Chapter

Aberrant Brain Neuroplasticity and Function in Drug Addiction: A Focus on Learning-Related Brain Regions

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Abstract

This chapter will review the altered brain structure and function associated to drug addiction, with a focus on brain regions involved in learning and motivated behavior. As evidenced by both clinical and preclinical studies, repeated drug exposure affects whole brain neuroplasticity including the mesolimbic system which is a main locus for reward, an action-control center such as the dorsal striatum, and limbic brain regions such as the prefrontal cortex, the hippocampus, and the amygdala that are involved in behavioral control, memory, and mood. In this way, the drug-seeking actions that were initially intentional responses become involuntary habits governed by the dorsal striatum. Drug addiction may also curse with a reduced ability to experience rewards that are unrelated to drugs and emotional dysregulation, while the impairment on limbic regions contributes to generate cognitive symptoms. These entail persistent memories for previous experiences with the drug contrasting with a global cognitive decline that may hamper the acquisition of new, adaptive learnings. Overall, these features promote a desire for the drug, leading to relapse in drug use. Further drug exposure, in turn, aggravates its consequences on the brain and behavior, creating the harmful "addiction cycle."

Keywords: substance use disorders, habits, motivation, memory, mood, accumbens, striatum, limbic regions

1. Introduction

The use of psychoactive drugs that induce dependence (including psychostimulants (such as cocaine, methamphetamine, etc.), opioids (heroin, methadone, etc.), cannabinoids, tobacco, and alcohol, among others) is widely extended in the first world countries [1, 2]. The widespread drug use entails a main socioeconomic burden, because drug use is associated to antisocial behavior and delinquency, violence and accidents, social exclusion, physical and psychiatric illnesses, and even disability and death [1, 2]. In this regard, it is worth mentioning that a recent global study identified alcohol as the leading risk factor for premature death in the population aged 15–49 years [1]. Considering the severity of the drug use problem, the World

Health Organization currently destines efforts for substance abuse management in order to improve both treatment and prevention programs (https://www.who.int/substance_abuse/publications/drugs/en/).

Nevertheless, while drug use entails significant risks, regular usage of drugs is not a synonym of suffering a drug addiction disorder. Drug addiction (or substance use disorder—SUD) is a chronic disorder with a high relapse rate, in which the person "loses control" over drug intake despite the negative consequences on their daily life and even against the desire to remain abstinent [3]. Drug addiction may only be experienced by a subgroup of more "vulnerable" individuals that get in contact with drugs. Specifically, approximately 11% of people that use drugs would develop a SUD, meaning an uncontrollable and harmful drug use pattern that may need treatment [2]. Therefore, the scientific community has invested in investigating those factors or mechanisms that cause and explain the onset and maintenance of a SUD. As the deleterious impact of addictive drugs on the brain—the organ that controls behavior—became evident, addiction has been considered as a "brain disease" [4]. The current "brain disease" model of addiction has important implications for SUD prevention and treatment, since medical interventions that regulate brain functioning (e.g., pharmacotherapy) may be valid for addiction, and persons with SUDs may benefit for public treatment policies reserved to other medical illnesses, while the social stigma is attenuated since drug addiction is a medical condition instead of a voluntary choice or an hedonistic act [4]. However, this model is not exempt of criticism [5, 6], partially because the relevance of social and psychological factors is diminished in favor of the biological elements, and freeing the person from responsibility underestimates the importance of the personal willpower and motivation toward therapeutic change.

Setting this controversy aside, there is a consensus in that drug addiction, being a "brain disease" or not, certainly involves a neurobiological brain dysfunction that affects behavior. Brain morphological alterations in persons using different drug types (such as alcohol, cannabis, cocaine, methamphetamine, heroin, or tobacco) have been consistently reported even at the macrostructural level, usually involving significant gray and/or white matter shrinkage [7–13]. Moreover, functional neuroimage techniques reveal that connectivity among brain regions is also dysregulated [14]. It is important to note that the aberrant brain structure and function associated to drug addiction most likely results from a combination of (biological) brain features that exist *previous to* drug use as vulnerability factors, with the neuroadaptations that are *induced by* the drug itself (**Figure 1A**). Solid evidence has been provided in both ways (reviewed in [15]). On the one hand, individual differences in the form of stable personality traits such as impulsivity, elevated anxiety, risk-taking, and sensation seeking that are assumed to entail a particular biological and brain basis [16, 17] may predispose to engage in both drug use and addiction. On the other hand, brain and behavioral abnormalities often correlate with drug use patterns (i.e., the amount of drug consumed and/or the number of years using the drug) and may be completely or partially recovered by protracted drug abstinence [7, 8, 11, 13, 15, 18], suggesting that they were directly induced by the continuous action of the drug. Notably, preclinical studies in laboratory animals (that allow the exposure to the drug to be controlled by the experimenter) have confirmed both evidences. Individual traits in rodents (e.g., increased impulsivity) predict their subsequently exacerbated response to drugs compared to rodents that do not show this feature (e.g., [19, 20]); and both brain and behavioral alterations are experimentally induced by administering drugs to naïve animals (e.g., [21–23]).

