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Neuroplastic and cognitive impairment in substance use disorders: a therapeutic potential of cognitive stimulation

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Highlights

- Addictive drugs induce lasting neuroadaptations in learning-related brain regions
- Cognitive deficits are common in addiction and predict a worse treatment outcome
- Cognitive training may alleviate cognitive decline, addiction symptoms, and relapse
- Environmental enrichment modulates drug seeking and neuroplasticity in rodents
- Cognitive stimulation may be a worthy adjuvant intervention to treat addiction

Abstract

Drug addiction is a chronic and relapsing disorder in which repeated drug exposure compromises brain neuroplasticity. Brain areas normally involved in learning and goal-directed behaviors become corrupted, which may lead to cognitive deficits that coexist with other addiction symptoms and predict a worse treatment outcome. New learning experiences that are not motivated by drugs may improve both cognitive deficits and drug-induced symptoms by promoting adaptive neuroplastic changes that could alleviate or reverse those involved in addiction. The present review will focus on whether potentiating healthy cognitive function, either by formal cognitive training or non-drug related environmental experiences, could exert beneficial effects in the therapeutics of addiction. Although additional studies are needed, the available clinical and preclinical evidence suggests that cognitive stimulation may provide a valuable adjuvant intervention in drug addiction.

Contents

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1. Introduction

Dependence-inducing drugs, including alcohol, are widely used in first world countries and entail significant health and socioeconomic burdens, such as the appearance of medical illnesses and infection diseases, deaths due to overdose, interpersonal problems, and involvement in illegal behaviors or accidents (EMCDDA, 2017; UNODC, 2017; WHO, 2014). This is aggravated by the fact that drug use may precipitate substance use disorders (SUD),

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a chronic and relapsing disease characterized by a loss of control of drug intake, despite negative life consequences.

Drug addiction can be viewed as a drug-induced neuroplastic disorder where the drug, acting on a vulnerable brain, compromises the function of numerous brain regions, including those involved in normal learning and memory **(section 2)**. Interestingly, both the drug-induced neuroadaptations and clinical symptoms may be (at least partially) reversed by protracted drug abstinence, suggesting that the brain still holds significant neuroplastic and regenerative abilities, enabling natural recovery [e.g. (Bates et al., 2013b; Connolly et al., 2013; Kril and Halliday, 1999; Sullivan et al., 2000; Vonmoos et al., 2014), **section 3.1.**]. Therefore, a primary concern is that patients with SUD may not have the capacity or resources to refrain from drug use to allow enough time-dependent healing. In fact, relapse may occur soon after completing treatment, usually within the first three months (Brown et al., 1989; Ferguson et al., 2005; Gossop et al., 2002; Hunt et al., 1971). In this Special Issue, we explore whether promoting experience-dependent recovery by cognitive stimulation could be a valuable addition in the therapeutics of SUDs. Cognitive training is a non-pharmacological intervention which involves guided practice on a set of tasks designed to train particular cognitive functions. In clinical settings, these tasks can be presented in paper and pencil or in computerized form.

This type of intervention could be a valuable addition in the therapeutics of SUD, thereby achieving new adaptive learning and strengthening alternative neural pathways that may compete with those engaged by drug addiction. After reviewing the effect of addictive drugs on cognition-related brain regions **(section 2)**, this review will discuss the etiology of cognitive deficits in patients with SUD and their relevance to SUD treatment outcome **(section 3)**. Lastly, we will review both preclinical **(section 4)** and clinical evidence **(section 5)** on the effects of cognitive stimulation on addiction-related symptoms.

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2. Disturbance of cognition-related brain regions in SUD

The initial experience with addictive drugs activates 'normal' learning and memory mechanisms, since the mesolimbic system –a main substrate for reward and motivated behavior- is widely interconnected with cognition-related limbic regions (Castilla-Ortega et al. 2016) **(Fig. 1).** In this way, the learning of memories for drug-stimuli associations encompasses action of the hippocampus and the amygdala (Castilla-Ortega et al., 2017; Castilla-Ortega et al., 2016; Day and Carelli, 2007; Everitt, 2014; Gremel and Cunningham, 2008; Hiroi and White, 1991; Milekic et al., 2006); while the prefrontal cortex regulates the initiation or inhibition of drug-seeking behaviors (Gourley and Taylor, 2016; Klenowski, 2018; Peters et al., 2009; Peters et al., 2013) **(Fig. 1)**. Nevertheless, chronic drug experiences are associated to widespread neuroplastic alterations that compromise cognitive processes. While we will focus on the limbic regions, it should be made clear that the effects of dependence-inducing drugs are not limited to these areas but they affect the whole brain. In fact, both functional and structural brain abnormalities in patients with SUD are reported, even at the macro-structural level (Battistella et al., 2014; Brody et al., 2004; Ersche et al., 2013b; Kril and Halliday, 1999; Sutherland et al., 2012; Thompson et al., 2004; Volkow et al., 2003).

Focusing on the limbic regions, reduced gray matter volume and neuronal loss have been documented in the prefrontal cortex, amygdala, and hippocampus in chronic drug users [e.g. alcohol: (Brust, 2010; Harper, 1998, 2009; Kril and Halliday, 1999); cannabinoids: (Battistella et al., 2014; Schacht et al., 2012); cocaine: (Barros-Loscertales et al., 2011; Castilla-Ortega et al., 2016; Ersche et al., 2011a; Fein et al., 2002; Makris et al., 2004); methamphetamine: (Mackey and Paulus, 2013; Orikabe et al., 2011; Thompson et al., 2004); nicotine: (Brody et al., 2004; Durazzo et al., 2013; Gallinat et al., 2006); opioids: (Liu et al., 2009; Upadhyay et al., 2010)]. Furthermore, a widely dysregulated expression of genes involved in neuroplasticity, specifically GABA and glutamate neurotransmission, are detected in in *post-*

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mortem samples (Enoch et al., 2014; Enoch et al., 2012; Liu et al., 2006). Preclinical research has supported the existence of wide brain neuroadaptations in drug-exposed animals, compared to their drug naïve counterparts. *In vivo* brain imaging in rodents, confirms that both structural brain changes induced by drugs (Vetreno et al., 2017; Wheeler et al., 2013) and a marked drug-induced modulation of brain functional activity and connectivity include the hippocampus, the amygdala, and the prefrontal cortex [alcohol: (Perez-Ramirez et al., 2017); cocaine: (Febo et al., 2009; Febo et al., 2005; Marota et al., 2000; Nicolas et al., 2017; Taheri et al., 2016); methamphetamine: (Dixon et al., 2005; Taheri et al., 2016); nicotine: (Li et al., 2008); opioids: (Chen et al., 2018)]. Importantly, these drug-induced functional signals are modified (i.e., either sensitized or blunted) after repeated drug exposures and withdrawal (Febo et al., 2009; Febo et al., 2005; Li et al., 2008; Nicolas et al., 2017), evidencing neuroadaptation. A *post-mortem* brain analysis of rodents exposed to addictive drugs shows neuroplastic changes in limbic regions, affecting their anatomy, neurochemistry, and the expression of inflammatory, neuroplastic, and brain damage-related markers (Bachis et al., 2017; Bengoechea and Gonzalo, 1991; Castilla-Ortega et al., 2017; da-Rosa et al., 2012; Ladron de Guevara-Miranda et al., 2017; Lundqvist et al., 1995; Obernier et al., 2002; Robinson and Kolb, 2004; Vetreno et al., 2017; Zhu et al., 2016).

Aberrant neuroplasticity in the brain limbic regions contributes to both initiation and maintenance of SUDs. The formation of drug seeking habits has been given a central role in relapse in drug use, because the presence of drug-associated stimuli (e.g., places of usual drug consumption, people involved in drug experiences, drug paraphernalia, internal signals, etc.) may automatically trigger drug intake as well as intense desire for the drug (i.e., '*craving*') (Belin and Everitt, 2008; Everitt, 2014; Everitt and Robbins, 2005, 2013; Gerdeman et al., 2003) **(Fig. 1).** An impaired function of the prefrontal areas contributes to formation of drug seeking habits (Chen et al., 2013; Jentsch and Taylor, 1999; Limpens et al., 2015; Renteria et al., 2018), since the initially conscious and planned goal-directed responses progressively become compulsive and uncontrollable striatal habits (i.e., sensory-motor

associations) as the prefrontal cortex 'losses control' (Belin and Everitt, 2008; Everitt, 2014; Everitt and Robbins, 2005, 2013; Gerdeman et al., 2003).

Moreover, impairment in the limbic regions contributes to the persistence of the maladaptive memories for drug-associated stimuli that are engrained and highly resistant to extinction and forgetting (Cleva, 2010; Hyman, 2005; Torregrossa et al., 2011). According to preclinical models, both the hippocampus and the amygdala not only promote the acquisition but also the long-term maintenance (retrieval) of drug-related memories (Castilla-Ortega et al., 2017; Castilla-Ortega et al., 2016; Gremel and Cunningham, 2008; Hiroi and White, 1991; Milekic et al., 2006), their reconsolidation (Wells et al., 2011) and their reinstatement ('relapse') (Bossert et al., 2013; Castilla-Ortega et al., 2017; Castilla-Ortega et al., 2016; See et al., 2003; Sharp, 2017) **(Fig. 1)**. Subsequently, collaboration of these regions with the prefrontal cortex is required in order to extinguish such memories when the drug is no longer paired with the conditioned stimulus (Cleva, 2010; Hitchcock and Lattal, 2018; Oliva et al., 2017; Peters et al., 2009; Schroeder and Packard, 2004). In support of this evidence, exposure to drug-associated cues consistently increases functional activity in the prefrontal cortex, the amygdala, and the hippocampus in both rodents [assessed by immediate early gene expression (Chauvet et al., 2011; Harris and Aston-Jones, 2003; Hill et al., 2007; Liu et al., 2014; Rivera et al., 2015)] and drug users (assessed by functional neuroimaging), in whom limbic functional activation correlates with drug *craving* scores and relapse probability [alcohol: (Grusser et al., 2004; Myrick et al., 2004); cannabinoids: (Goldman et al., 2013); cocaine: (Childress et al., 1999; Fotros et al., 2013); nicotine: (Franklin et al., 2007); opioids: (Langleben et al., 2008)].

Finally, malfunction of the learning system in addiction is frequently associated with a variable degree of cognitive impairment **(Table 1; Section 3)** that may affect also affect SUD clinical outcome **(Section 3.2.).**

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3. Cognitive impairment in substance-use disorder (SUD)

As discussed in the previous section, brain regions and processes that underlie addiction overlap extensively with those that are involved in essential cognitive functions. The prefrontal cortex is the locus of personality (Chow, 2000) and it 'rules' behavior by performing executive functions such as decision-making, planning, reasoning, or behavioral control, which includes inhibition of behavior and behavioral flexibility (Barbas and Zikopoulos, 2007; Chow, 2000; Szczepanski and Knight, 2014). It also holds attentional processes (Clark et al., 2015) and an active short-term memory storage for manipulating information *online* known as 'working-memory' (Funahashi, 2017) (**Fig. 1**). The hippocampus supports processing (i.e., learning, long-term storage, retrieval, re-consolidation, extinction, and updating) of declarative memory that encompasses the semantic memory (i.e., verbal memory, general knowledge, facts, and concepts), the episodic memory (i.e., memory for life events integrating the what, when, and where, aspects) and the spatial memory (i.e., topographical orientation) (Squire, 1992; Tulving and Markowitsch, 1998) (**Fig. 1**). There is a wide body of evidence showing that cognitive deficits associated to drug use involve both prefrontal and hippocampal-dependent cognitive domains (**Table 1**). Nonetheless, it is interesting to mention that a recent critical review focused on the effects of cocaine use on cognition reports methodological limitations in these type of studies (e.g., lack of appropriately matched control group and no comparison to normative data), as well as a certain language bias that emphasizes the 'abnormalities' found in the SUD group (Frazer et al., 2018). Thus, while evidence of cognitive impairment in SUD is abundant, data must still be interpreted with certain caution.

In relation to this, cognitive deficits associated with SUD may strongly vary in severity across patients. Some studies report affectation of specific domains while others are preserved [e.g. alcohol: (Fama et al., 2004; Jones and Parsons, 1972); cannabis: (Grant et al., 2003; Manschreck et al., 1990; Nusbaum et al., 2017); opiates: (Wang et al., 2008); **Table 1**].

Additionally, more severe cases seem better characterized by a global cognitive impairment across several different functions [e.g. alcohol: (Alarcon et al., 2015; Fitzpatrick and Crowe, 2013); amphetamine: (Kalechstein et al., 2003; Scott et al., 2007); cannabis: (Bolla et al., 2002); cocaine: (Spronk et al., 2013; Vonmoos et al., 2013; Vonmoos et al., 2014); opiates: (Rapeli et al., 2007); **Table 1**]. As discussed in the following, a complex diversity across patients with SUD may be explained by both their previous vulnerability traits and their drug use patterns.

