 2010). These data are consistent with reports that EE has attenuating effects on impulsivity (Perry et al. 2008; Kirkpatrick et al. 2013; Wang et al. 2017) and behavioral inflexibility (Sampedro-Piquero et al. 2015; Zeleznikow-Johnston et al. 2017), behaviors believed to be controlled by the PFC and to contribute to compulsive continuation of drug use. A number of studies have shown that chronic exposure to methamphetamine and other drugs of abuse promotes neuroadaptations in the PFC (Tian et al. 2010), a region whose dysfunctionality is associated with compulsive drug taking (Jentsch and Taylor 1999; Goldstein and Volkow 2002). One can argue that EE, by stimulating the PFC, may help individuals increase behavioral flexibility and regain control over their impulsivity.

5.2 Effects of EE on the striatum

Other prime targets of EE-induced neural adaptations are the NAc and dorsal striatum, the brain regions critical for motivation (Ikemoto and Panksepp 1999) and habit formation (Gerdeman et al. 2003; Yin et al. 2004), respectively, and where drug-induced synaptic plasticity appears to play a pivotal role in the development and maintenance of addiction-type behaviors. Implementation of EE offers opportunities to experience sensory stimulation and physical activity that function as rewards in their own right and, through behavioral

contrast mechanisms, are thought to diminish the rewarding value of drugs (Ranaldi et al. 2011; Peck and Ranaldi 2014) and reduce motivation to seek drug. These pronounced behavioral changes are often accompanied by EE-induced long-term synaptic plasticity in the NAc and dorsal striatum (caudate and putamen). For example, rats raised in EE not only show persistent changes in drug-related behaviors but also alterations in expression of CREB signaling, FosB, and PKC signaling in the NAc (Green et al. 2002, 2003; Solinas et al. 2008; Lichti et al. 2014; Zhang et al. 2014). Mice raised in EE showed reduced behavioral sensitization to cocaine that was associated with reduced cocaine-induced expression of the immediate early gene, zif268, in the NAc as compared to mice raised in standard housing (non-EE) (Solinas et al. 2009). In addition, EE mice also have higher basal levels of FosB, a transcription factor known to be increased by sustained activation of striatal neurons (Thiriet et al. 2008; Solinas et al. 2009). Repeated administration of cocaine increases FosB levels in non-EE mice but decreases it in EE mice (Solinas et al. 2009).

It's been reported that housing in a complex multidimensional environment for 3.5 months leads to an increase in dendritic arborization in medium spiny neurons in the NAc (Kolb et al. 2003b). In addition, EE alters the expression of a large number of NAc proteins that promote strengthening as well as maturation of excitatory synapses (Lichti et al. 2014; Zhang et al. 2016b) and that might contribute to the putative protective and therapeutic effects of EE. Similar types of EE-induced neuroadaptations occur in the dorsal striatum. Mice reared in EE show alterations in the levels of mRNA coding for proteins involved in cell proliferation, cell differentiation, signal transduction, transcription and translation and cell structure and metabolism (Thiriet et al. 2008). In the striatum (as well as in the hippocampus and substantia nigra) EE also increases the expression of brain-derived neurotrophic factor (BDNF) (Bezard et al. 2003), itself implicated in the survival of existing neurons, the growth and differentiation of new neurons, formation of synapses and long-term memory (Acheson et al. 1995; Huang and Reichardt 2001; Bekinschtein et al. 2008). The neuroplastic changes that occur in the NAc and dorsal striatum of mice raised in EE are believed to contribute to the protective mechanisms of EE working against drug effects. However, it is quite reasonable to propose that similar neuroplastic changes might be involved in the therapeutic effects of EE when EE is introduced after drug exposure. Given that the NAc is implicated in reward and incentive motivation, one may imagine that EE, by offering alternative rewards, rewires the local accumbal circuitry so that the value of drugs is relatively diminished and incentive motivation shifts to non-drug rewards. Likewise, EE-induced neuroplasticity in the dorsal striatum, which is considered critical in the formation and maintenance of habitual drug taking (Everitt and Robbins 2005, 2013) may contribute to reductions in drug seeking and propensity to relapse. There is some evidence supporting these hypotheses.

For example, EE promotes the insertion of non-calcium permeable AMPA receptors into silent synapses that typically express stable NMDA receptors without AMPA receptors and that are generated by cocaine exposure (Huang et al. 2009, p. 009). During forced abstinence from cocaine, the calcium permeable AMPA receptors are inserted into cocaine-generated silent excitatory synapses, contributing to their maturation ("un-silencing" the synapse) and incubation of craving (Ma et al. 2014). Dong's lab has recently demonstrated that EE has the ability to re-silence these silent synapses through insertion of non-calcium permeable AMPA

receptors (Ma et al. 2016). These unique synaptic changes induced by EE introduced *after* cocaine-self-administration are believed to contribute to the seemingly therapeutic effects of EE on the incubation of craving for cocaine (Ma et al. 2016).