Therefore, while it is difficult—especially for clinical research—to elucidate whether the observed behavioral and brain features are cause or consequence of drug use, both drug vulnerability factors and drug-induced brain effects are likely

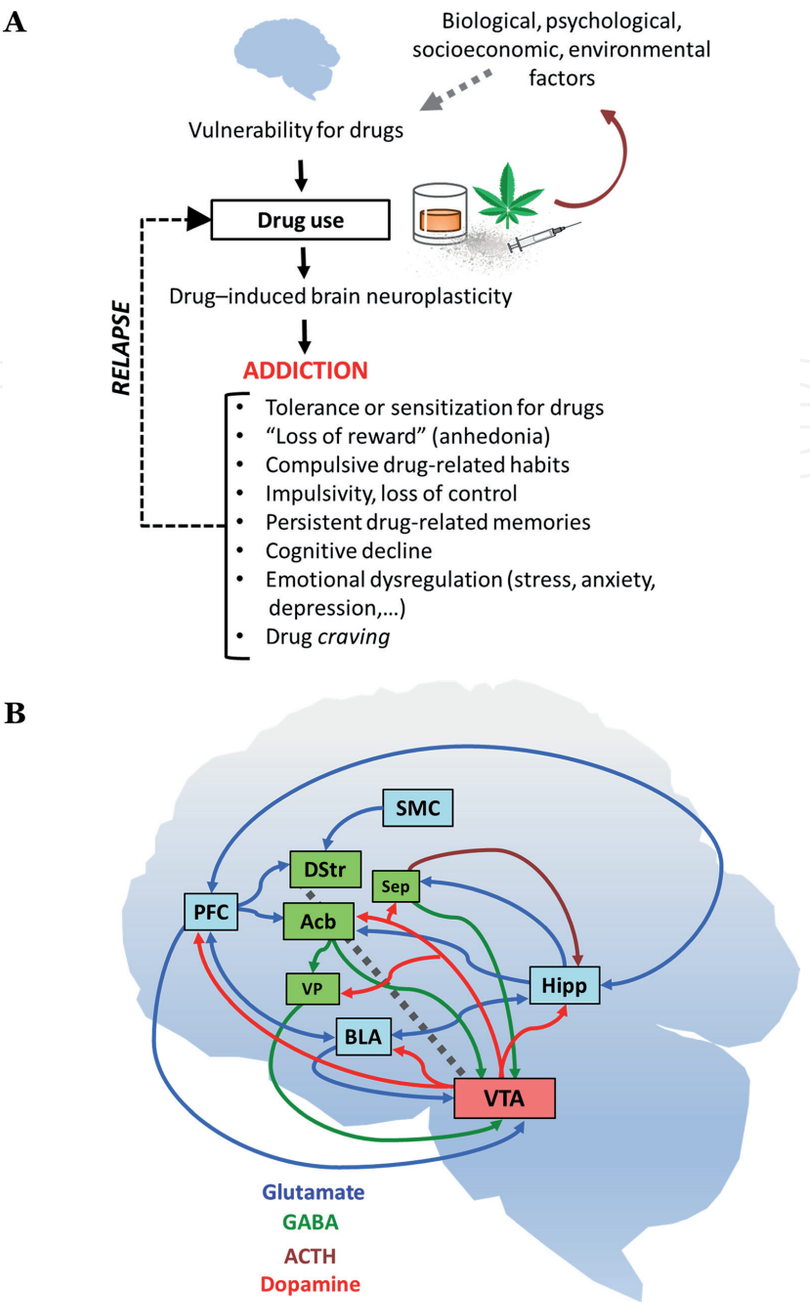


Figure 1.
(A) The "drug addiction cycle." Numerous factors intervene in the vulnerability for drugs, including a "vulnerable brain." Drug consumption induces widespread brain neuroadaptations that, in vulnerable individuals, would be addiction-like behavioral alterations that are likely to promote further drug use, aggravating its effects. (B) A non-exhaustive schematic representation of the brain structures and connections involved the brain circuit of learning, reward, and motivated behavior. A maladaptive functioning of this circuit supports the etiology and maintenance of drug addiction. Brain structures are colored on the basis of their main neurochemical content. The dashed line represents the "spiraling" nigrostriatal connections. Abbreviations: Acb, accumbens; ACTH, acetylcholine; BLA, basolateral amygdala; Dstr, dorsal striatum; GABA, γ-aminobutyric acid; Hipp, hippocampus; PFC, prefrontal cortex; Sep, septum; SMC, sensorimotor cortex; VP, ventral pallidum; VTA, ventral tegmental area.

to coexist and be interrelated. In the worst case scenario, a "vulnerable" brain is exposed to the drug, triggering an exacerbated response to the substance that increases the amount of drug subsequently consumed, thus also increasing the potential drug-induced harm (**Figure 1A**). Without the intent of underestimating the notable importance of psychological, social, economic, and environmental factors in the etiology and maintenance of drug addiction, this chapter will focus on the neurobiological component. In particular, we will review that the integrity of key brain regions that are normally involved in control of reward, planning,

learning, and motivated behavior is compromised in drug addiction to favor uncontrollable drug intake as well as other behavioral symptoms. Specifically, we will focus on the mesolimbic system, the dorsal striatum, and the limbic regions as key components of the "brain addiction circuit."

2. The mesolimbic system: a locus for drug and non-drug-related rewards

2.1 Experiencing rewards and learning to predict them