3.1. Cognitive deficits in patients with SUD: Cause or consequence of drug use?

A relevant question regarding the relationship between cognition and addiction is whether the cognitive attributes in patients with SUD are caused by the drug-induced brain neuroplasticity **(section 2)** or that they precede drug exposure, entailing a 'vulnerability' factor to engage in chronic drug use and/or addiction. SUD-vulnerability behavioral traits are assumed to have biological correlates, reflecting dysfunction in the cognition-related areas involved in the brain addiction circuitry **(section 2, Fig. 1)**, which will make a person more prone to drug use or to respond to drugs in a maladaptive way, explaining individual differences in the risk of developing a SUD (Ersche et al., 2012a; White, 2017). Accordingly, not every drug user develops a SUD, which is prevalent in approximately 11% of drug-using individuals (UNODC, 2017)].

A genetic vulnerability for SUDs is evidenced by family studies (Ersche et al., 2013a; Kendler et al., 2012). For instance, the risk for drug abuse is significantly elevated in the adopted offspring of biological parents with SUD (Kendler et al., 2012). Nevertheless, it is well known that both genetic and environmental sources of risk (adoptive parental history of divorce, death, criminal activity, among others) are involved in SUD etiology. Other individual factors for SUD vulnerability include behavioral traits and cognitive attributes. An interesting study performed by Ersche et al. characterized an anxious-impulsive endophenotype related to

SUD, identifying deficits in response inhibition –i.e. the suppression of actions that are inappropriate in a given context and that interfere with goal-driven behavior (Mostofsky and Simmonds, 2008)- and impulsive traits in both the stimulant-dependent individuals and in their non-drug-dependent siblings (Ersche et al., 2012b). Moreover, response inhibition and other measures of executive function may be impaired in adults and children with family histories of alcohol, despite not having issues with alcohol use (Acheson et al., 2011; Nigg et al., 2004). In longitudinal prospective studies, attention-deficit hyperactivity disorder in children (Molina and Pelham, 2003) or executive measures in healthy individuals, such as disadvantageous decision-making (Bo et al., 2017; Goudriaan et al., 2011) or behavioral disinhibition [assessed either by performance-based neuropsychological tests (Groenman et al., 2015; Nigg et al., 2006) or by a 'disinhibition' subscale included in the Zuckerman's Sensation-Seeking Scale (Cadet and Bisagno, 2015; Clapper et al., 1994; Pedersen, 1991; Sher et al., 2000; Zuckerman et al., 1964)] may predict future drug use or abuse. Furthermore, in laboratory studies where healthy volunteers were administered the drug, positive subjective effects often correlated with measures of the sensation-seeking disinhibition subscale (Hutchison et al., 1999; Perkins et al., 2000; Zacny, 2010). Hence, we must consider pre-existing cognitive traits, especially those involving weakness in prefrontal-related executive functions and behavioral control, as risk factors that could facilitate drug use.

Likewise, there is a wide body of literature indicating that cognitive deficits in SUD largely reflect drug-induced impairment. In this regard, the amount of drugs consumed (i.e., grams per week) and/or the duration of drug use (i.e., age of drug use onset or total years of drug intake) are habitual predictors of both the magnitude of structural brain abnormalities (Battistella et al., 2014; Connolly et al., 2013; Harding et al., 1996; Mackey and Paulus, 2013; Yuan et al., 2009) and the severity of cognitive dysfunction (Battisti et al., 2010a; Battisti et al., 2010b; Bolla et al., 2002; Bolla et al., 1999; Goriounova and Mansvelder, 2012; Hanson et al., 2011; Lopes et al., 2017; Madoz-Gurpide et al., 2011; Mashhoon et al., 2018; Solowij

et al., 1995; Vonmoos et al., 2013; Vonmoos et al., 2014). Importantly, aberrant neuroadaptations (Connolly et al., 2013; Garavan et al., 2013; Korponay et al., 2017; Kril and Halliday, 1999; Wang et al., 2012a) and cognitive impairment (Adams et al., 1980; Bates et al., 2005; Brandt et al., 1983; Drake et al., 1995; Fein et al., 2006; Forsberg and Goldman, 1985; Forsberg and Goldman, 1987; Hanson et al., 2010; Pitel et al., 2009; Pope et al., 2001; Rapeli et al., 2006; Rapeli et al., 2005; Rezapour et al., 2016; Schafer et al., 1991; Stavro et al., 2013; Sullivan et al., 2000; Vonmoos et al., 2014) frequently demonstrate complete or partial recovery after some duration of ceasing or reducing drug use. This time-dependent rehabilitation strongly supports the existence of detrimental effects caused by the sustained action of addictive drugs on both the brain and cognition.

Nevertheless, it is also true that studies may occasionally report cognitive deficits that do not seem to be ameliorated by protracted drug abstinence (Block et al., 2002; Medina et al., 2007; Medina et al., 2004; Rezapour et al., 2016; Solowij, 1995; Yohman et al., 1985), which may yield ambiguous and complex interpretations. The effects of certain drug use patterns on the brain could be beyond recovery, such as in the case of heavy alcohol consumption [that may induce neurotoxicity and lasting dementia (Bates et al., 2002; Brust, 2010; Goldman, 1990)] or the initiation of drug use at an early age, when the brain is still developing (Schneider, 2008). Alongside this, it is not possible to rule out that some of the persistent cognitive symptoms were present prior to drug use. Even in studies that report restoration of cognition by abstinence, pre-existing individual differences may contribute to the ability to stop using drugs. Finally, it is also possible that cognitive deficits are indeed a consequence of addiction but not directly caused by the neurobiological actions of drugs. Socio-economic factors contribute to the risk for drug use (Hawkins et al., 1992) but they are also modulated by drug addiction. For example, social exclusion may be aggravated in patients with SUD and have a deleterious impact on mental health, including cognitive function (Baumeister et al., 2002; Otten and Jonas, 2013; Xu et al., 2017; Xu et al., 2018).

Considering that human studies may not answer these questions, preclinical research is a valuable tool, since it allows the experimenter to control for drug exposure. Interestingly, studies of animal models have supported both pre-existing and drug-induced cognitive features associated with addiction. Several cognitive-like traits in drug naïve animals [e.g., increased risk assessment or taking: (Momeni et al., 2014; Palm et al., 2014); high response to novelty: (Belin et al., 2011; Falco and Bevins, 2015); disadvantageous decision-making: (Ferland and Winstanley, 2017); reduced behavioral flexibility: (Istin et al., 2017); increased impulsivity: (Falco and Bevins, 2015; Jupp et al., 2013; Winstanley et al., 2010); worse spatial memory performance: : (Zhu et al., 2015)] predict their subsequent sensitivity to a drug's neurobiological or behavioral actions. Alternatively, chronically exposing rodents to addictive drugs (administered by the experimenter or self-administered at its will) induces lasting cognitive impairments evidenced in hippocampal-dependent memory tasks, such as spatial navigation or object recognition (Brolin et al., 2018; Garcia-Moreno and Cimadevilla, 2012; Kamei et al., 2006; Ladron de Guevara-Miranda et al., 2017; Lipaus et al., 2018; Tramullas et al., 2008), as well as in prefrontal functions, such as impulsivity or response inhibition, behavioral flexibility, risk taking, and decision-making (Boutros et al., 2014; Dandy and Gatch, 2009; Hankosky and Gulley, 2013; McMurray et al., 2014; Seip-Cammack and Shapiro, 2014).

Taken together, the relationship between neurocognitive impairment and drug use is likely bidirectional, with certain biologically based cognitive profiles contributing to risk for drug use or addiction, and drug use further disrupting brain neuroplasticity and cognitive function. Nevertheless, the extent to which cognitive deficits are pre-existing or induced by drug consumption may not reduce the interest of cognitive training for the treatment of SUD.

3.2. Relevance of cognitive deficits for SUD treatment outcome

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One of the key challenges in drug dependence research is determining who is at risk of relapse. Dropout from treatment has long been identified as a major obstacle (Sayre et al., 2002; Simpson et al., 1997), and even after completion, effective psychosocial therapies are associated with relapse rates of 60 to 70% in post-treatment follow-ups (Bisaga et al., 2010; Dutra et al., 2008; Knapp et al., 2007). Predictors of drug relapse include socio-demographic factors, psychiatric or medical comorbidities, and population-specific clinical characteristics such as lower socio-economic support, personality disorders, alcohol use, stress reactivity, craving, and low self-efficacy (Back et al., 2010; García-Fernández et al., 2011; McKay et al., 2005; McMahon, 2001; Reske and Paulus, 2008).

Recently, cognition has been successfully incorporated to predict SUD treatment retention, as cognitive impairment is one of the most consistent risk factors for addiction treatment drop-out identified across studies (Bates et al., 2013b; Brorson et al., 2013). For instance, performance in a variety of cognitive domains (attention, reasoning, verbal memory, spatial processing, etc.) are significant predictors of addiction treatment completion and attendance at follow-ups (Aharonovich et al., 2008; Aharonovich et al., 2006; Aharonovich et al., 2003; Streeter et al., 2008; Teichner et al., 2002; Turner et al., 2009; Verdejo-Garcia et al., 2014; Verdejo-García et al., 2012). Furthermore, cognitive measures may also predict relapse, since patients with SUD with impairments in verbal memory and executive skills, such as decision-making, are more likely to resume drug use (Bates et al., 2006; Fox et al., 2009; Passetti et al., 2008; Verdejo-Garcia et al., 2014; Wehr and Bauer, 1999). Despite interest, the clinical implications of these findings have received limited attention, due to variability across individuals and type of drug, as well as the reversibility of some cognitive deficits after an extensive period of abstinence (Block et al., 2002; Vonmoos et al., 2014).

There are several and non-exclusive avenues by which cognitive decline may contribute to SUD treatment drop-out and relapse. Cognitive deficits may correlate with malfunction of limbic brain regions that are also implicated in drug related memories, emotional regulation

and craving, and which are also functionally connected to other addiction-related brain areas involved in habit and reward **(section 2)**. In fact, the neural activation pattern during cognitive tasks may be a more sensitive predictor of SUD treatment response than cognitive performance itself (Brewer et al., 2008). Cognitive performance may, therefore, be used as a correlate or marker of underlying brain alterations and/or additional behavioral impairments relevant to drug addiction. Additionally, cognitive decline may hamper SUD treatment because engaging in therapeutic change and assimilating behavioral interventions demand cognitive effort. For example, evidence-based therapies (such as cognitive behavioral therapy, exposure-based therapies, motivational-enhancement therapy, or contingency management) require the same set of cognitive skills that may be impaired in SUD, including attention, reasoning, decision-making, planning or memory, and learning skills (Aharonovich et al., 2006; Brorson et al., 2013; Perry and Lawrence, 2017; Torregrossa et al., 2011). Even motivation, the first step toward change, is highly correlated with cognitive functions such as abstraction, learning, and memory, and also with general intellectual functioning (Blume et al., 1999). Better cognitive functioning may also promote social inclusion and support (Lee et al., 2013), which has important health implications. Finally, the major review of Sofuoglu et al. (2016), remarked an association between cognitive deficits and psychiatric comorbidities in SUD, which are predictive of poor treatment retention and clinical outcomes.

In conclusion, neuropsychological assessment in the treatment of SUD may be useful to identify patients with significant cognitive impairment that would have a higher probability of a negative treatment outcome. Likewise, these patients may have specific treatment needs, and may benefit from including cognitive-enhancing approaches within the SUD treatment intervention (Sofuoglu, 2010).

4. Preclinical evidence: New experiences reshape addiction-related neuroplasticity and behavior

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4.1. Cognitive training in animal models of addiction: A breach between preclinical and clinical studies

As discussed in the following **(section 5)**, clinical research has focused on strengthening a specific or several cognitive functions in patients with SUD, normally by structured cognitive training, to assess its effect on cognition and/or SUD treatment outcome. Unfortunately, preclinical research has not mirrored this approach and there is scarce evidence on how training animals in structured cognitive tasks (i.e., spatial navigation, object recognition, working memory, etc.) may affect addiction-like features. Two common animal models to assess addiction-related behaviors are the drug self-administration paradigm and the drug-induced conditioned place preference (CPP) paradigm (**Fig. 2**).