5.3 Effects of EE on the amygdala

The amygdala (basolateral and central), which sends glutamatergic efferents to the NAc and PFC, is critically involved in drug craving and seeking (Di and Everitt 2004; Stuber et al. 2011; Stefanik and Kalivas 2013; Li et al. 2015b; Venniro et al. 2018). When given the choice between methamphetamine or social interaction rats decrease self-administration and also do not show incubation of methamphetamine craving after 30 days of forced abstinence (Li et al. 2015b; Venniro et al. 2018). Shaham's group reported that the protective effect of concurrent reward derived from social interaction was associated with activation of PKC-expressing inhibitory neurons in the central amygdala and with inhibition of the anterior insula (Venniro et al. 2018). It has been proposed that home-cage forced abstinence from methamphetamine leads to recruitment of central amygdala output neurons contributing to long-lasting incubation of craving while volitional social choice remodels this connectivity leading to reduced drug seeking. In addition, given that social-choice induced abstinence is associated with inhibition of the anterior insula, whose glutamatergic neurons project to the central amygdala, it is conceivable that social-choice exposure prevents incubation of craving by inhibiting this anterior insula-central amygdala pathway (Venniro et al. 2018). These findings are consistent with previous reports that mice exposed to EE or social interaction after cocaine conditioning show increases in the expression of the immediate early gene, Early Growth Response protein 1 (EGR1, Zif268) in the basolateral and central amygdala during the re-acquisition or reinstatement of cocaine CPP (Fritz et al. 2011). However, when social interaction is presented as an alternative reward during cocaine CPP, it reverses cocaine CPP-induced expression of the immediate early gene, Zif268 in the BLA (as well as in the NAc and VTA), suggesting that social interaction as a feature of EE may decrease the incentive salience of drug-related stimuli by recruiting BLA neurons (Zernig et al. 2013; Zernig and Pinheiro 2015). It's been also reported that EE as a therapeutic intervention introduced after cocaine exposure reduced cocaine CPP-induced expression of cFos in BLA and central amygdala as well as in other limbic regions such as the anterior cingulate cortex, dorsal striatum, NAc shell, hippocampus, bed nucleus of the stria terminalis and the VTA (Chauvet et al. 2011).

Other EE-induced neuroplastic changes in the BLA have also been reported. For example, *in situ* hybridization studies have shown that EE increased the cannabinoid CB1 receptor and fatty acid amide hydrolase (FAAH) mRNA levels in the BLA and hypothalamus, two brain regions critical for stress responses. Converging evidence suggests that the endocannabinoid system, which modulates the mesolimbic DA system (Xi et al. 2011), plays a critical role in reward and stress processes (Gardner 2005; Solinas et al. 2007; Gorzalka et al. 2008). It has been proposed that EE induced neuroplasticity in the endocannabinoid system, particularly in the BLA and hypothalamus, most likely reduces responses to stress and ultimately deters stress-induced drug seeking (El Rawas et al. 2011).

Converging evidence indicates that the primary cellular mechanism involved in the synaptic plasticity underlying learning and memory is the insertion of AMPA receptors in postsynaptic neurons (Malinow and Malenka 2002). Direct phosphorylation of GluR1 by PKA, which is crucial for AMPA receptor trafficking and synaptic plasticity (Lee et al. 2003; Man et al. 2007), has been shown to be differentially altered by cocaine-self-administration and EE intervention. In rats with a history of cocaine self-administration brief EE interventions, introduced both 24 h before and immediately after extinction sessions, facilitated extinction of cocaine seeking and reduced the re-acquisition of cocaine self-administration (Gauthier et al. 2017). EE has been shown to increase GluA1 and phosphorylated GluA1 at serine 845 (pSer845GluA1) protein levels in the BLA and NAc but to decrease pSer845GluA1 level in the PFC (Gauthier et al. 2017). These neuroadaptations are believed to contribute to the EE-induced behavioral changes in drug self-administration and seeking. Given that GluA1-containing AMPA receptors are located primarily on GABA interneurons in the BLA (which control excitability of BLA projection neurons) (McDonald 1996) and that BLA GABA interneurons receive direct inputs from PFC glutamatergic neurons (Rosenkranz and Grace 2002), it is conceivable that EE, by modulating this circuitry, facilitates the extinction of cocaine seeking and reduces propensity for relapse (Gauthier et al. 2017).

5.4 Effects of EE on the hippocampus

The literature provides an abundance of convincing evidence that EE can induce structural, biochemical and functional changes in the hippocampus, a limbic region highly implicated in learning and memory. For example, EE can alter neuronal behavior (i.e., excitatory postsynaptic potentials, long-term potentiation and long-term depression) in the hippocampus (Foster et al. 1996; Duffy et al. 2001; van Praag et al. 2005; Artola et al. 2006; Hosseiny et al. 2014). Other forms of EE-induced hippocampal neuroplasticity include: neurogenesis (Kempermann et al. 1997, 1998; Brown et al. 2003; van Praag et al. 2005), synaptogenesis (Sager et al. 2018; Cefis et al. 2019), alterations in BDNF (Neeper et al. 1996; Ickes et al. 2000; Vaynman et al. 2003; Zajac et al. 2010) and nerve growth factor (NGF) (Neeper et al. 1996; Pham et al. 1999; Hall and Savage 2016), both of which support the viability and functions of neurons and are likely mediators of activity-dependent changes in the hippocampus. EE-induced morphological changes in the hippocampus include increases in hippocampal thickness (Rosenzweig 1966), dendritic arborization (Fiala et al. 1978) and the number of glial cells (Walsh et al. 1969). EE-induced modification in hippocampal glutamatergic (Mlynarik et al. 2004; Naka et al. 2005; Segovia et al. 2006; Andin et al. 2007), cholinergic (Hall and Savage 2016), GABAergic (Frick et al. 2003; Segovia et al. 2006), norepinephrinergic (Galani et al. 2007) and serotonergic (Rasmuson et al. 1998; Galani et al. 2007; Pang et al. 2009) transmission have also been reported. Likewise, alterations in the expression of proteins related to hippocampal ERK, CREB, PKA, PKC, CAMKII, MAPK signaling have also been noted in rodents exposed to EE (Shen et al. 2001; Williams et al. 2001; Zhang et al. 2016a; Cardoso et al. 2017). Given that these signaling molecules play critical roles in synaptic plasticity (Malinow et al. 1989; Meffert et al. 1991; Schulman 1995; Lisman et al. 2002) and addiction-related behaviors (Ortiz et al. 1995; Levine et al. 2005; Lu et al. 2006; Lee and Messing 2008) and can be altered by environmental experiences, it is reasonable to suggest that EE, by providing