The mesolimbic system has been a traditional focus of drug addiction research, since it is a key substrate for reward and motivated behavior. The mesolimbic system comprises the accumbens (also called "ventral striatum") and the midbrain ventral tegmental area (VTA) as its main brain nodes and dopamine (often considered as the molecule of "pleasure and happiness" [24]) as its major neurotransmitter [25, 26]. The dopaminergic projection neurons in the VTA release dopamine to the accumbens—either at its core or shell subdivisions—as well as to memory-related limbic brain regions such as the prefrontal cortex, the hippocampus, and the amygdala (**Figure 1B**) [25, 27]. Conversely, these brain regions regulate VTA activity. Specifically, GABAergic inhibitory pathways from the accumbens may either stimulate [28] or exert inhibitory feedback control [29] over dopamine release by targeting either the dopaminergic VTA projection neurons or the inhibitory VTA interneurons [30, 31]. For their part, the glutamatergic limbic regions are all reciprocally interconnected, and they also project to the accumbens and to the VTA either directly or by indirect polysynaptic pathways, to stimulate dopamine release [27, 28, 32, 33] (**Figure 1B**). This illustrates that reward and memory systems in the brain are closely interrelated, which makes sense considering that learning is often driven by rewards, punishments, and their anticipation (**Figure 1B**) [34].

The dopaminergic mesolimbic system is involved in experiencing pleasure, and it is directly activated by primary rewards such as palatable food or sexual behavior [24], novel stimuli [35], or pleasant music [36]. By engaging its reciprocal connections to the limbic regions, the accumbens is important for determining the motivational valence of stimuli and for assessing learning incentives. In other words, the accumbens discriminates appetitive from aversive stimuli and decides in which degree they are "liked" or "wanted" [24, 37]. In agreement to this, preclinical research reveals a role of the accumbens in many forms of learning such as in spatial navigation [38], novel object and place recognition [39], fear conditioning [40], or instrumental behavior [41] (see "preclinical models of learning" in **Box 1**), and dopamine in the mesolimbic system promotes an activated state of alertness, arousal, or "seeking" that would facilitate exploration and reward gathering [42]. Moreover, the accumbens has an important role in anticipating the occurrence of rewards by learning which stimuli predicts them (i.e., acquiring conditioned reward-stimuli associations; **Table 1**) [43]. By association with a rewarding stimulus, a neutral stimulus becomes a conditioned reward and gains incentive motivational salience, being able to activate the mesolimbic reward system by itself [34].