Since a defective cognitive performance is proposed as a vulnerability factor for drug addiction **(section 3.1.)**, rodents may be trained in cognitive abilities *before* being exposed to a drug of abuse. A recent work (Boivin et al., 2015) has evidenced that training in a complex cognitive task (involving stimuli discrimination, associative memory, cognitive flexibility, and inhibitory control of behavior in order to obtain a food reward) reduced the preference for a context associated to cocaine in a subsequently acquired CPP paradigm. Consequently, a key report has demonstrated the effects of cognitive training applied *after* the animals had been exposed to drugs (Baratta et al., 2015). Cocaine-withdrawn rats trained in an operant task (consisting of rotating a wheel to terminate an electric tail shock) accelerated subsequent extinction of cocaine self-administration through increased activation of the prefrontal cortex that is involved in behavioral control and inhibition (Baratta et al., 2015). This supports that different memory systems in the brain are in competition; therefore, strengthening neural pathways involved in goal-directed and 'normal' learning may debilitate the striatal control over compulsive drug seeking behavior, alleviating addiction-like responses (Goodman and Packard, 2016). However, relapse in cocaine-self administration was not prevented by training abstinent animals in a reversal learning task, which also depends on the prefrontal

cortex (Bechard et al., 2018). This may suggest a relevance of the specific cognitive demands involved in the training protocol, considering that animals in this study were tested at short memory retention periods and the task was relatively simple and based on egocentric orientation –i.e. learning to always turn their body in the same direction when choosing between two possible paths on a T-shaped maze-; probably requiring a low memory engagement.

New learning experiences engage wide brain neuroplastic changes -which may be especially evident in the limbic regions- that are a potential mechanism for cognitive training to modulate addiction-related behaviors. The prefrontal cortex undergoes synaptic reorganization and functional connectivity changes after training animals in tasks that involve acquisition of operant responses, associative memory processing, memory extinction, stimuli discrimination, reversal learning, spatial memory and/or working memory functions (Comeau et al., 2010; Baratta et al. 2015; Hugues and Garcia, 2007; Kolb et al., 2008; Kolb and Gibb, 2015; Schoenbaum et al., 2000). The hippocampus is another brain region where neuroplasticity has been extensively evidenced after cognitive training paradigms. For example, trained animals usually enhance adult hippocampal neurogenesis and regulate hippocampal levels of neurotransmitters and neuroplasticity markers (e.g. monoamines, neurotrophins and others), inducing synaptic modifications such as long-term potentiation (Bekinschtein et al. 2010; Castilla-Ortega 2017; Kutlu and Gould, 2016; Sampedro-Piquero et al., 2018). Interestingly, these hippocampal learning mechanisms overlap with those hijacked by addictive drugs (**Section 2**.; Goodman and Packard, 2016; Castilla-Ortega et al. 2017; Kutlu and Gould, 2016), which leads to propose that neuroplasticity induced by drugs may be reverted by new learning experiences.

In relation to this, initial preclinical evidence shows that cognitive training can trigger brain neuroplasticity in drug-withdrawn animals, though not as strongly as in a drug naïve condition. A behavioral assessment including spatial reference memory training in the water maze and

motor skills learning produced wide dendritic changes in the prefrontal cortex and nucleus accumbens of mice exposed to nicotine prenatally (Muhammad et al., 2013). However, approximately one third of these neuroplastic responses variated (mostly blunted their magnitude compared to trained controls) as result of the previous nicotine exposure (Muhammad et al., 2013). This coincides with data from mice withdrawn from cocaine. After completion of a large behavioral test battery (including training in object recognition, working, and associative memory) the cocaine-withdrawn mice showed notably worse cognitive performance and their experience-dependent plasticity was reduced in their hippocampus compared to their control counterparts (Ladron de Guevara-Miranda et al., 2017). It is unclear whether the altered neuroplasticity prevented learning, or the reduced learning abilities blunted the neuroplastic changes (Dalla et al., 2007). In any case, drug-withdrawn animals still showed some experience-dependent neuroadaptations (Ladron de Guevara-Miranda et al., 2017), suggesting that prolonged training may exert behavioral changes in the long-term, despite their initially low learning performance.

While additional evidence is undoubtedly necessary, preliminary preclinical data points out that cognitive training may protect from or alleviate the neurobehavioral consequences of drugs. Further preclinical research on the effect of structured cognitive training in animal models of addiction (ideally comparing trained animals with pseudotrained animals that received similar manipulation and exposure to the maze, but without learning demands) could provide a valuable tool for a better understanding of the available data on cognitive training in patients with SUD.

4.2. Insights from the environmental enrichment (EE) paradigm

4.2.1. The preclinical EE protocol: Some concerns and caveats

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Most preclinical research on how cognitive-engaging experiences modulate addiction-related behaviors has focused on the EE paradigm. The fact that environmental complexity and external environmental manipulations affect both the brain and behavior started to be investigated in the sixties and it was widely acknowledged in the late eighties (Renner and Rosenzweig, 1987; Rosenzweig et al., 1967). Since then, neuroscience has investigated the beneficial impact of EE on numerous health and disease conditions, usually exerting wide brain neuroplasticity and facilitating 'desirable' behavioral outcomes, including potentiated memory and emotional regulation (Fischer, 2016; Frick and Benoit, 2010; Hirase and Shinohara, 2014; Mora et al., 2007; Olson et al., 2006; Pang and Hannan, 2013; Simpson and Kelly, 2011; van Praag et al., 2000).

While defining what may be considered an 'enriched environment' for patients' daily life is difficult, EE in a preclinical setting normally consists of a large home cage full of 'friends and toys', allowing for more opportunities for sensory and social stimulation in contrast with impoverished housing (van Praag et al., 2000). Enriched rodents are then provided with a large group of cage companions (usually of the same sex) and a bigger and more complex cage to explore, containing several objects or 'toys' to examine, play, and/or chew (e.g., nesting material, plastic toys, and wood pieces) which are re-arranged in location and/or replaced by new objects several times a week to maintain novelty and curiosity (Simpson and Kelly, 2011; van Praag et al., 2000) **(Fig. 3A)**.

Nonetheless, the EE research holds important caveats. Potentially the most significant issue is the difficulty to elucidate which of the observed outcomes may be specifically attributed to each component of the paradigm; EE is a complex mix of cognitive, sensorial, social elements, and even physical activity. This is especially true in numerous studies that included voluntary running (i.e., free access to running wheels) in their EE setting -in the following referred to as 'EE+running' protocols- (Simpson and Kelly, 2011; van Praag et al., 2000); because voluntary running by itself has potent neurobehavioral actions (Greenwood et al.,

2011; Kobilo et al., 2011; Vivar et al., 2013). Since we intend to focus on the cognitive-like aspects of EE, in the following we will lay emphasis on EE, rather than on EE+running studies. It should be noted that, even in EE settings that do not include running wheels, physical activity remains a confounding factor, because the bigger and more complex home cages facilitate the activity of rodents. The method to disentangle the effects of each element that comprises EE would be providing the control group with a mostly identical setting that only varies in the presence of the specific stimuli of interest. However, EE experiments frequently use a control group that is housed in very different and impoverished conditions (i.e., isolated animals in empty cages) compared to EE animals (Simpson and Kelly, 2011). This sometimes calls into question whether the effects of EE, or rather the effects of stimuli deprivation, are being studied. Another caveat is that animals are exposed to the enriched setting, but measures of performance or interaction (e.g., amount of running, object exploration and social contacts) are rarely provided. Finally, the diversity of EE and EE+running protocols employed among laboratories [i.e., variation in duration, housing conditions, age of the animals, or control groups used (Simpson and Kelly, 2011)] may explain the existence of dissimilar results.

Nevertheless, while considering the difficulty of isolating the specific contribution of the 'cognitive' component, the cognitive-challenging environment created by EE protocols have provided consistent evidence in the experience-dependent modulation of drugs.

4.2.2. EE protects from addiction-related behaviors

Some studies have investigated the value of EE as a way of *preventing* drug effects by exposing EE housed animals to drugs of abuse (i.e., EE is applied *before* and/or *while* experiencing the drug). Compared to controls, EE animals frequently show altered responsiveness to the activating and sensitizing psychomotor effects of the drugs, though there is not yet a consensus on whether these responses are either enhanced or decreased

[increased motor stimulant response: cocaine: (Boyle et al., 1991); methamphetamine: (Bowling and Bardo, 1994; Fukushiro et al., 2012; Gehrke et al., 2006); nicotine: (Gomez et al., 2015); decreased: cocaine: (Smith et al., 2009); methamphetamine: (Fukushiro et al., 2012); nicotine: (Adams et al., 2013; Green et al., 2003; Hamilton et al., 2014)].

Independent of the locomotor effects, it is important that literature agrees, in that EE housed animals are usually less willing to experience drugs, as they engage in less voluntary ethanol drinking and drug self-administration behaviors than their control counterparts [reduced voluntary alcohol drinking: (Bahi, 2017; Deehan et al., 2011; Holgate et al., 2017; Lopez and Laber, 2015; McCool and Chappell, 2009); reduced drug self-administration: alcohol: (Deehan et al., 2011; McCool and Chappell, 2009; Schenk et al., 1990); cocaine: (Boyle et al., 1991; Gipson et al., 2011; Puhl et al., 2012; Schenk et al., 1987; Yajie et al., 2005; Yates et al., 2017); methamphetamine: (Bardo et al., 2001; Green et al., 2002; Hofford et al., 2014; Meyer and Bardo, 2015; Stairs et al., 2006); nicotine: (Gomez et al., 2015; Venebra-Munoz et al., 2014); opioids: (Hofford et al., 2017)] **(Fig. 3C)**. Interestingly, the reduced drug intake was found either in animals that were exposed to the drug after experiencing an EE period (Bahi, 2017; Deehan et al., 2011; Gomez et al., 2015; Lopez and Laber, 2015; McCool and Chappell, 2009; Schenk et al., 1990; Yajie et al., 2005) and in animals that were exposed to the drug while experiencing EE (Bardo et al., 2001; Boyle et al., 1991; Gipson et al., 2011; Hofford et al., 2014; Hofford et al., 2017; Holgate et al., 2017; Schenk et al., 1987; Stairs et al., 2006; Venebra-Munoz et al., 2014). Some divergent results have been reported by studies that found either reduced or unchanged drug intake after EE [voluntary ethanol intake: (Fernandez-Teruel et al., 2002) or cocaine self-administration (Hofford et al., 2015; Phillips et al., 1994; Smith et al., 2009)]; but overall findings support a role of experience-dependent stimulation in the etiology of drug addiction and vulnerability, so EE would be a protective factor for engaging in drug use. Interestingly, EE+running and even running alone are also generally considered protective interventions against drug self-administration responses in

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animal models, similar to EE (Laviola et al., 2008; Lynch et al., 2013; Mesa-Gresa et al., 2013; Pang et al., 2018; Solinas et al., 2010).

It is unclear, however, whether a reduced drug intake in EE housed animals may be attributed to a reduced drug reward sensitivity. The acquisition of drug-induced CPP has been reported as either increased or reduced in animals conditioned after (or while) experiencing EE [unchanged CPP: cocaine: (Ribeiro Do Couto et al., 2009); reduced CPP: alcohol: (Bahi, 2017); cocaine: (Zakharova et al., 2009); methamphetamine: (Gehrke et al., 2006); increased CPP: cocaine (Smith et al., 2009); methamphetamine: (Bowling and Bardo, 1994); nicotine: (Ewin et al., 2015); opioids: (Smith et al., 2005); accordingly, mixed results are found for EE+running: unchanged CPP: (Galaj et al., 2017; Pautassi et al., 2017; Thiriet et al., 2011); reduced CPP: (de Carvalho et al., 2010; El Rawas et al., 2009; Freese et al., 2018; Nader et al., 2012); increased CPP: (Nader et al., 2012; Rae et al., 2018)].

It should be noted that studies using CPP are less numerous than self-administration studies, and differences among them are likely attributed to methodological disparities. For example, focusing on the studies using cocaine, Ribeiro Do Couto et al. (2009) –that found unchanged cocaine CPP after EE- used an EE protocol based on social stimuli only. Regarding Zakharova et al. (2009) –reduced cocaine CPP- and Smith et al. (2009) –increased cocaine CPP-, they employed both social and sensorial stimulation but they differed in key methodological factors such as the duration of the EE intervention (20 days or 42-56 days, respectively), the subjects studied (male Sprague-Dawley rats or female Long-Evans rats) or the CPP conditioning protocol. Regardig the EE+running studies using cocaine, Galaj et al. (2017) –unchanged cocaine CPP- housed both control and enriched rats in isolation, while others (Freese et al., 2018; Nader et al., 2012) –reduced cocaine CPP- maintained rodents in groups. The key work of Nader et al. (2012) stressed the importance of the duration of the enrichment protocol, since mice permanently housed in EE+running conditions showed reduced cocaine CPP, but their vulnerability to cocaine increased if mice were to lose

enrichment in adulthood (Nader et al., 2012). Finally, it is also worth mentioning that the CPP paradigm involves a cognitive-related component of associative memory **(Fig. 2)** which may lead to ambiguous results. Applying memory-enhancing interventions such as EE *before* acquiring drug CPP memories may potentiate the learning component of this task (Castilla-Ortega et al., 2017; Mustroph et al., 2011); while memory-impaired animals may be prevented to show CPP behavior independently of their sensitivity to the drug.