multidimensional stimulation, rewires hippocampal-centered circuits, generates new connections that augment the values of non-drug rewards while weakening the values of drug-based memories. In support of this hypothesis are findings that mice exposed to 30 days of EE intervention after cocaine conditioning show a lack of CPP and less CPP-induced cfos activation in the hippocampus (Chauvet et al. 2011). It's been reported that for mice engaged in alcohol consumption 21 days of concurrent exposure to a running wheel were sufficient to increase BDNF hippocampal levels and reduce alcohol consumption (Gallego et al. 2015). Morphine-treated rats that received EE exposure (group housing) concurrent with morphine treatment had higher hippocampal BDNF levels that correlated with better water-maze performance as compared to morphine-treated rats housed in isolation (non-EE exposure) (Famitafreshi et al. 2016). BDNF together with its receptor TrkB is essential for hippocampal neurogenesis that has been suggested as a key mediator underlying EE-induced reductions in drug-related effects, including methamphetamine self-administration and reinstatement of methamphetamine seeking (Mandyam and Koob 2012; Recinto et al. 2012). However, recent studies demonstrated that EE (wheel running)-induced reductions in the escalation of methamphetamine self-administration and drug seeking occurred independently of EE-induced neurogenesis (Engelmann et al. 2014; Sobieraj et al. 2016), suggesting that other forms of neuroplasticity might control these beneficial effects of EE. Clearly, more studies are needed to fully understand the neurobiology of EE's therapeutic and preventative benefits against drug effects.

6. Summary

The complexities of the behavioral and neurobiological factors underlying SUDs create enormous challenges in efforts to develop effective pharmacological treatments. Although traditional pharmacological approaches to combat SUDs have provided encouraging results at a preclinical level, limited success has been achieved at a clinical level. Despite many years of intense research in medication development, SUDs still remain a serious problem, affecting millions of lives and for which long-term effective treatments are at best sparse. Given the current opioid crisis and the urgent need for more efficacious treatments, new strategies are being explored. Current preclinical and clinical data indicate that EE is an effective intervention for the treatment of SUDs as it has the ability to control impulsive drug taking, attenuate the rewarding (and reinforcing) effects of drugs, reduce the effectiveness of drug cues, and, very importantly, reduce craving and relapse. Importantly, EE might be effective because it does not depend on new learning that is effective only within specific (e.g., clinical) contexts and under specific conditions. EE produces profound neuroplasticity in regions of the brain that are strongly implicated in reward processing, incentive motivation, reward-related learning and habit formation and compulsivity, all behaviors at the heart of addiction development, maintenance and recurrence. The identification of the neuroplastic changes induced by EE over the past few decades has shed new light on the underlying mechanisms by which EE produces its protective and therapeutic effects against drug addiction and may constitute a pathway through which we may expand the therapeutic possibilities for treating SUDs.

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Abbreviations

5-HT	serotonin
Akt	protein kinase B
AMPA	A-Amino-3-Hydroxy-5-Methyl-4-Isoxazolepropionic Acid
BDNF	Brain derived neurotropic factor
BLA	basolateral amygdala
BMA	basomedial amygdala
cAMP	cyclic adenosine monophosphate
CB	cannabinoid receptor
c-fos	early immune gene cfos
CREB	cAMP response element-binding protein
CXCR	C-X-C chemokine receptor type 4
DARPP	dopamine and cAMP regulated phosphoprotein-mw 32
DAT	dopamine transporter
DEC	decorin
delta fos B	transcription factor delta fos b
DNM1L	dynamin 1-like
EE	environmental enrichment
ERK	extracellular regulated kinase
FAAH	Fatty-acid amide hydrolase
GABA	gamma-aminobutyric acid
GAD	glutamic acid decarboxylase
IC	isolated condition
ILC	infralimbic cortex
LTP	long-term potentiation
LTD	long term depression

MAP3K12	mitogen-activated protein kinase 12
MAPK	mitogen activated protein kinase
mEPSC	miniature excitatory post synaptic current
MGL	Monoacylglycerol lipase
mGlu (1–5)	metabotropic glutamate receptors
mRNA	messenger ribonucleic acid
MSN	medium spiny neuron
mTOR	mammalian target of rapamycin
NA	sodium
NE	norepinephrine
NET	norepinephrine transporter
NGF	nerve growth factor
NR2A NR2B	Glutamate receptor, ionotropic, N-methyl D-aspartate 2A and 2B
OFC	orbitofrontal cortex
p38	p38 mitogen-activated protein kinase
P70S6K	p70 ribosomal protein S6 kinase
pCREB	cAMP response element binding protein
pERK	protein kinase R-like endoplasmic reticulum kinase
PFC	prefrontal cortex
PKA	cAMP-dependent protein kinase
PKC	protein kinase C
Prkcl	Protein kinase C, lambda
PSMD4	Proteasome 26S subunit, non-ATPase, 4
SD	standard condition
SDF-1	stromal cell-derived factor 1
sEPSC	spontaneous excitatory post synaptic current
TH	Tyrosine Hydroxylase
VMAT2	Vesicular monoamine transporter 2

VMAT	vesicular monoamine transporter
Zif268	early immune gene/ zinc finger transcription factor 268

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Highlights

Preclinical research suggests environmental enrichment is an effective behavioral strategy to reduce drug-related behaviors

Environmental enrichment leads to neural adaptations in brain regions highly implicated in drug reward and use disorder

Evidence suggests that environmental enrichment is beneficial for individuals struggling with substance use disorder

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Table 1:

A summary of preclinical studies assessing therapeutic potential of EE as a behavioral intervention implemented after or concurrently to drug exposure in animal models of addiction.