When in the presence of dependence-inducing drugs, the dopaminergic mesolimbic system is highly activated, engaging different neurobiological mechanisms depending on the substance (e.g., inhibition of dopamine reuptake cocaine and methamphetamine [44, 45], stimulation of dopaminergic VTA neurons alcohol, methamphetamine, nicotine, cannabinoids [46–49], inhibition

Anhedonia: A reduced ability to feel pleasure or joy; a loss of interest for activities or stimuli that were previously engaging for the individual and elicited positive emotions. It is often a symptom of low mood (depression-like behavior). Persons with SUDs may suffer anhedonia or "loss of reward" for experiences that are not related to drugs.

Appetitive, aversive: Qualities of stimuli: rewarding (appetitive) or disliking (aversive).

Craving: An intense, uncontrollable, and anxious desire to use the drug. It is usually elicited by drug-associated stimuli and it may lead to relapse in drug use.

Declarative memory: This memory overlaps with the most common concept of "memory" as it refers to the ability to learn (and also recall, forget, etc.) facts, concepts, or words, life events, and spatial or contextual stimuli (e.g., when America was discovered, what you had for dinner yesterday, where the car was stationed, etc.).

Dorsal striatum: A motor control brain center that works in consonance with cortical brain regions (cortico-striatal circuit) to select and initiate appropriate goal-directed responses. The dorsal striatum also transforms the goal-directed actions that are repeatedly rewarded into automatic habits.

Drug sensitization (vs drug tolerance): Exacerbation of the rewarding or psychomotor effects of the drug, as a result of the neuroadaptations induced by repeated drug exposure. There is also evidence of the opposite effect, drug tolerance, meaning that the drug progressively blunts its actions.

Drug-associated stimuli: Those stimuli (objects, places, people, feelings, etc.) that, by associative learning processes, have been "linked" to the effects of the drug or to drug availability. The presence of these stimuli is a main cause of relapse, as they trigger both craving feelings and uncontrollable drug-seeking and drug-taking habits.

Escalation (in drug intake): The phenomenon by which the person progressively increases drug use, leading to excessive drug intake. It is also evidenced in the preclinical drug self-administration model, where the animal progressively self-administers more quantities of the drug as the task progresses.

Executive functions: A set of high-level cognitive skills that is important for "ruling" behavior. They involve decision-making, planning, reasoning, attentional control, cognitive flexibility, inhibition of undesired behaviors, etc.

Goal-directed behavior: Response directed to obtain a reward. It is planned, conscious, and often useful.

Habits: "Automatic" and involuntary responses that require minimal cognitive resources to be executed. They are generated after a goal-directed response has been repeated and rewarded numerous times. While habits are adaptive for everyday functioning, a main problem in drug addiction is that behaviors associated to drugs (drug-seeking, drug-taking, etc.) also become uncontrollable habits, contributing to relapse in drug use.

Incentive (motivational) salience: Refers to the intensity of attention, attraction, or desire ("wanting") that is elicited by a stimulus. It is usually related to its rewarding value. Drugs and drug-related stimuli gain incentive motivational salience in addiction.

Limbic regions: Brain regions mainly involved in the regulation of cognition and emotion. This review considers the prefrontal cortex, the hippocampus, and the amygdala as main brain limbic areas. They are impaired by addictive drugs.

Long-term potentiation (LTP), long-term depression (LTD): A form of neuroplasticity that changes the strength of a synapse, for example, as a result of learning processes or after exposure to a drug of abuse. In the LTP, the postsynaptic neuron increases its response (e.g., more neurotransmitter is released, or more neurotransmitter receptors are generated), while in the LTD the postsynaptic response is debilitated.

Mesolimbic system: Brain system mainly comprised by the VTA and the accumbens. It is important for experiencing, predicting, and assessing rewards and thus for motivated (i.e., goal-directed) behavior. It is also involved in the motor-activating effects of drugs.

Neuron: The main nerve cell in the brain that processes and transmits information through the synapsis. The main parts of a neuron are depicted in **Figure 2**. **Projection neurons** possess long axons that allow communication between distant brain regions, while **interneurons** have shorter axons, limited to a single brain area.

Neuroplasticity: Neuroplasticity or neuroadaptation refers to changes in the anatomical structure (dendrites, axon, nuclei, etc.) and function (synaptic strength, neurotransmitter release, etc.) of neurons, in response to environmental or internal stimuli. Another form of neuroplasticity is the generation of new neurons in the adult brain (adult hippocampal neurogenesis). Brain neuroplasticity is modulated by drugs of abuse, yielding an aberrant pattern of brain functioning that contributes to generate and maintain addiction.