4.2.3. EE treats addiction-related behaviors

Importantly, EE has also been investigated as a *therapy* for drug addiction. This line of evidence may be in more agreement with the historic research of EE, as it was first studied as a 'cure' or 'treatment' to recover from disease conditions (Will et al., 2004).

This is accomplished by first exposing animals to the drug while they are housed in 'standard' conditions and subsequently performing EE, usually during a drug-withdrawal period (i.e., EE is applied *after* experiencing the drug). Such protocols proliferated after the seminal work of Solinas et al. (2008), which showed that addiction-like behaviors (i.e. cocaine-induced CPP) were reversed by when animals underwent EE+running (Solinas et al., 2008). Since then, EE+running has been attributed as a potent *anti-craving* action, since it consistently reduces drug-seeking responses when applied to animals previously exposed to different classes of drugs [e.g. CPP paradigm: (Chauvet et al., 2011; Galaj et al., 2017; Li et al., 2015; Solinas et al., 2008); self-administration paradigm: (Chauvet et al., 2012; Chauvet et al., 2009; Galaj et al., 2016; Gauthier et al., 2017; Sikora et al., 2018)]. However, results in these experiments may be attributed specifically to the 'running' component, because voluntary wheel running is enough to reduce both drug self-administration and CPP responses (reviewed in Lynch et al., 2013). Unfortunately, fewer studies have tested whether EE in absence of running affects previously acquired addiction-like responses, but currently available data supports EE as a worthy therapeutic intervention for drug addiction. For example, mice that lived isolated in a

deprived environment preferred to drink alcohol over water, but they markedly reduced their preference for ethanol after they were moved to a more complex environment that allowed social interaction opportunities (Holgate et al., 2017). Rodents that self-administered cocaine and were then submitted to social or novel enrichment during a withdrawal period displayed less cocaine seeking when they returned to the self-administration chamber (i.e., they faced a cocaine-associated context), and were faster to extinguish the self-administration behavior and reduced drug-induced 'relapse' (Li and Frantz, 2017; Ranaldi et al., 2011) **(Fig. 3C)**. Accordingly, the preference for the compartment, paired with cocaine in a CPP apparatus, was reinstated less and/or extinguished faster after an abstinence period living in EE conditions (Mustroph et al., 2016; Ribeiro Do Couto et al., 2009).

4.2.4. Potential mechanisms for EE to modulate drug addiction

Abundant evidence demonstrates that EE exposure notably sculpts the whole brain **(Fig. 3B)**, triggering neuroplasticity in regions involved in reward, habits, emotional regulation, and cognitive performance. Thus, while both novelty exploration and social activity may be considered cognitively-engaging components of EE, they are also motivational and emotional events. Both novelty and social interaction are natural rewarding experiences for rodents (Bevins and Bardo, 1999; Calcagnetti and Schechter, 1992) and activate the mesolimbic system as well as limbic brain regions. Novel stimuli enhance dopaminergic transmission and functional activity in the hippocampus, which is strongly involved in novelty detection (Knight, 1996), as well as in the nucleus accumbens, dorsal striatum, prefrontal cortex, and amygdala (Blackford et al., 2010; Bunzeck and Duzel, 2006; Feenstra and Botterblom, 1996; Menegas et al., 2017) **(Fig. 3A,B)**. Regarding social stimulation in rodents, pro-social communicative signals (e.g., certain ultrasonic vocalizations in rats or social play) increase levels of dopamine and other monoamines in the nucleus accumbens to elicit social reward (Dolen et al., 2013; Vanderschuren et al., 1997; Willuhn et al., 2014), while the limbic regions participate in controlling social interactions and social cognition, such as in recognizing a

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familiar individual (Felix-Ortiz and Tye, 2014; Ko, 2017; Kogan et al., 2000). Accordingly, chronic exposure to EE involves numerous brain neuroadaptations, including the nucleus accumbens and the dorsal striatum (Bowling et al., 1993; Lichti et al., 2014; Mychasiuk et al., 2014; Ravenelle et al., 2013; Wang et al., 2012b; Zhang et al., 2014) and the cognition-related limbic brain regions [amygdala: (Lambert et al., 2016; Lopes et al., 2018; Novaes et al., 2017; Wang et al., 2012b); prefrontal cortex: (Brenes and Fornaguera, 2008; Darna et al., 2015; Sampedro-Piquero et al., 2016; Wang et al., 2012b; Zhu et al., 2004); hippocampus: (Artola et al., 2006; Birch et al., 2013; Falkenberg et al., 1992; Gagne et al., 1998; Lopes et al., 2018; Mora-Gallegos et al., 2015; Olson et al., 2006); **Fig. 3B**]. In agreement with the different behavioral outcomes, the drug-induced brain correlates and neuroadaptations also vary in animals previously submitted to EE (Gill et al., 2014; Howes et al., 2000; Rahman and Bardo, 2008; Zhang et al., 2014).

Regarding voluntary wheel running, it is similar to EE in that it is a rewarding experience for rodents that improves cognitive performance and triggers whole brain neuroplasticity, including in the limbic regions (Greenwood et al., 2011; Hamilton and Rhodes, 2015; Zlebnik et al., 2014). The EE+running protocols also provide a wide number of neuroplastic adaptations that may resemble the findings found with EE only (Chauvet et al., 2011; Solinas et al., 2010) and, additionally, EE and EE+running have comparable effects in reducing drug seeking (**section 4.2.2**. and **section 4.2.3**.). Nonetheless, EE and running may involve both shared and dissociable neurobiological mechanisms (Fabel et al., 2009; Gregoire et al., 2018; Kobilo et al., 2011; Olson et al., 2006; Pang and Hannan, 2013), to the point that these interventions could have additive or complementary actions. For example, running increases the quantity of new neurons that are generated in the adult rodent hippocampus, while EE favors these neurons to survive and become integrated in the hippocampal circuitry; EE+running provides greater adult neurogenesis increases than either treatment separately (Fabel et al., 2009; Shors, 2014). Moreover, EE+running increases the number of dopaminergic midbrain neurons in the ventral tegmental area and substantia nigra more

effectively than running (Aumann et al., 2013) or EE alone (Wang et al., 2012b). The fact that the combination of both treatments may exert unique neurobehavioral consequences is an interesting topic that deserves further investigation to understand the interaction between cognitive stimulation and environmental or physical factors.

Considering that environmental enrichment widely exerts brain neuroplasticity entailing a complex mix of social, emotional, novelty stimulation, and eventually physical activity, the mechanisms by which EE (or EE+running) could affect drug-related responses are numerous and not mutually exclusive. Notably, mechanisms proposed here overlap with those first proposed by Solinas et al. (2010) in an exhaustive and comprehensive review (Solinas et al., 2010). First, since EE is a reinforcing experience, the rewarding value of drugs may be diminished, as alternative rewards are available in the enriched environment. The ability of non-drug rewards to reduce drug intake is evidenced in animals that would usually reduce drug self-administration when primary rewards, such a sweet solution, are provided as an alternative (Ahmed, 2005; Carroll et al., 2016; Carroll et al., 1989; Huynh et al., 2017; Solinas et al., 2010). In clinical research, occasional cocaine users would frequently choose money over experiencing the drug (Higgins, 1997), and increased frequency of non-drug enjoyable life events in patients with SUD predicts better treatment outcome (Van Etten et al., 1998).

Additionally, EE may also improve emotional regulation during drug withdrawal by reducing anxiety (Lopes et al., 2018; Ravenelle et al., 2013; Sampedro-Piquero et al., 2016) and depression-like responses (Ravenelle et al., 2013; Veena et al., 2009) while increasing stress resilience (Pang et al., 2018). Stress is a main risk factor for relapse in drug use, and the ability of environmental enrichment to modulate plasticity in stress-related areas –including the limbic regions- has leaded to propose EE-related interventions as a rehabilitation method for addiction, particularly for alcohol consumption (Pang et al., 2018). As a preventive strategy, environmental enrichment may attenuate the consequences of stressful life events in promoting drug vulnerability, as evidenced in animal models of maternal separation (Khalaji

et al. 2018). Influence of sex on the effects of EE is also a relevant issue that need more extensive studies. Skwara et al. (2012) have found that hormonal stress responses to nicotine withdrawal were reduced in EE female rats compared to males, suggesting that females are more sensitive to the anxiolytic effects of EE. Sex differences have also been reported in behavioral dyscontrol related to SUD and preclinical data suggests sex-dependent effects of EE on drug seeking behavior; so females seem more prone tan males to reduce drug intake when non-drug rewards are available (Carroll and Smethells, 2015).

Regarding the cognitive aspects, neuroadaptations in the limbic system induced by EE usually correlate with improvements in both prefrontal- and hippocampal-dependent cognitive functions (Birch et al., 2013; Falkenberg et al., 1992; Mora-Gallegos et al., 2015). Stimulating regions involved in goal-directed behavior, such as the prefrontal cortex, may help to regain control over the habitual drug seeking responses (Chen et al., 2013), increase behavioral flexibility (Sampedro-Piquero et al., 2015; Zeleznikow-Johnston et al., 2017) and reduce impulsive choices (Perry et al., 2008; Wood et al., 2006). An alleviation of the cognitive decline induced by drug use may also facilitate new learnings, including engagement in therapies that require a cognitive effort [e.g., the extinction of memories for drug-stimuli associations, since associative memory is extinguished faster after EE (Hegde et al., 2017)]. Finally, EE stimulates adult hippocampal neurogenesis. While the existence of this neuroplastic phenomenon is currently controversial in humans (Boldrini et al., 2018; Sorrells et al., 2018), research in rodent models suggest that the addition of new hippocampal neurons could benefit from the acquisition of new hippocampal-dependent learnings (Castilla-Ortega et al., 2011) while providing forgetting and clearance of previous memories, such as memories for drug-related experiences (Ladron de Guevara-Miranda et al., 2018). While not extinct of limitations, EE-dependent stimulation appears to be a valuable approach to modulate drug-induced altered cognition.

5. Clinical evidence: Cognitive training intervention in the therapeutics of SUD

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Despite cognitive impairment in drug users being described in numerous studies **(Table 1)** and its relevance in SUD treatment outcomes **(section 3)**, neuropsychological assessments are not a mandatory aspect in treatment programs due to time and resource consumption. Over the past 20 years, several cognitive approaches in SUD therapeutics have received empirical support and they could be used to complement existing intervention programs by targeting cognitive, emotional, and behavioral areas, as well as their brain correlates **(Table 2)**. In this review we focus on cognitive training, which consists of repetitive exercises, computerized or not, to strengthen memory, attention, planning, and other aspects of executive functioning. Through these designed exercises, cognitive training aims to improve behavior by promoting adaptive neuroplastic changes in impaired neural systems (Caeyenberghs et al., 2018; Galetto and Sacco, 2017). Cognitive training appears to be a promising treatment approach for several brain disorders. Thus, this type of therapy has been carried out in patients following brain injury (e.g., cerebral infarction), neurodegenerative conditions (e.g., Alzheimer's disease), developmental disorders (e.g., Attention Deficit Hyperactivity Disorder), and other neuropsychiatric disorders (e.g., schizophrenia, bipolar, or major depression) showing good and promising results (Cramer et al., 2011). Moreover, other cognitive-related interventions, such as music, art therapy, or more novel treatment approaches (e.g., mind-body practices, including mindfulness training and yoga) have shown to positively impact not only emotion regulation and stress management, but also cognitive measures and reduction of craving response **(Table 2)**.

Drug addiction may resemble an impoverished environment where drug-related stimuli are more relevant in the person's life compared to other natural rewards (Nader et al., 2012). In this regard, most of the existing addiction treatment programs could be considered as an opportunity to offer an 'enriched environment' to these patients in which different stimulating and non-drug related activities are arranged (Anton et al., 2006; Marlatt, 2007). These treatments programs frequently provide physical activities, psychological therapy, cognitive

training, as well as an enhancement of social interaction or social support which is frequently defective in patients with SUD (Maurage et al., 2012; Room, 2005) and is relevant to cognitive functioning (Cacioppo et al., 2015; Otten and Jonas, 2013; Themanson et al., 2014; Xu et al., 2017; Xu et al., 2018). Accordingly, a notable situation where SUD treatment affects a person's whole life environment would be enrolling in a therapeutic community, which involves moving to a completely new residential and social surroundings where daily activities and duties are highly structured (CSAT, 1999.; Vanderplasschen et al., 2013). In such an 'enriched' clinical setting, it should be determined whether cognitive training may act as a relevant aspect. Due to the potential influence of the therapeutic context that cognitive training takes place, we will differentiate evidence in different clinical SUD settings: inpatient treatments, outpatient treatments, and non-treatment seekers.