Type of EE	Treatment duration and onset	Species	Drug	Outcome	Reference
Intravenous self-administration					
wheel	19 days concurrent with drug acquisition session	Rats	Cocaine	Self-administration ↓	Cosgrove et al. 2002
wheel	16 days concurrent with drug acquisition session	Rats	Cocaine	Self-administration ↓	Zlebnik et al. 2012
wheel-concurrent	14 days concurrent with drug acquisition session	Rats	METH	Self-administration ↓	Miller et al. 2012
wheel	19 days (22 hrs daily) concurrent with drug acquisition	Rats	METH	Self-administration ↓	Aarde et al. 2015
social, toys	23 days concurrent with drug acquisition	Rats	Cocaine	Self-administration ↓	Puhl et al. 2012
social, toys, wheel	4 hr-sessions prior and after 3 extinction sessions	Rats	Cocaine	Reacquisition of self-administration ↓	Gauthier et al. 2017
Extinction					
social, toys, wheel	4 hr-sessions prior and after 3 extinction sessions	Rats	Cocaine	Extinction responding ↓	Gauthier et al. 2017
social, toys, wheel	30 or 90 days during forced abstinence	Rats	Cocaine	Extinction responding ↓	Chauvet et al. 2009
wheel	10 days (2 hrs daily) during forced abstinence + 5 extinction days	Rats	Nicotine	Extinction responding ↓ in males but not females	Sanchez et al. 2014
wheel	10 days (2 hrs daily) during forced abstinence + 5 extinction days	Rats	Nicotine	Extinction responding ↓	Sanchez et al. 2013
wheel	21 days during forced abstinence + 6 extinction days	Rats	METH	Extinction responding ↓	Sobieraj et al. 2016
wheel	14 days (2 hrs daily) during forced abstinence	Rats	Cocaine	Extinction responding ↓	Lynch et al. 2010
wheel	10 days (2 hrs daily) during forced abstinence + 5 extinction days	Female Rats	Nicotine	Extinction responding ↓ during estrus	Lynch et al. 2019
wheel	14 days during forced abstinence (1, 2, 6 hrs daily) + 5 days	Rats	Cocaine	Extinction responding ↓ with 6 hr access	Peterson et al. 2014b
toys, wheel	30 days during forced abstinence + 15 days during extinction	Rats	Heroin	Extinction responding –	Galaj et al. 2016
social, toys	60 days of forced abstinence + 6 extinction days	Rats	Cocaine	Extinction responding ↓ in adolescents Extinction responding – in adults	Li and Frantz 2017
social, toys, wheel	21–28 days during forced abstinence + 6 extinction days	Rats	Heroin	Extinction responding ↓	Sikora et al. 2018
			METH	Extinction responding ↓	
			Nicotine	Extinction responding ↓	
wheel	First \Last 7 or all 14 days (2hrs daily) of forced abstinence + 5 days	Rats	Cocaine	Cue induced reinstatement ↓ (EE during first 7 days) Cue induced reinstatement ↓ (EE during 14 days)	Beiter et al. 2016
wheel	14 days 6 hrs daily during extinction	Female Rats	Cocaine	Extinction responding –	Zlebnik et al. 2010