Neurotoxicity: The effect of a hazardous substance that may involve an irreversible loss of the neuron's anatomy and function and even its death. Addictive drugs such as alcohol, methamphetamine, or heroin have demonstrated neurotoxicity.

Neurotransmitters: Chemical messengers synthetized by the neurons that transmit information between them, acting on specific receptors in the synapse. **Glutamate** is the main excitatory brain neurotransmitter, as it "activates" the target neuron, while **GABA** has an inhibitory role; **dopamine** is critical in the mesolimbic reward system regulating reward and arousal.

Preclinical models of addiction: Paradigms or "tasks" that are designed to assess addiction-related behaviors in animals, usually rodents (i.e., "preclinical" refers to laboratory research—animal or in vitro—previous to clinical studies in humans). For example, the **drug-induced conditioned place preference** assesses drug reward and the learning of drug-stimuli associations, by examining how much the rodent prefers to stay in a maze compartment where the drug was previously administered (which is distinguishable from a neutral maze compartment as they have different contextual cues). The **drug self-administration** paradigm assesses motivation for the drug, by examining how much the rodent presses a level that results in drug delivery (or how much the rodent keeps insisting in pressing the lever even when the drug is no longer provided). Pressing the lever is considered as a drug-seeking (or taking) behavior. There are other models such as the "voluntary drinking" paradigms used for ethanol.

Preclinical models of learning: There are a wide variety of tasks to assess different forms of learning and memory in rodents. For example, in the **spatial navigation** tasks, the animal learns to orientate in the surrounding space to find a particular place in a maze (e.g., the maze exit, or hidden food rewards). In **novelty-based** tasks, the animal prefers to explore a novel object or place as long as it remembers the familiar one(s). Tasks based on **associative learning** require the animal to associate stimuli; for example, in fear conditioning, a compartment of the maze where an electric shock is provided is discriminated by its contextual cues (shock-cue association). In **instrumental learning tasks** (operant conditioning), the animal learns to perform a specific response, such as pressing a lever, to obtain a reward, such as food.

Psychiatric comorbidity: Different psychiatric disorders that occur simultaneously in the same individual, usually worsening the therapeutic outcome. Drug addiction is often associated to high psychiatric comorbidity, including mood and anxiety disorders (depression, generalized anxiety, phobias, etc.) and personality disorders.

Relapse: Resuming drug use after a period of abstinence.

Reward: A stimuli or outcome that is pleasurable and/or beneficial for the individual. **Primary rewards** are those stimuli intrinsically pleasurable (e.g., a delicious food), while **conditioned rewards** are those that have gained their reinforcing value by being associated with a rewarding stimuli (e.g., the sound of a bell that rings when the food is ready to serve becomes rewarding).

Substance use disorder (SUD), drug addiction: A chronic and highly relapsing disorder which its main characteristic is an uncontrollable (and usually excessive) drug intake. Furthermore, addiction frequently carries a socioeconomic and health burden for the individual, including motivational, emotional, and cognitive impairment. Unfortunately, these symptoms induced by drugs contribute to further drug use, generating a "vicious cycle."

Stress: A physiological response generated by a stimulus perceived as threatening or aversive. The stress response is dysregulated by addictive drugs, and experiencing stress contributes to relapse in drug use.

Synapse: It is the region where chemical or electrical information is transmitted from one neuron to another. A typical chemical synapse uses neurotransmitters that are synthetized by the presynaptic neuron and released through the axon terminals (**Figure 2**); and then they bind with specific neurotransmitter receptors in the postsynaptic neuron that may be located in the dendritic spines but also in the axon or soma.

Vulnerability: Referred to addiction, "vulnerability" entails both biological features and behavioral (personality) traits that predispose the individual to initiate and maintain drug use or to generate a SUD. For example, exacerbated impulsivity and reduced inhibition of behavior, inclination to take risks, preference for experiencing novel stimuli or seeking sensations, or an anxious personality are associated to increased risk for drug abuse. Importantly, the behavioral attributes are assumed to be a reflection of a particular pattern of brain functioning (i.e., they entail a biological-brain-correlate).

Working memory: It is a short-term memory capacity for concepts or stimuli that do not need to be remembered in the long-term, but they should be processed (i.e., mentally manipulated or "worked with") for a short period of time. For example, working memory is needed for reasoning, planning, and solving problems or mathematical operations.