5.1. Structured cognitive training

5.1.1. Studies with inpatient participants

Inpatient SUD treatment could be considered to be a type of environmental enrichment where relevant novel activities, social skills, and healthy life habits are trained as an alternative to drug use, promoting cognitive reserve and better cognitive performance (Hannan, 2014; Solinas et al., 2010). This 'enriched' clinical setting allows for the inclusion of structured cognitive training as an additional therapeutic activity.

Several studies of inpatient participants have shown improved cognition, as well as prolonged abstinence and higher treatment commitment when a single cognitive function was trained or if it was a multi-component program in which several domains were included (Goldstein et al., 2005; Roehrich and Goldman, 1993) **(Table 2)**. For instance, Bickel et al. (2011) found that neurocognitive training on working memory (WM) decreased delay discounting in stimulant use patients (Bickel et al., 2011a). This finding could constitute an indirect indicator

of improvement of addiction-related measures, as a person with SUD often prefers a sooner, but smaller reward instead of a later, but larger one (Bickel and Marsch, 2001; Martin et al., 2015). A recent report (Brooks et al., 2017) described that WM training in methamphetamine users enhanced impulsivity control and feelings of self-regulation in relation to a healthy group with no history of SUD. Nevertheless, there are also studies where WM training did not result in a positive effect (Wanmaker et al., 2017). In this study, WM training improved performance in the cognitive tasks trained, but it has no effect on craving, substance use, impulsivity, attention bias, or psychopathology. The lack of effect on these measures could be because the control group's WM capacity was also trained, although at an easier level than the SUD group.

Problem-solving techniques, visuospatial skills, and memory are cognitive functions also trained in inpatient treatments. In regard to problem-solving abilities (i.e., identify the goal and relevant information, simplify the problem, learn from mistakes, and look for patterns), subjects with alcohol dependency that received 2 weeks of this type of training improved significantly more on problem-solving tests, such as a Block design [Wechsler Adult Intelligence Scale; (Wechsler, 1981)], Abstraction test (Shipley, 1940) or Conceptual Level Analogy test (Willner, 1971) than the no-training group (Yohman et al., 1988). With respect to visuospatial skills, training in alcohol-dependent men over 2 weeks resulted in improved visuospatial performance and transfer to novel stimulus material presented via the same sensory modality as the training task (Forsberg and Goldman, 1985; Forsberg and Goldman, 1987).

Finally, hippocampal-dependent declarative memory training programs, which involved remembering items in the same order they were presented, associating faces with names or names with features, verbal recall strategies or visual imagery for verbal materials have shown mixed results about their effect in cognition and drug consumption in inpatients settings. Steingass et al. (1994) carried out memory training in 14 alcohol-dependent patients

that had been abstinent for at least 6 weeks, showing improved performance in verbal memory tests and reproduction of drawings, although training did not restore normal functioning (Steingass et al., 1994). In contrast, several studies have not found benefits after memory training or they were very limited (Godfrey and Knight, 1985; Hannon et al., 1989; Yohman et al., 1988). It is important to remark that this result could be explained by the sample of alcohol-dependent individuals used in these studies being of older age (Yohman et al., 1988) and having severe memory deficits (Godfrey and Knight, 1985).

In general, studies that have trained several cognitive functions (e.g., attention, memory, and executive skills) have shown promising results in different patients with SUD, improving cognition (Gamito et al., 2014; Goldstein et al., 2005; Roehrich and Goldman, 1993; Rupp et al., 2012), treatment effectiveness (Czuchry et al., 2003) psychological well-being, and the compulsion aspect of craving (Rupp et al., 2012). In this regard, abundant computerized packages are available (e.g., PSSCogRehab, mHealth, NeurXerciseTM, Cogmed, or Cogpack), but these multi-component trainings have not demonstrated better efficacy than more specific WM programs (Gamito et al., 2014; Rupp et al., 2012; Verdejo-Garcia, 2016) or even than protracted drug abstinence (Peterson et al., 2002). An inconvenience of these computer-based programs is that they were not specifically designed for patients with SUD, but for other clinical samples, such as those involving traumatic brain injury, neurodegenerative diseases, or stroke. To solve this issue, Rezapour et al. (2015) developed a paper and pencil cognitive rehabilitation package called NECOREDA (Neurocognitive Rehabilitation for Disease of Addiction) to improve neurocognitive deficits associated with drug dependence (attention, calculation, visuospatial processes, memory, verbal skills, and logic/problem solving) particularly caused by stimulants (e.g., amphetamine and cocaine) and opiates (Rezapour et al., 2015). NECOREDA was administered to participants with opioid use disorder for two months, combined with methadone maintenance treatment (Rezapour et al., 2017). Results provided evidence that cognitive training had beneficial effects on

neurocognitive functions and abstinence in patients maintained on methadone, which remained up to 6 months after the patients completed the residential program.

5.1.2. Studies with outpatient participants

Outpatient drug treatment is less restrictive than inpatient programs and usually requires several hours per week spent visiting a local treatment center. This ambulatory service fits for individuals with SUD who do not meet diagnostic criteria for inpatient treatment or for those who are discharged from 24-hour care in an inpatient treatment facility (McCarty et al., 2014). This type of rehabilitation has consistently reported equivalent reductions in problem severity and increases in days abstinent at follow-up for participants compared with those in inpatient treatments (Guydish et al., 1999; Guydish et al., 1998; McCarty et al., 2014; Schneider et al., 1996).

Regarding cognitive training programs in outpatient treatment, they have shown positive results, either when several cognitive functions were trained or they only focused on one function (Bell et al., 2016; Frías-Torres et al., 2016; Rass et al., 2015). For instance, a WM training by Cogmed QM software in methadone patients resulted in an improvement in WM performance on some measures (Digit Span and Visuospatial WM), and a reduction of drug use (Rass et al., 2015). A higher self-efficacy (Hansen, 1980) and cognitive improvements in visual attention, as well as executive functions (Bell et al., 2017) were observed after cognitive training in which several cognitive domains were included. However, a longitudinal study (Frías-Torres et al., 2016) revealed that although cognitive improvements were found at the end of training, they tended to be lost 6 months after the end of intervention.

In other studies, cognitive training in outpatient treatment combined with contingency management (Kiluk et al., 2017) or work therapy (Bell et al., 2017; Bell et al., 2016) consisting of doing entry level duties at medical center job sites supervised by regular medical staff, also

showed cognitive benefits. Hence, cognitive training plus work therapy led to improvements in verbal memory and learning that were not achieved by work therapy alone. Nevertheless, the work therapy only condition produced similar SUD outcomes at either 3- or 6-month follow-ups (Bell et al., 2017). Cognitive training plus contingency management (participants received a monetary reward each time their performance on the subsequent trial improved from their prior performance) showed greater improvements on a sequenced recall task and the Trail Making Test (part B) related to visual attention and cognitive flexibility (Kiluk et al., 2017).

5.1.3. Studies with non-treatment seeking participants

Last, cognitive training has been applied to non-treatment seeking participants who were recruited through flyers, advertisements, word of mouth, and postings on community bulletin boards (Alcorn et al., 2017; Houben et al., 2011a; Houben et al., 2011b; Kaag et al., 2017; Kaag et al., 2018; Smith et al., 2017). These studies are interesting as they will evaluate the effects of cognitive training in absence of any direct intervention in patient's daily life and social environment. However, it should also be noted that non-treatment seeking participants have shown significant demographic and clinical differences (usually entailing less SUD severity) compared to treatment seekers (Anton et al., 1996; Ray et al., 2017).

Again, positive results are generally found not only in cognitive performance (Alcorn et al., 2017; Snider et al., 2018), but also in the reduction of drug consumption (Back, 2010; Black and Mullan, 2015; Houben et al., 2011a; Houben et al., 2011b; Smith et al., 2017) and craving (Kaag et al., 2018; May et al., 2010). Most studies were carried out in alcohol and nicotine users who were engaged in cognitive training programs focused on working memory (Houben et al, 2011b; Kaag et al., 2018; Snider et al., 2018), inhibitory control (Houben et al, 2011a; Smith et al., 2017), planning-ability (Black and Mullan, 2015), and visuospatial skills (May et al., 2010). In these interventions, benefits were found by comparing these subjects with other

patients with SUD that engaged in standard treatment or on the waitlist (**Table 2**). Inhibitory control was also enhanced with five sessions of cognitive training in subjects who met the criteria for cocaine-use disorder, despite not looking to undergo treatment (Alcorn et al., 2017). In contrast, a recent study with adult treatment-seeking smokers, who were trained for 12 weeks in cognitive training exercises that targeted working memory, attention, and response inhibition did not reveal reductions in subjective withdrawal or craving symptoms (Loughead et al., 2016).

5.2. Other cognitively engaging approaches in SUD treatment

Within the field of addiction, an interest is growing in alternative therapies to complement existing treatment programs **(Table 2)**. New research provides evidence that other treatment approaches, such as *mindfulness*, *music,* or *art therapy* could be promising interventions for SUD due to its impact on cognitive processes, especially executive functions known to be highly impaired in this type of patient (Hagen et al., 2016; Manning et al., 2017). Thus, the activities included in these therapies involve cognitive processes classified as executive control, such as sustained attention, goal-directed behavior, and cognitive flexibility, as well as skills for emotion regulation, which could induce neurobiological changes in brain networks altered by drug consumption (Garland et al., 2014; Jaschke et al., 2018; Metzler-Baddeley et al., 2014).

Mindfulness is a psychological process involving attention, non-judgmental acceptance, and receptivity to what is happening in one's moment by moment experience (Baer, 2006; Hölzel et al., 2011; Kabat-Zinn, 1982). The practice of mindfulness activates different cognitive functions during the mindful state including attentional vigilance, attentional re-orienting, executive monitoring of working memory, response inhibition, and emotion regulation (Vago et al., 2012). Consequently, several studies performing mindfulness training (Brewer et al., 2011), as well as different modalities of mindfulness practices combined with goal

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management treatment (Alfonso et al., 2011), based on relapse prevention (Bowen et al., 2009), orientated to recovery enhancement (Garland et al., 2014) or brief meditation (Tang et al., 2013) have reported cognitive improvements, reduction of stress, consumption and craving, along with an increase of self-efficacy. Despite these positive results, the neural mechanisms underlying these improvements are largely unknown. Recent evidence has shown increased functional connectivity among prefrontal and corticolimbic regions involved in executive function during mindfulness training and active meditation (Froeliger et al., 2012; Luders et al., 2011; Taren et al., 2017). Brief meditation training carried out with adult treatment-seeking smokers produced increased activity in prefrontal cortical areas related to self-control, linked to a significant reduction in smoking (Tang et al., 2013).

Different types of *music therapies* have been performed within inpatient treatments for drug addiction (Baker et al., 2007) with the aim to rehabilitate neurological impairments (Sihvonen et al., 2017), as well as to promote well-being and a positive self-perception through its rewarding value and the social interactions underlying this type of activity (Weigmann, 2017). These were composed essentially of listening to self-made music, lyric analysis, rhythm activities, song-writing, and group-drumming, among others. The benefits observed after this sort of therapy included increases of self-control (Fritz et al., 2015) and efficacy (Silverman, 2014), motivation (Silverman, 2015), feelings of acceptance, joy, and happiness (Jones, 2005), as well as enhancement of treatment attendance and retention rates (Blackett and Payne, 2005). Additionally, reduction of anxiety, depression, anger, and craving (Cevasco et al., 2005; Silverman, 2011) were also described, whereas significant benefits on cognitive functions have not been reported. Brain imaging has provided remarkable insights about the positive impact of music on brain plasticity (Altenmüller and Schlaug, 2015; Pantev and Herholz, 2011; Schlaug, 2015) showing positive changes in the auditory and sensorimotor systems (Herholz and Zatorre, 2012), basal ganglia and cerebellum (Penhune and Steele, 2012; Zatorre et al., 2007), as well as in prefrontal cortical areas involved in inhibition of behavior observed in addiction disorders (Goldstein and Volkow, 2011). Nevertheless, the

variability between different studies applying music therapy for SUD leads to non-comparable results which could question its efficacy (Hohmann et al., 2017). Moreover, music therapists often take on the role of the researcher by collecting and interpreting data; it is recommended they include external researchers for analyzing the results along with follow-up measurements.