Type of EE	Treatment duration and onset	Species	Drug	Outcome	Reference
Cue-induced Reinstatement					
toys, wheel	30 days during forced abstinence + 15 days during extinction	Rats	Heroin	Cue induced reinstatement ↓	Galaj et al. 2016
social, toys, wheel	31 days during forced abstinence	Rats	Heroin	Cue induced reinstatement ↓	Thiel et al. 2010
wheel	10 days (2 hrs daily) during forced abstinence + 5 extinction days	Rats	Nicotine	Cue induced reinstatement –	Sanchez et al. 2013
social, toys, wheel	21 days during forced abstinence + 1 extinction/reinstatement day	Rats	Cocaine	Cue induced reinstatement ↓	Thiel et al. 2009
wheel	10 days (2 hrs daily) during forced abstinence + 5 extinction days	Rats	Nicotine	Cue induced reinstatement –	Sanchez et al. 2014
wheel	14 days during forced abstinence (1, 2, 6, 24 hrs daily) + 5 days	Rats	Cocaine	Cue induced reinstatement ↓ in males Cue induced reinstatement ↓ in non-estrus females Cue induced reinstatement – in estrus females	Peterson et al. 2014a
social, toys, wheel	30 or 90 days during forced abstinence	Rats	Cocaine	Cue induced reinstatement ↓	Chauvet et al. 2009
social, toys	60 days during forced abstinence + 6 extinction days	Rats	Cocaine	Cue-induced reinstatement ↓ in adolescents Cue-induced reinstatement – in adults	Li and Frantz 2017
Wheel running	21 days during forced abstinence + 6 extinction days	Rats	METH	Cue induced reinstatement ↓	Sobieraj et al. 2016
Wheel running	14 days (2 hrs daily) during forced abstinence	Rats	Cocaine	Cue induced reinstatement ↓	Lynch et al. 2010
Wheel running	10 days (2 hrs daily) during forced abstinence + 5 extinction days	Female Rats	Nicotine	Cue induced reinstatement ↓ during estrus Cue induced reinstatement – during non-estrus	Lynch et al. 2019
Wheel running	First \Last 7 or all 14 days (2hrs daily) of forced abstinence + 5 days	Rats	Cocaine	Cue induced reinstatement ↓ (EE during first 7 days) Cue induced reinstatement ↓ (EE during 14 days) Cue induced reinstatement – (EE during last 7 days)	Beiter et al. 2016; Abel et al. 2019
social, toys	30 days during forced abstinence + 10 days during extinction	Rats	Cocaine	Cue induced reinstatement ↓	Ranaldi et al. 2011
social, toys, wheel	21–28 days during forced abstinence + 6 extinction days	Rats	Heroin	Cue induced reinstatement ↓	Sikora et al. 2018
			METH	Cue induced reinstatement ↓	
			Nicotine	Cue induced reinstatement ↓	
wheel + atomoxetine	15 days during cocaine use + 14 extinction days (6 hrs daily)	Rats	Cocaine	Cue induced reinstatement ↓	Zlebnik and Carroll 2015
wheel	14 days during forced abstinence (1, 2, 6 hrs daily) + 5 days	Rats	Cocaine	Cue induced reinstatement ↓ with 6 hr daily access	Peterson et al. 2014b
Stress-induced reinstatement					
social, toys, wheel	30 or 90 days during forced abstinence	Rats	Cocaine	Stress-induced reinstatement ↓	Chauvet et al. 2009
treadmill	42 days (1 hr daily) during forced abstinence	Female Rats	Cocaine	Stress-induced reinstatement ↓	Robison et al. 2018a

Type of EE	Treatment duration and onset	Species	Drug	Outcome	Reference
Drug-induced reinstatement					
social, toys, wheel	30 or 90 days during forced abstinence	Rats	Cocaine	Cocaine induced reinstatement –	Chauvet et al. 2009
social, toys	60 days during forced abstinence + 6 extinction days	Rats	Cocaine	Cocaine induced reinstatement ↓	Li and Frantz 2017
treadmill	6 weeks during forced abstinence	Rats	Cocaine	Cocaine induced reinstatement ↓	Thanos et al. 2013
wheel	14 days 6 hrs daily during extinction	Female Rats	Cocaine	Cocaine induced reinstatement ↓	Zlebnik et al. 2010
social, toys, wheel	5 days during CPP extinction	Mice	Ethanol	Ethanol induced CPP reinstatement ↓	Li et al. 2015a
social, toys, wheel	30 days during forced abstinence	Mice	Cocaine	Cocaine induced reinstatement ↓	Solinas et al. 2008
wheel + atomoxetine	15 days during cocaine use + 14 extinction days (6 hrs daily)	Rats	Cocaine	Cocaine induced reinstatement –	Zlebnik and Carroll 2015
Abstinence-Conflict model					
toys, wheel	until abstinence criteria	Rats	Heroin	Abstinence ↑	Peck et al. 2015
toys, wheel	until abstinence criteria	Rats	Cocaine	Abstinence ↑	Ewing and Ranaldi 2018
Conditioned place preference					
wheel	22 days during forced abstinence + 8 days concurrent with extinction	Mice	Cocaine	CPP ↓	Mustroph et al. 2011
	18 days prior to drug exposure + 12 during conditioning/extinction			CPP ↑	
social, toys, wheel	30 days during forced abstinence	Mice	Cocaine	CPP ↓	Solinas et al. 2008
wheel	4 weeks concurrent with extinction	Mice	Cocaine	CPP ↓	Mustroph et al. 2016
social	as drug alternative during conditioning	Rats	Cocaine	CPP ↓	Fritz et al. 2011
social	as drug alternative during conditioning	Rats	AMPH	CPP ↓	Yates et al. 2013
toys, wheel	30 days during forced abstinence	Rats	Heroin	CPP ↓	Galaj et al. 2016
social, toys	30 days during forced abstinence	Rats	Cocaine	CPP ↓	Chauvet et al. 2011
social, toys, wheel	30 days during forced abstinence	Rats	Cocaine	CPP ↓	Galaj et al 2017

Table 2.

A summary of preclinical studies assessing the effects of EE on neuronal plasticity.