Finally, *art therapy* could constitute a method by which a person learns to express their feelings through a non-verbal, imaginative, and creative exercise. The activities included in this therapy involve drawing emotions, creating an art journal, or sculptures which supposes an important creative process (Aletraris et al., 2014). Other studies have included interpretation and contemplation of established works of art, observing an improvement in emotion expression, self-awareness, and self-efficacy (Feen-Calligan et al., 2008). Again, the prefrontal cortex seems to be a key brain region which displays an increased activation during creative activities (fluency performance or generation of alternative uses) (Abraham, 2014; Fink and Neubauer, 2006; Kleibeuker et al., 2017). Moreover, regions of the frontal-parietal network have been implicated in divergent thinking (Gonen-Yaacovi et al., 2013) which is associated with executive functions such as working memory, suppression of unrelated thoughts, and task-set switching (Niendam et al., 2012; Sun et al., 2016). Although several drugs may increase creative function (Holm-hadulla, 2014), it is unknown which phase of the creative process is improved or what dosages, duration, and pattern of substance use are harmful. For instance, Ludwig (1992) analyzed the biographies of 34 heavy drinkers which were highlighted for being famous writers, artists, and composers/performers during the 20th century. He found that alcohol use had a detrimental effect on creativity in over 75% of the sample, and this negative effect increased with time and higher doses of alcohol (Ludwig, 1992).

5.3. Conclusions and limitations

Seminal reviews in this field (Bates et al., 2013b; Rezapour et al., 2016; Sofuoglu et al., 2016) have highlighted the importance of considering the cognitive deficits associated to drug use due to its impact on treatment outcome and retention. Besides, in these studies different treatment approaches are discussed -pharmacological, physical exercise, meditation, as well as behavioral interventions-, which may also be efficacious when delivered in conjunction with cognitive training. In general, cognitive training, targeting single or multiple functions, showed positive results on neuropsychological functioning when applied to both SUD inpatient and outpatient treatments, and even in non-treatment seekers **(Table 2)**. Nevertheless, the benefits of cognitive training may depend on the patient's baseline cognitive performance [e.g., patients with lower, but not too severe, cognitive functioning may be more likely to obtain benefits; (Mehta et al., 2004)], and the cut-off point of basal cognitive abilities that may advise using cognitive training has yet to be determined (Rezapour et al., 2016). Cognitive rehabilitation training must be patient tailored, because neurocognitive deficits vary depending on the type, amount, and duration of drug consumed, as well as on environmental factors and personal characteristics (Bates et al., 2013a; Rezapour et al., 2016).

Although many studies of cognitive interventions in SUD have described a positive effect on the functions trained, there is still a limited number which evaluated SUD clinical outcomes (i.e., relapse-related measures, adherence to treatment, or reduction of drug use) or included follow-up assessments or meaningful longer-term outcomes, such as improved social or occupational functioning (**Table 2**). In relation to this, a common concern is the questionable ecological validity of cognitive rehabilitation, and whether cognitive improvement is transferred to non-trained functions or skills needed for everyday problem. Alternatively, studies that used only pre- and post-training measures may not rule out the existence of time-dependent improvement caused by abstinence. To obtain unequivocal results of the effect of cognitive training, it is necessary to provide an appropriate control group, matched in age, education, sex, and drug use outcomes (i.e., amount of drug used, time in abstinence, etc.)

(Frazer et al., 2018), who should be performing an alternate activity in the place of cognitive training. Finally, the sample frequently consists of men and does not include female participants, which is a relevant limitation as sex could be a moderating variable for cognitive deficits in SUD (Becker and Hu, 2008).

Little is known about the structural and functional brain changes related to cognitive interventions in individuals with SUD (Verdejo-Garcia, 2016), which may be revealed by brain imaging techniques. For instance, Brooks et al. (2016) demonstrated that daily adjunctive working memory training was associated with specific brain volume changes than did usual SUD treatment (psychological therapy). The cognitive training group showed more pronounced increases in volume that extended across large areas of the dorsal striatum, as well as reduced cerebellar volume, which was associated with improvements in self-reported affect regulation and reduced impulsivity (Brooks et al., 2016). Moreover, cognitive inhibition training produced the functional recruitment of key frontal cortical regions from the inhibitory control network that regulates craving in cigarette smokers (Luijten et al., 2014).

Finally, alternative therapies such as mindfulness, music, and art can induce benefits by impacting both non-cognitive and cognitive processes, especially executive functions known to be highly impaired in patients with SUD. Hence, a combination of cognitive training along with these alternative interventions could constitute a new therapeutic approach, like an environmental enrichment condition where different types of stimulation are provided. To date, it is unknown if these combinations of therapies operate in complementary or synergistic fashions (Potenza et al., 2011).

6. Conclusions

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In this Special Issue, we have described drug addiction as a chronic, recidivating disease where whole brain neuroplasticity, including learning-related brain regions is compromised by drugs, which may in turn induce cognitive symptoms and aggravate the addiction disorder.

Concerning preclinical research, experiments on the effects of structured cognitive training in animals previously exposed to drugs are currently scarce, but additional research on this topic could contribute to the understanding of and support clinical evidence of cognitive training effects in addiction. To date, there is abundant preclinical data on the potential therapeutic actions of enriched environments (include cognitive, social, and physical stimulation) to reduce craving and drug intake. It is important to elucidate the specific contribution of the 'cognitive' component of the enrichment protocols, since physical activity alone may also exert notable effects. In this regard, preclinical evidence suggests a potential synergic interaction of cognitive stimulation and exercise, so the combination of both treatments may induce stronger outcomes. This has inspired the development of new clinical interventions that combine physical activity and effortful learning to improve mental health (Shors et al., 2014), which could be useful in the therapeutics of SUD. Preclinical research allows the control of environmental and drug-related variables; therefore, it provides an advantageous framework for the initial study of interactions between cognitive stimulation and adjuvant interventions.

The cognitive deficits in drug using or drug abstinent persons, which may both precede or be caused by drug use, have relevant therapeutic implications as they predict a worse SUD treatment outcome. In this regard, the available clinical data overall supports the usefulness of including structured cognitive training programs as an adjuvant intervention to habitual SUD treatment (carried out either in inpatient or outpatient settings) to improve the cognitive performance of patients with SUD. Furthermore, strengthening cognitive function could also improve SUD prognosis, though the number of studies that tested relevant SUD outcomes (e.g., treatment retention or relapse) is relatively reduced and insufficient to establish strong

conclusions. Moreover, additional evidence is needed to determine which SUD symptoms may most benefit from cognitive stimulation, which cognitive-engaging experiences or training protocols are most appropriate for patients with SUD, and which type of therapeutic settings or population of patients with SUD (which are highly heterogeneous) may most benefit from cognitive intervention.

In summary, while the current preclinical data points out that either EE or EE+running protocols have beneficial effects acting in a similar direction, future experiments must strength whether cognitive training may induce more (or different) improvement than other type of stimulation. In relation to this, the hypothesis of that interventions combining different therapeutic factors -such as cognitive stimulation and exercise- would yield stronger effects (i.e. 'a healthy mind in a healthy body' or 'more stimuli is better'), is worth to be studied by animal models of drug-related behaviors. Similarly, despite promising initial results, clinical research has yet to unveil the advantages of using cognitive training over other types of therapeutic interventions. In any chase, although patients with SUD may often present with cognitive deficits, they should not be assumed to have a passive *sick role,* leading others to believe that they cannot do daily functions (Mik-Meyer and Obling, 2012; Rezapour et al., 2016). Instead, this line of evidence supports that patients should be encouraged to adopt an active role, since engaging in stimulating and challenging activities may favor treatment success.

Finally, neurocognitive assessments in patients with SUD may be used as a valuable diagnostic tool to predict both the risk of developing drug addiction and SUD treatment outcomes. This may be complemented by and benefit from the identification of putative biomarkers relevant in SUD. For example, performance in specific neurobehavioral tests of impulsivity and stress reactivity may reflect ventral prefrontal cortex hypofunction in SUD, which is involved in processing the consequences of future actions, inhibition of behavior, and control of emotions (Volkow et al., 2015). Other authors have proposed WM as a marker

of peripheral expression of dopamine-related genes and response to dopamine agonist drugs (Ersche et al., 2011b), and cognitive deficits in abstinent alcohol-dependent patients have been associated with reduced circulating levels of neurotrophins (Silva-Peña et al., 2018). Along with this, neuroimaging studies have shown that brain activity during the execution of cognitive tasks could be predictive of SUD treatment results. For instance, functional brain activation during WM, monetary incentives, and Stroop tasks were found to be indicators of SUD treatment retention (Brewer et al., 2008; Jia et al., 2011; Moeller et al., 2010). Despite this evidence, the introduction of biomarkers in this research area is still at an early stage, but it has potential. In this regard, biological markers could also contribute to the development of future targeted and personalized cognitive remediation therapies (e.g., identifying individuals who might benefit most from cognitive stimulation treatment) (Ersche et al., 2011b). Cross species studies may facilitate this goal, since animal models allow a more profound examination of brain neuroplasticity, as well as the ability to control for drug exposure.

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Figure Legends

Figure 1. The 'drug addiction brain circuit' overlaps with learning systems in the brain. A schematic, not exhaustive view, of the numerous brain regions that are affected by drugs, which are functionally and anatomically interconnected (Castilla-Ortega et al. 2016). After repeated drug exposure, drug-induced neuroadaptations corrupt the original function of brain regions involved in learning and motivated goal-directed behavior and generate addiction. Behavioral functions are linked to the main brain region that supports them, though many brain regions collaborate for each behavioral process

Abbreviations: Amg: amygdala; DS: dorsal striatum; DLS: dorsolateral striatum; DMS: dorsomedial striatum; D-S: drug-stimuli; Hipp: hippocampus; NAc: nucleus accumbens; SMC: sensorimotor cortex; PFC: prefrontal cortex; SN: substantia nigra; VTA: ventral tegmental area. References: (Belin and Everitt, 2008; Castilla-Ortega et al., 2016; Everitt, 2014; Haber, 2016; Ikemoto, 2007) and in the main text.

Figure 2. Two common animal models to assess drug seeking and taking behaviors. **(A)** In the drug self-administration paradigm, the animal learns to perform an operant response (i.e. pressing a lever) to receive a drug infusion; so drug exposure is controlled by the animal. This paradigm measures motivation for drug or, in other words, how much drug the animal is willing to take or how much effort it is willing to use to obtain it. **(B)** In the CPP paradigm, the animal is forcibly administered the drug when it is placed in one maze compartment –which is distinguishable by its contextual cues- but it receives a saline administration in the opposite

compartment. This process is repeated across several 'conditioning' sessions. The CPP paradigm measures sensitivity to drug reward as well as the learning of drug-contextual associations. Both phenomena are evidenced when the animal is allowed to freely choose between both compartments and it prefers to stay in the drug-paired one, probably seeking or expecting the drug. For ethanol, it is also common the voluntary ethanol drinking paradigm (not shown in the figure), that consists of placing a bottle filled with water and a bottle containing ethanol in the animal's home cage, and allowing it to drink freely for several hours or days.

Figure 3. The preclinical environmental enrichment (EE) paradigm. **(A)** Photographs of a typical control (impoverished) housing condition compared to a typical EE housing, based mainly on novelty and social stimulation (i.e., no running wheels). **(B)** Exposure to EE activates neuroplasticity in the whole brain, including regions involved in reward and cognition. The picture shows a rat brain. **(C)** Animals housed in EE before or after exposure to drugs generally reduce subsequent drug-taking and drug-seeking behavior compared to their control counterparts. The picture shows a rat tested in both a drug self-administration and a drug-induced CPP paradigm (explained in Figure 2).

Abbreviations: Amg: amygdala; DS: dorsal striatum; EE: environmental enrichment; Hipp: hippocampus; NAc: nucleus accumbens; PFC: prefrontal cortex; SN: substantia nigra; VTA: ventral tegmental area. References are in the main text.