Type of EE	EE duration + onset	Species	Outcome	Reference
PREFRONTAL CORTEX				
social, toys, wheel	10 weeks from P 21	Rats	no change in dendritic arborization	Kolb et al. 2003
social, toys	60 days from P 21	Rats	mGluRs ↓ IC rats relative to EE or SD; no change in EE	Melendez et al 2004
social	50 days from P 22	Rats	pruning of dendritic length	Himmler et al. 2013
social			dendritic arborization ↓	
			cell responsiveness to nicotine ↑	
social	20 days from P 21	Hamsters	dendritic arborization ↓	Burleson et al. 2016
social, toys	32–35 days from P 21	Rats	DAT cell surface expression ↓	Zhu et al. 2005
social, toys	70 days from P 21	Rats	does not alter VMAT2 function	Hofford et al. 2014
social, toys	2 months from P 532	Rats	Parvalbumin GABA positive cells ↑	Sampedro-Piquero et al. 2016
social, toys	77 days from P 30	Rats	extracellular 5-HT concentration ↑	Brenes et al. 2008
			no change in extracellular NE concentration	
social, toys	21 days from P 30	Rats	c-fos ↑ in PFC and OFC as compared to IC	Sampedro-Piquero et al. 2015
			c-fos ↓ in IFC as compared to IC	
social	1 session (15 min) at P 21	Rats	no change in opioid receptor binding	Vanderschuren et al. 1995
social	13 days from P 21	Rats	D2-expressing cells as compared to IC ↓	Han et al 2012
social	9 weeks from P 21	Mice	AMPA (GluR1, 2, 5) expression as compared to IC ↓	Araki et al 2014
social, toys	30 days at P 84	Rats	no change in NE or DA concentration	Galani et al. 2007
			no change in NE or DA concentration	
social	8 weeks from P 21	Rats	NMDA NR2A, as compared to IC ↓	Turnock-Jones et al.2009
			no change in NMDA NR1A, NR2B mRNA and protein level	
social	9 weeks from P 21	Rats	dendritic arborization and length ↑	Wang et al. 2012
wheel	21 days from P 90	Rats	cocaine-induced cfos ↑	Zlebnik et al. 2014
social, toys	30 days from P 30	Rats	DAT function ↓	Zhu et al. 2004
			DA metabolism ↓	
			AMPA pSer845GluA1 expression ↓ (when EE+ extinction training)	
social, toys, wheel	32–35 days from P 21	Rats	DAT function ↓ in mPFC but not OFC	Darna et al. 2015
social, toys	2 months from P 21	Mice	no change in FAAH, CB1, MGL mRNA	El Rawas et al. 2011
treadmill	7 days from P 280	Rats	BDNF Activity ↑	Cefis et al. 2019
			BDNFp-TrkB receptors ↑	
			synaptophysin (synaptogenesis) ↑	
			exercise-induced cfos activation ↑	
social	4 sessions (15 min) after cocaine CPP	Rats	no change in cocaine cue-induced fosB	El Rawas et al. 2012
wheel	14 days (2 hrs daily) during forced abstinence	Rats	pERK levels ↓ as compared to sedentary	Lynch et al. 2010

Type of EE	EE duration + onset	Species	Outcome	Reference
social, toys, wheel	30 days after cocaine exposure	Mice	cocaine cue-induce cFos activation ↓	Chauvet et al. 2011
social, toys, wheel	6 sessions after cocaine exposure	Rats	AMPA pSer845GluA1 expression ↑ (when EE alone)	Gauthier et al. 2017
social, toys, wheel	31 days during forced abstinence	Rats	cocaine cue induced cFos activation ↓	Thiel et al. 2010
wheel	14 days during forced abstinence + 5 days	Rats	BDNF exon IV expression ↓	Peterson et al. 2014b
wheel	7 or 14 days after cocaine use	Rats	mGlu5 mRNA expression ↑ (with EE during first 7 days) no change in mGlu5 mRNA expression (with EE during last 7 days)	Abel et al. 2019
NUCLEUS ACCUMBENS				
social, toys, wheel	10 weeks from P 21	Rats	dendritic arborization ↑	Kolb et al. 2003
social	4 sessions (15 min) at P 50–63	Rats	mitogen-activated protein kinase p38 ↓	Salti et al. 2015
social	1 session (15 min) at P 21	Rats	opioid receptor binding ↓	Vanderschuren et al. 1995
social, repeated handling	64 days from P 21	Rats	DA release in response to amphetamine in IC ↑ no effect on DA-induced cAMP accumulation D2 inhibition of DA-induced cAMP accumulation in IC ↓	Hall et al. 1998
social, toys	30 days from P 28	Rats	no change in AMPA GluR1 NMDA NR1 ↑ as compared to IC	Wood et al. 2005
social	13 days from P 21	Rats	D2-expressing cells as compared to IC ↓	Han et al 2012
social	9 weeks from P 21	Mice	no change in AMPA (GluR1, 2, 5) expression no change in GluR1 Ser845 phosphorylation	Araki et al 2014
social	8 weeks from P 21	Rats	pulse-induced DA release as compared to IC ↓ no change in VMAT2, Synaptogyrin-3, Syntaxin-1, Munc13–3 TH expression as compared to IC ↓	Karkhanis et al. 2019
social	4 weeks from P 21	Mice	sEPSC and mEPSC, as compared to IC ↓ intrinsic excitability of MSNs, as compared to IC ↓	Zhang et al 2019
social, toys	77 days from P 30	Rats	no change in extracellular 5-HT concentration extracellular NE concentration ↑	Brenes et al. 2008
social	8 weeks from P 21	Rats	no change in NMDA receptor mRNA and protein level	Turnock-Jones et al.2009
social	8–9 weeks from P 28	Rats	dendritic length ↑	Wang et al. 2012
wheel	21 days from P 90	Rats	cocaine-induced cFos ↑	Zlebnik et al. 2014
wheel	6 weeks in young adulthood	Rats	Delta-opioid receptor mRNA ↑ D2 receptors ↓ no change in kappa-opioid, D1, dynorphin mRNA wheel running-induced cFos ↑	Greenwood et al. 2011