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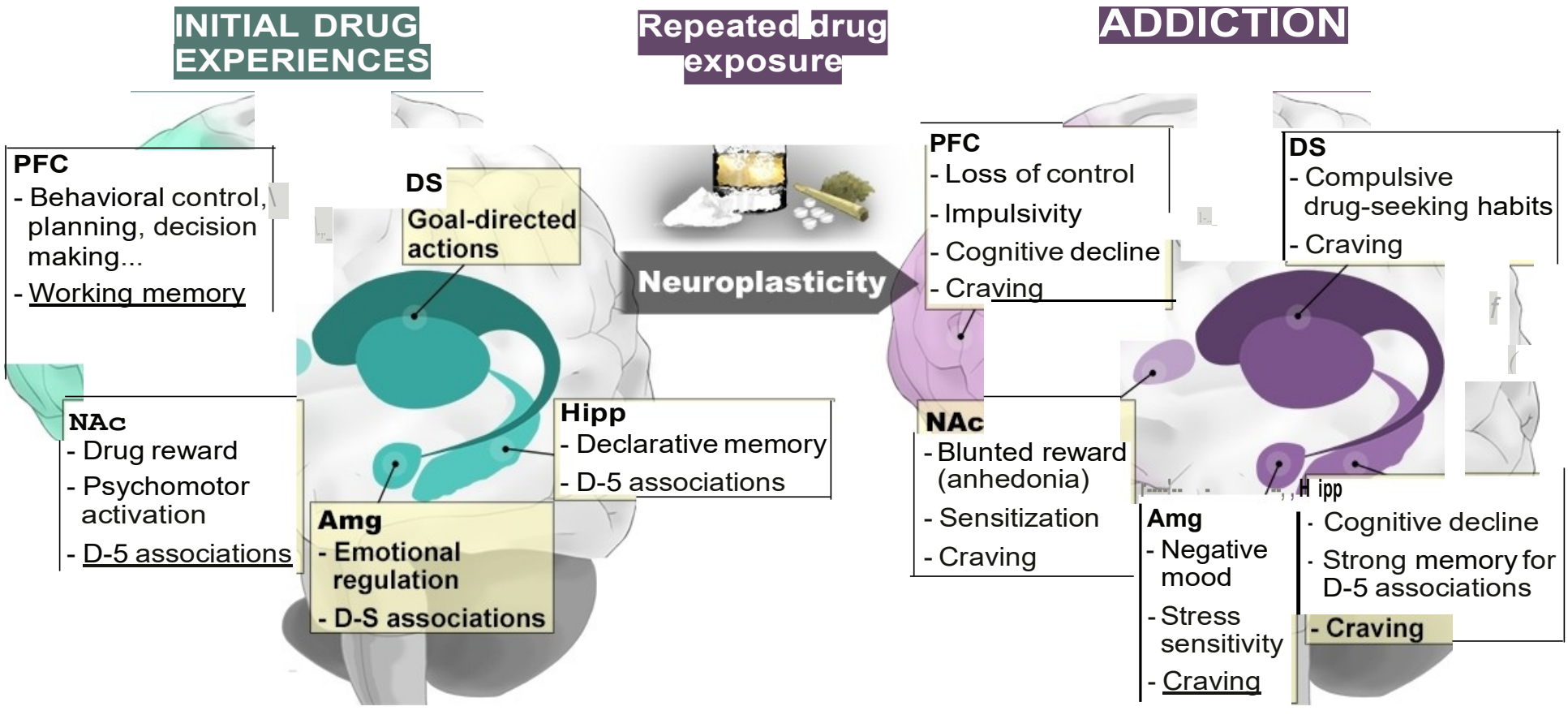

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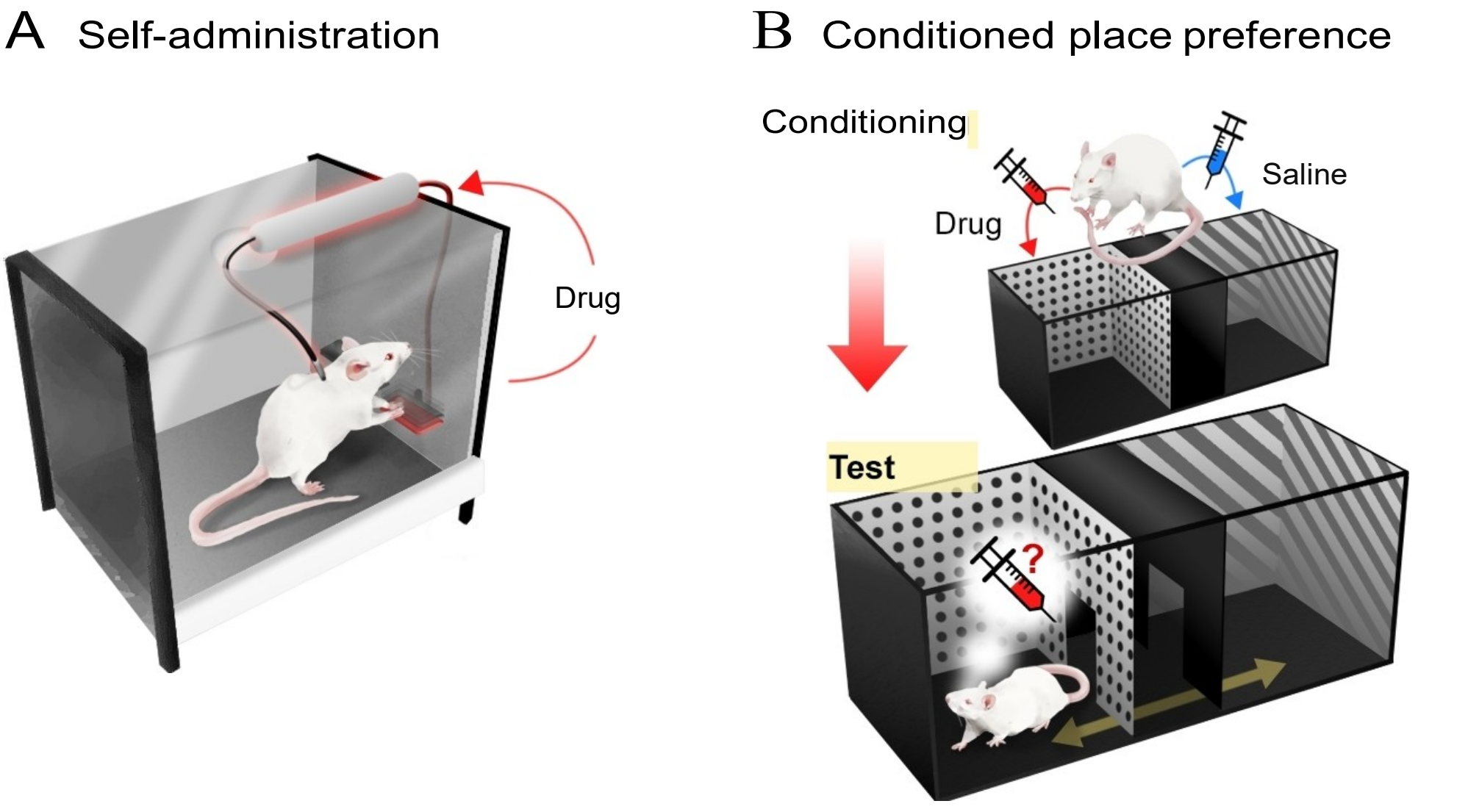

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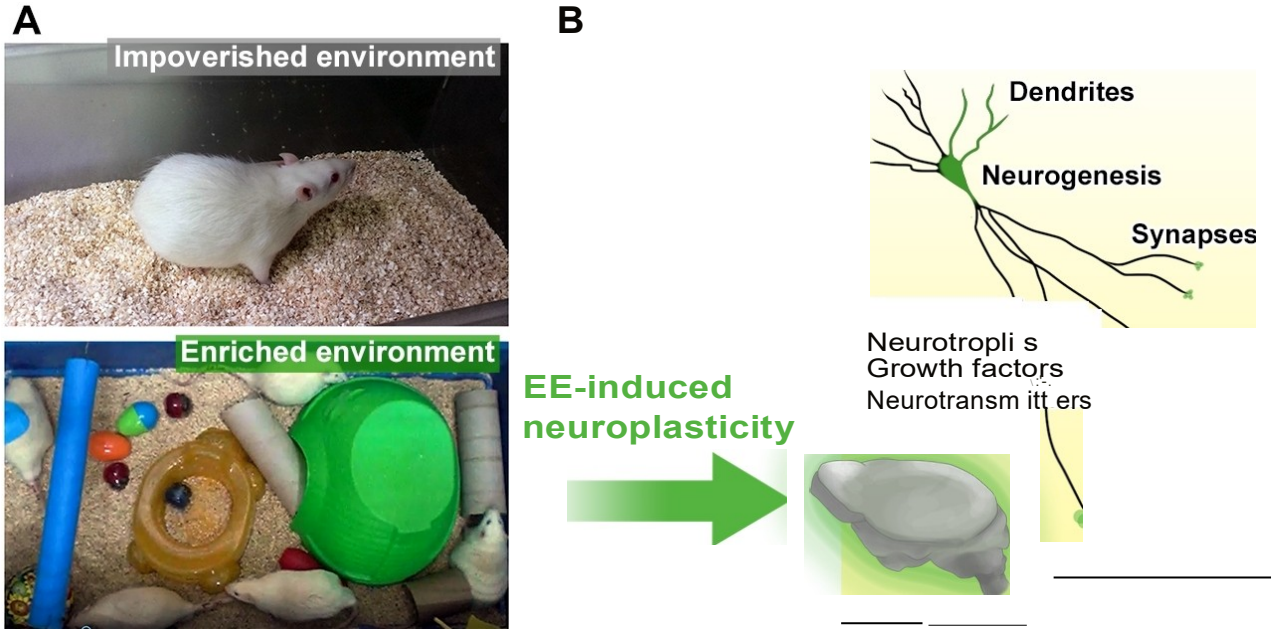

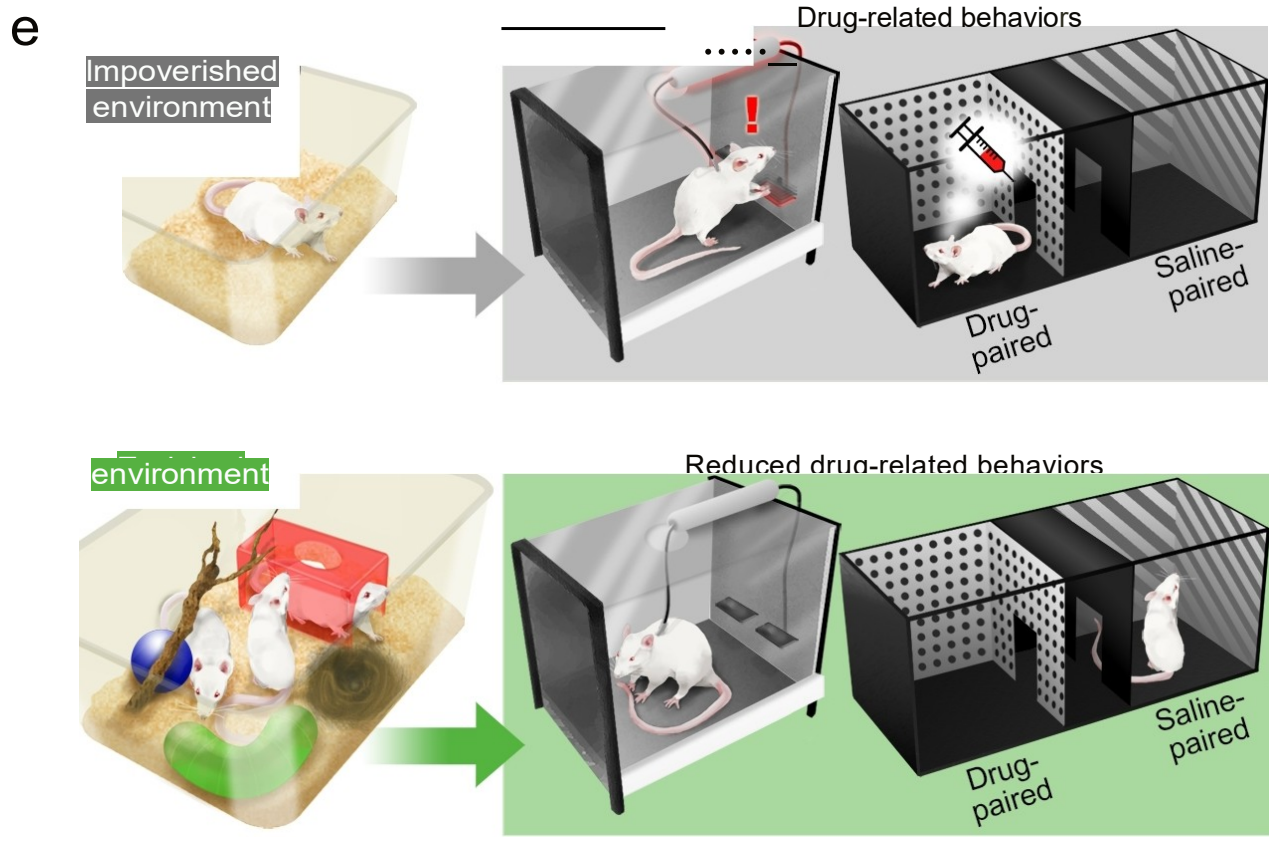

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TABLE 1. Studies that reported cognitive deficits in drug users.