Type of EE	EE duration + onset	Species	Outcome	Reference
treadmill	5 min, 5 days or 6 weeks at P 60	Rats	D1 receptor binding ↓ no change in DAT binding	Robinson et al. 2018
social, toys	30 days from P 30	Rats	no change in DA clearance/ DAT function	Zhu et al. 2004
social, toys	30 days from P 30	Rats	in NAc core baseline and nicotine DA clearance nicotine DA clearance ↑ in NA shell but ↓ in NA core	Zhu et al. 2013
social, toys/ no toys	20 days from P 23	Rats	cocaine-induced DAT protein ↑ in IC, but ↓ in EE no change in cocaine-induced DARPP-32 cocaine-induced TH ↑ in IC, no change in EE	Zakharova et al. 2009
social	4 sessions (15 min) after cocaine CPP	rats	cocaine-induced Zif-268 ↓	Fritz et al. 2011
social, toys, wheel	2–3 months from P 21	Mice	cocaine-induced Zif-268 activation ↓	Solinas et al. 2009
social, toys, wheel	2 months from P 21	Mice	MAP3K12 mRNA expression ↑ DNM1L mRNA expression ↑ PKC lambda mRNA expression ↑ DEC mRNA expression ↓ PSMD4 mRNA expression ↓	Thiriet et al. 2008
social, toys	2 months and during cocaine use from P 21	Rats	PKC signaling ↑ CREB signaling ↑ ERK/ MAPK signaling ↑ proteins needed for energy production, mRNA splicing, and ubiquitination ↑ vesicular glutamate and monoamine transporters expression ↑	Lichti et al. 2014
social, toys	30 days at P 84	Rats	Serotonin concentration ↓ Norepinephrine concentration ↑ no change in dopamine concentration	Galani et al. 2007
social, toys, wheel	6 sessions after cocaine exposure	Rats	no change in AMPA GluA1 or pSer845GluA1 expression AMPA pSer845GluA1 expression ↓ (when EE+ extinction training)	Gauthier et al. 2017
social, toys, wheel	2 months from P 21	Mice	cocaine-induced c-Fos activation ↓ BDNF ↑ no change in D1 or D2 mRNA	Bezard et al. 2003
social, toys, wheel	30 days after cocaine exposure	Mice	cocaine cue-induced cFos activation ↓	Chauvet et al. 2011
social, toys	7 days from P 28–30	Rats	Non-CA permeable AMPAR's ↑	Ma et al. 2016
social, toys, wheel	1, 7 or 30 days	Mice	cocaine cue-induced cFos activation ↓	Solinas et al. 2008
social, toys, wheel	31 days during forced abstinence	Rats	cocaine cue induced cfos activation ↓	Thiel et al. 2010
social, toys, wheel	Rearing (1 month)	Rats	no change in cocaine induced FosB	Zhang et al. 2014

Type of EE	EE duration + onset	Species	Outcome	Reference
DORSAL STRIATUM				
treadmill running	5 min, 5 days or 6 weeks at P60	Rats	D2 receptor-binding ↑ no change in DAT binding	Robinson et al. 2018
social, toys, wheel	2 months from P 21	Mice	cocaine-induced C-fos mRNA ↑ BDNF ↑ DAT mRNA and binding ↓ no change in D1 or D2 mRNA	Bezard et al. 2003
social, toys, wheel	30 days after cocaine exposure	Mice	cocaine cue-induced cFos activation ↓	Chauvet et al. 2011
social, toys	30 days from P 30	Rats	no change in DAT function	Zhu et al. 2004
social, toys	70 days from P 21	Rats	no change in DAT function	Hofford et al. 2014
social, toys	2 months from P 21	Mice	no change in FAAH, CB1, MGL mRNA	El Rawas et al. 2011
social	4 sessions (15 min) after cocaine CPP	Rats	no change in cocaine cue-induced fosB activation	El Rawas et al. 2012
social, toys, wheel	31 days during forced abstinence	Rats	no change in cocaine cue-induced cFos activation	Thiel et al. 2010
social, toys, wheel	2–3 months from P 21	Mice	cocaine-induced Delta-Fos B activation ↑	Solinas et al. 2009
AMYGDALA				
social	1 session (15 min) at P 21	Rats	no change in opioid receptor binding	Vanderschuren et al. 1995
social	10 sessions with discrete choice trials	Rats	c-fos activation in PKC-expressing inhibitory neurons ↑	Venniro et al. 2018
social	6 weeks from P 21	Rats	DAT ↓ as compared to IC no change in NET alcohol-induced DA release as compared to IC ↑ alcohol-induced NE release as compared to IC ↓	Karkhanis et al. 2015
social	8–9 weeks from P 28	Rats	dendritic arborization and length ↓	Wang et al. 2012
social	4 sessions (15 min) after cocaine CPP	Rats	cocaine-induced Zif-268 activation ↓	Fritz et al. 2011
social, toys	4 sessions (15 min) after cocaine CPP	Rats	cocaine cue-induced fosB activation ↓ pCREB ↑	El Rawas et al. 2012
social, toys, wheel	30 days after cocaine exposure	Mice	cocaine cue-induced cFos activation ↓	Chauvet et al. 2011
social, toys	2 months from P 21	Mice	FAAH mRNA ↑ CB1 mRNA in BLA ↑ but ↓ in BMA no change in MGL	El Rawas et al. 2011
social, toys, wheel	6 sessions after cocaine exposure	Rats	no change in AMPA GluA1 or pSer845GluA1 expression	Gauthier et al. 2017
social, toys	4, 15 minute sessions	Rats	zif268 activation ↓ as compared to IC	Zernig and Pinheiro 2015
social, toys	4 sessions (15 min) after cocaine CPP	Rats	no change in cocaine cue-induced fosB	El Rawas et al. 2012
HIPPOCAMPUS				