COGNITIVE FUNCTION	
Attention, processing speed and psychomotor functions	**ALCOHOL:** Alarcon et al (2015); Fitzpatrick and Cowe (2013); Kopera et al (2012); Loeber et al (2009); Naim-Feil et al (2014); Sewell et al (2009); Yohman et al (1985). **COCAINE:** Bauer (1993, 1994); Bolla et al (1999); Colzato et al (2009b); De Oliveria et al (2009); Goldstein et al (2004); Hanlon et al (2011); Herning et al (1985); Jovanovski et al (2005); Kübler et al (2005); Lopes et al (2017); Moeller et al (2004); O´Malley et al (1992); Roberts and Bauer (1993); Robinson et al (1999); Rosselli and Ardilla (1996); Soar et al (2012); Vonmoos et al (2013); Woicik et al (2009). **AMPHETAMINE:** Chang et al (2002); Kalechstein et al (2003); Iudicello et al (2010); London et al (2005); Newton et al (2004); Scott et al (2007); **CANNABIS:** Bolla et al (2002); Ehrenreich et al (1999); Fried et al (2005); Hanson et al (2010); Huestegge et al (2010); Indlekofer et al (2009); Kelleher et al (2004); Medina et al (2007); Messinis et al (2006); Pope et al (2001); Pope and Yurgelun-Todd (1996); Shrivastava et al (2011); Solowij (1995); Solowij et al (2002); Varma et al (1988). **OPIATES:** Darke et al (2012); Gruber et al (2007); Rapeli et al (2007, 2011); Verdejo et al (2005). **NICOTINE:** Durazzo et al (2012); Harrison et al (2009); Jacobsen et al (2005); Mashhoon et al (2018); Wagner et al (2013).
Visuospatial and visuoconstruction functions	**ALCOHOL:** Alarcon et al (2015); Beatty et al (1996); Fein et al (2006); Fitzpatrick and Cowe (2013). **COCAINE:** Bolla et al (1999). **AMPHETAMINE:** Scott et al (2007). **OPIATES:** Gruber et al (2007); Prosser et al (2006). **NICOTINE:** Durazzo et al (2012).
Declarative memory and learning	**ALCOHOL:** Alarcon et al (2015); Bates et al (2002); Beatty et al (1996); Becker et al (1983); Brandt et al (1983); Carbia et al (2017); Chanraud et al (2009); Chen et al (2018); Davies et al (2005); Fama et al (2004); Fitzpatrick and Cowe (2013); Gross et al (2018); Heffernan et al (2002); Hyman et al (2006); Kopera et al (2012); Nixon et al (1987); Pitel et al (2007); Schaeffer et al (1987). **COCAINE:** Abi-Saab et al (2005); Bolla et al (2000); De Oliveria et al (2009); Fox et al (2009); Goldstein et al (2004); Jovanovski et al (2005); Lopes et al (2017); Moeller et al (2010); O´Malley et al (1992); Rosselli and Ardilla (1996); Soar et al (2012); Vonmoos et al (2013, 2014); Woicik et al (2009). **AMPHETAMINE:** Hoffman et al (2006); Iudicello et al (2010); Kalechstein et al (2003); Moon et al (2007); Scott et al (2007); Simon et al (2000). **CANNABIS:** Bartholomew et al (2010); Battisti et al (2010b); Becker et al (2014); Bolla et al (2002); Fried et al (2005); Gonzalez et al (2012); Grant et al (2003); Hanson et al (2010); Indlekofer et al (2009); Lamers et al (2006); Manschreck et al (1990); McClure et al (2015); McHale and Hunt (2008); McKetin et al (2016); Medina et al (2007); Messinis et al (2006); Pope et al (2001); Pope and Yugelun-Todd (1996); Schwartz et al (1989); Shrivastava et al (2011); Smith et al (2015); Solowij et al (2002, 2011). **OPIATES:** Darke et al (2012); Gruber et al (2007); Hanks et al (1995); Kerr et al (1991); Prosser et al (2006); Rapeli et al (2007). **NICOTINE:** Durazzo et al (2012); Jacobsen et al (2005).
Working memory	**ALCOHOL:** Ambrose et al (2001); Davies et al (2005); Kopera et al (2012); Uekermann et al (2007). **COCAINE:** Kübler et al (2005); Lopes et al (2017); Madoz-Gúrpide and Ochoa-Mangado (2012); Tomasi et al (2007); van der Plas (2009); Vonmoos et al (2013, 2014). **AMPHETAMINE:** Gonzalez et al (2007); Chang et al (2002); Newton et al (2004). **CANNABIS:** Becker et al (2014); Cousijn et al (2014); Crean et al (2011); Hanson et al (2010); Vo et al (2014). **OPIATES:** Baldacchino et al (2012); Ersche et al (2006); Liang et al (2016); Mintzer and Stitzer (2002); Rapeli et al (2007, 2011); Rass et al (2015); Verdejo et al (2005); Vo et al (2014); Wang et al (2008). **NICOTINE:** Jacobsen et al (2005, 2007); McClernon et al (2016); Mendrek et al (2006); Patterson et al (2010).
Executive functions	**ALCOHOL:** Alarcon et al (2015); Bates et al (2002); Czapla et al (2016); Fitzpatrick and Cowe (2013); Körner et al (2015); Loeber et al (2009); Miranda et al (2009); Naim-Feil et al (2014); Noël et al (2001); Pitel et al (2007); Poulton et al (2016); Yohman et al (1985). **COCAINE:** Bolla et al (1999); Camchong et al (2011); Colzato et al (2007, 2009a); Ersche et al (2008); Fernandez-Serrano et al (2012); Fillmore et al (2002); Goldstein et al (2004); Hester et al (2007); Jovanovski et al (2005); Li et al (2006); Liu et al (2011); Lopes et al (2017); Madoz-Gúrpide and Ochoa-Mangado (2012); Moeller et al (2004); Soar et al (2012); Rahman and Clarke (2005); Verdejo-García et al (2007); van der Plas (2009); Vonmoos et al (2013, 2014); Woicik et al (2009, 2011). **AMPHETAMINE:** Barr et al (2006); Gonzalez et al (2007); Iudicello et al (2010); Kalechstein et al (2003); Kim et al (2006); Monterosso et al (2005); Paulus et al (2002, 2003); Potvin et al (2018); Salo et al (2002, 2005); Scott et al (2007); Simon et al (2000). **CANNABIS:** Almeida et al (2008); Battisti et al (2010a); Becker et al (2014); Bolla et al (2002); Cohen and Weinstein (2018); Crean et al (2011); Fontes et al (2011); Gonzalez et al (2012); Lamers et al (2006); McHale and Hunt (2008); Medina et al (2007); Messinis et al (2006); Pope and Yugelun-Todd (1996); Shrivastava et al (2011). **OPIATES:** Baldacchino et al (2012); Brand et al (2008); Darke et al (2012); Davydov and Polunina (2004); Ersche et al (2006); Liao et al (2014); Mintzer and Stitzer (2002); Pirastu et al (2006); Lee and Paul (2002); Prosser et al (2006); Rapeli et al (2011); Verdejo et al (2005); Verdejo-García et al (2007). **NICOTINE:** Dawkins et al (2007); Dinur-Klein et al (2014); Durazzo et al (2012); Ettinger et al (2017); Flaudias et al (2016); Harrison et al (2009); Mashhoon et al (2018); Wagner et al (2013).

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TABLE 2. Cognitive training and other cognitive-engaging therapies employed in SUD patients.

Cognitive training	Drug	Type of treatment	Control group	Effect				Relapse prevention	Reference
				Reduction of craving	Cognitive function	Mood /self-steem/ self-regulation	Adherence / reduction of drug use		
Working memory	Methadone	Outpatient	DU		↑↑		↑↑		Rass et al. (2015)*
	Psychostimulants	Inpatient	DU		↑↑				Bickel et al. (2011b)
	Alcohol	Non-treatment seeking participants	DU		↑↑		↑↑		Houben et al. (2011b)*
	Alcohol	Non-treatment seeking participants	DU		↑↑				Snider et al. (2018)
	Alcohol	Non-treatment seeking participants	DU	↑↑	↑↑				Kaag et al. (2018)
	Methamphetamines	Inpatient	DU			↑↑			Brooks et al. (2016, 2017)
	Cannabis, cocaine and alcohol	Inpatient	DU		=				Wanmaker et al. (2017)
Inhibitory control	Alcohol	Non-treatment seeking participants	DU				↑↑		Houben et al. (2011a)*+
	Cocaine	Non-treatment seeking participants	DU		↑↑				Alcorn et al. (2017)+
	Alcohol	Non-treatment seeking participants	DU				↑↑		Smith et al. (2017)*+
	Alcohol	Non-treatment seeking participants	PP				↑↑		Bowley et al. (2013)+
Problem solving	Alcohol	Inpatient	DU		↑↑				Yohman et al. (1988)
Planning-ability intervention	Alcohol (binge drinking)	Non-treatment seeking participants	DU				↑↑		Black and Mullan (2015)*
Memory	Alcohol	Inpatient with important memory problems	DU		=				Godfrey and Knight. (1985)
	Alcohol	Inpatient	DU		↑				Yohman et al. (1988)
	Alcohol	Inpatient	DU		=				Hannon et al. (1989)
	Alcohol	Inpatient	DU		↑↑				Steingass et al. (1994)
Visuospatial skills	Alcohol	Inpatient	HC		↑↑				Forsberg and Goldman (1985)
	Alcohol	Inpatient	DU and HC		↑↑				Forsberg and Goldman (1987)
	Nicotine	Non-treatment seeking participants	DU	↑↑					May et al. (2010)
Several cognitive functions	Alcohol	Inpatient	DU		↑				Gamito et al. (2014)
	Alcohol	Inpatient	DU	↑↑	↑	↑↑			Rupp et al. (2012)
	Alcohol	Outpatient	PP		↑				Frías-Torres et al. (2018)
	Alcohol	Inpatient	PP		↑↑				Roehrich and Goldman (1993)

	Alcohol	Inpatient	DU		↑↑			Goldstein et al. (2005)
	Polysubstance abusers	Inpatient	DU			↑↑	↑↑	Czuchry and Dansereau (2003)*
	Alcohol	Inpatient.	P		↑↑	↑↑		Hansen (1980)
	Alcohol	Inpatient	DU		=			Peterson et al. (2002)
	Opioids	Inpatient	PP		↑↑		↑↑	↑↑ Rezapour et al. (2017)**
	Nicotine	Adult treatment-seeking	DU		=		=	= Loughead et al. (2016)
Combined with contingency management	Alcohol and drugs	Outpatient	DU		↑↑			Kiluk et al. (2017)
Combined with work therapy	Alcohol	Outpatient	DU		↑↑			Bell et al. (2016)
	Primarily abused alcohol (~60%) or opiates/cocaine (~29%) and polysubstance abusers that had more than one primary drug of abuse in addition to alcohol (~10%)	Outpatient	DU		↑↑			Bell et al. (2017)
Other therapies								
Mindfulness								
Combined with goal management training	Alcohol and polysubstance abusers	Outpatient	DU		↑↑			Alfonso et al. (2011)
Mindfulness-based relapse prevention	Alcohol and polysubstance abusers	Outpatient	DU	↑↑			↑↑	↑↑ Bowen et al. (2009)
Mindfulness-oriented recovery enhancement	Alcohol	Inpatient	Review	↑↑		↑↑		Garland et al. (2014)
Mindfulness training	Nicotine	Adult treatment-seeking	DU				↑↑	↑↑ Brewer et al. (2011)
Brief meditation	Nicotine	Adult treatment-seeking	DU			↑↑	↑↑	Tang et al. (2013)
Music therapy								
Listening to self-made music	Participants that consumed more than two drugs regularly during the pre-clinic period (polydrug use; 77,7%)	Inpatient	DU			↑↑		Fritz et al. (2015)
Lyric analysis	N.s.	Inpatient	DU			=	=	Silverman (2009)
	N.s.	Inpatient	DU			↑		Silverman (2014)
	N.s.	Inpatient	DU				↑↑	Silverman (2015)
	Alcohol and narcotics	Inpatient	PP			↑↑		Jones et al. (2005)
Rhythm activities	N.s.	Outpatient	PP			↑↑		Cevasco et al. (2005)
Rockumentary music therapy	Alcohol, heroin and prescription drugs	Inpatient	PP	↑↑		↑↑		Silverman (2011)
Recreational music therapy	Alcohol, heroin and prescription drugs	Inpatient	PP	↑↑		↑↑		Silverman (2011)
Song writing	Alcohol and narcotics	Inpatient	PP			↑↑		Jones et al. (2005)

Group-drumming	Heroin, crack-cocaine and polydrug use	Inpatient	PP		↑↑	Blackett and Payne (2005)
Art	N.s.	Inpatient	P	↑↑		Feen-Calligan et al. (2008)

Abbreviations: N.s.: Not specified. HC: healthy control group; DU: drug user group in an alternative/standard/wait list treatment; PP: pre- and post-treatment measures; P: post-treatment measures (i.e., patient's self-reported 'improvement' after treatment completion).

Symbols: (↑↑) improvement; (↑) partial or transient improvement; (=) improvement was not found. The effects were assessed by using either control or pre-treatment groups measures. The blank spaces indicate that the effect was not evaluated. (*) highlights studies in which treatment adherence and reduction of drug use was assessed, employing a control group (DU) in an alternative/standard/wait list treatment. (**) corresponds to studies in which relapse prevention was also tested. (+) inhibitory control training studies employed stimuli related to the drug in the NoGo condition (e.g., Beer NoGo). The rest of studies employed non-drug related stimuli for cognitive training.