Type of EE	EE duration + onset	Species	Outcome	Reference
social, toys, wheel	8 weeks from P 21	Mice	morphological changes in astrocytes	Viola et al. 2009
social, toys	4–5 weeks from P 36–45	Rats	synaptic strength ↑	Foster et al. 1996
social, toys, wheel	40 days from P 21	Mice	Neurogenesis ↑	Kempermann et al. 1997
social, toys, wheel	68 days from P 168 or P 504	Mice	Neurogenesis ↑	Kempermann et al. 1998
wheel	45 days from P 84 or P 504	Mice	Neurogenesis ↑	van Praag et al. 2005
social, toys	34 days from P 50	Rats	BDNF ↑	Fakelnberg et al. 1992
social, toys	6 weeks from P 70	Rats	BDNF ↑ glucocorticoid receptor ↓ no change in AMPA GluR1 and mGluR5	Bakos et al 2009
social	9 weeks from P 21	Mice	no change in AMPA (GluR1, 2, 5) expression no change in GluR1 Ser845 phosphorylation	Araki et al 2014
wheel	2, 4, 7 nights from P 100	Rats	BDNF ↑ NGF ↑	Neeper et al. 1996
social, toys	4 weeks from P 25 or 12 weeks from P 145	Rats	Dentritic branching ↑ in adolescents	Fiala et al. 1978
social, toys	90 days from P 25	Rats	Glial Cells ↑ no change in thickness	Walsh et al. 1969
social, toys	33 days from P 56	Rats	AMPA GluR1 mRNA ↑ no change in AMPA NR2A or NR2B	Mlynarik et al. 2004
wheel	2 weeks after thiamine deficiency	Rats	Cholinergic functioning ↑ NGF ↑	Hall and Savage 2016
social, toys, wheel	25 days from P 196	Mice	GAD ↑ no change in synaptophysin (synaptogenesis)	Frick et al. 2003
social, toys	30 days from P 84	Rats	5-HT concentration ↓ NE concentration ↑ no change in dopamine concentration	Galani et al. 2007
social, toys	30 days from P 52	Rats	5-HT1A mRNA and binding ↑ no change in 5-HT2A or 5-HT2C receptor mRNA	Rasmuson et al. 1998
wheel	1, 3 or 7 days from P 84	Rat	CREB phosphorylation ↑ MAPK phosphorylation ↑	Shen et al. 2001
social, toys, wheel	30 days afer cocaine exposure	Mice	cocaine cue-induced cFos activation ↓	Chauvet et al. 2011
wheel	21 days concurrent with alcohol from P 25	Mice	BDNF mRNA and protein level ↑	Gallego et al. 2015
social, toys, wheel	8 weeks from P 28	Mice	PKA dependent LTP ↑	Duffy et al. 2001
social, toys, wheel/ no wheel	43 days at P 84	Mice	Neurogenesis ↑	Brown et al. 2003
treadmill	7 days at P 280	Rats	BDNF Activity ↑ BDNFp-TrkB receptors ↑ synaptophysin (synaptogenesis) ↑	Cefis et al. 2019

Type of EE	EE duration + onset	Species	Outcome	Reference
			exercise-induced cfos activation ↑	
social, toys	1 year at P 56	Rats	NGF concentration and NGF receptor density ↑	Pham et al. 1999
social, toys, wheel	40 days from P 28	Mice	AMPA GluR2 and GluR4 mRNA ↑	Naka et al. 2005
social, toys, wheel	8 weeks from P 54 or P 700	Rats	Neurogenesis in young rats ↑	Segovia et al. 2006
			Extracellular GABA in old rats ↑	
		Rats	Extracellular Glutamate in old rats ↑	
social, toys, wheel	59 days from P 35 or P 100	Mice	CREB expression ↑ in young mice	Williams et al. 2001
social, toys, wheel	30 days in adulthood (age not specified)	Rats	BDNF expression ↑	Zhang et al. 2016a
			CREB phosphorylation protein expression ↑	
			SDF-1 receptor protein expression ↑	
			CXCR4 receptor protein expression ↑	
			no change in PKA C-alpha protein expression	
			Neurogenesis of neurons but not astrocytes ↑	
social	3–5 weeks from P 96	Rats	LTP ↑	Artola et al. 2006
			LTD ↑	
treadmill	10 days from P 504	Rats	ERK activation ↓	Cardoso et al. 2017
			p38 activation ↓	
			no change in Akt, mTOR, pTOS6K, CREB protein expression	
social, toys, wheel		Mice	Glutamatergic synapses ↑	Hosseiny et al. 2014
			LTP ↑ (after 8 weeks of EE)	
			LTP ↓ (after 4 weeks of EE)	
			No change in LTP (after 6 weeks of EE)	
social, toys, wheel	6 sessions after cocaine exposure	Rats	no change in AMPA GluA1 or pSer845GluA1 expression	Gauthier et al. 2017
VENTRAL TEGMENTAL AREA				
social	1 session (15 min) at P 21	Rats	no change in opioid receptor binding	Vanderschuren et al. 1995
wheel	6 weeks in young adulthood	Rats	TH mRNA ↑	Greenwood et al. 2011
			no change in D2 mRNA	
social	4 sessions (15 min) after cocaine CPP	Rats	cocaine-induced Zif-268 activation ↓	Fritz et al. 2011
social, toys	2 months from P 21	Mice	no change in FAAH, CB1, MGL mRNA	El Rawas et al. 2011
social	4 sessions (15 min) after cocaine CPP	Rats	no change in cocaine cue-induced fosB	El Rawas et al. 2012
social, toys, wheel	30 days after cocaine exposure	Mice	cocaine cue-induce cFos activation ↓	Chauvet et al. 2011
social, toys, wheel	31 days during forced abstinence	Rats	Cue induced cfos activation ↓	Thiel et al. 2010