Box 1.
Definitions.

of VTA GABAergic interneurons opioids and cocaine [50, 51]. According to the accumbens' role for experiencing rewards, the accumbens is involved in enjoying the recreational feelings induced by drugs [52], in their "activating" psychomotor effects [53, 54], and in learning the stimuli that are predictive of the drug's effects or its availability (i.e., drug-stimuli associations [43, 55]). In this way, rodents with lesions in the accumbens will reduce the expression of drug-seeking or drug-taking behaviors when they are tested in common preclinical models for addiction-like responses, such as conditioned place preference or self-administration paradigms [54, 56–58].

	"Normal" functioning	Drug addiction
Mesolimbic system	• Reward • Incentive assessment ("liking") • Associative learning, reward prediction • Alertness, activation	• Drug reward (sensitization, tolerance) • Anhedonia • Incentive assessment ("wanting" drugs) • Drug-stimuli associations • Drug psychomotor activation • Drug craving • Relapse
Dorsal striatum	• Motor learning • Behavior-optimizing habits • Goal-directed responses	• Drug-related habits • Drug craving • Relapse
Limbic regions	• Behavioral control • Executive functions • Working memory • Declarative memory (associative learning) • Emotional regulation	• Behavioral disinhibition • Cognitive decline • Drug-stimuli associations • Emotional dysregulation • Drug craving • Relapse

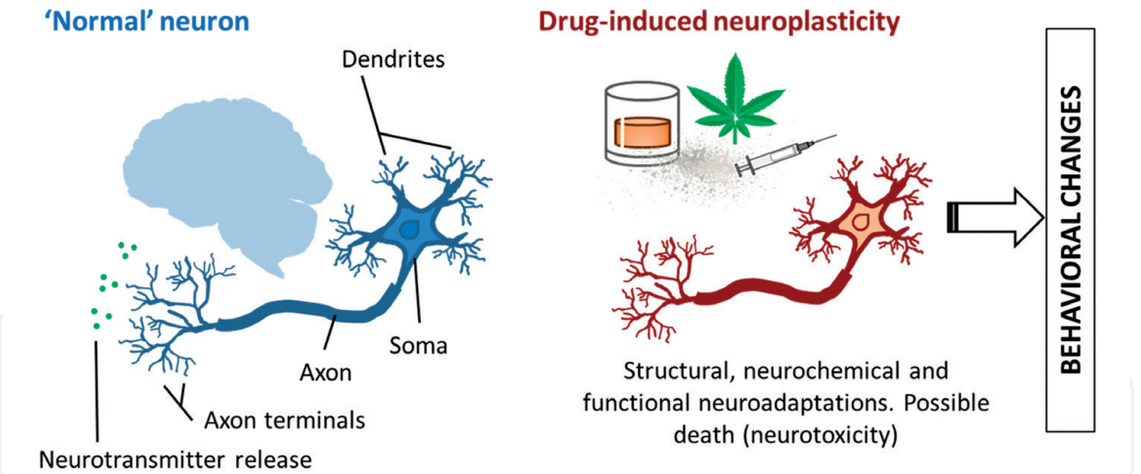
*Behavioral functions and addiction symptoms are linked to the main brain region(s) that supports them, but it should be noted that these reward and learning-related brain systems act in close synchrony (***Figure 1B***) to support behavior.*

Table 1.
Impaired function of learning-related brain regions in drug addiction.

2.2 Desire for drug overcomes natural rewards in addiction

As a result of its repeated activation by chronic drug exposure, the mesolimbic system may undergo long-lasting neuroadaptations which are involved in addiction (**Figure 2**). In clinical population with SUDs, a reduced volume of the accumbens has been reported [59, 60], and one *postmortem* study in cocaine users reveals a loss of dopaminergic neurons in the midbrain [61]. In drug-withdrawn animals, experiments have described persistent changes in accumbens dendrite branching and spine density (that are normally increased for alcohol, cocaine, methamphetamine, and nicotine [62, 63] but decreased for morphine or cannabinoids [63, 64]) as well as in the VTA (where psychostimulants tend to increase dendritic arborization and spines [65] but cannabinoids and opioids induce visible morphometrical reductions in the soma of the dopaminergic neurons [64, 66]).

Importantly, these structural modifications concomitantly occur with profound neurochemical and functional changes (**Figure 2**, **Table 1**), including modifications of the synaptic strength (long-term potentiation, LTP, or long-term depression, LTD) [67, 68]. The drug-induced neuroplastic and neurochemical adaptations, involving dopamine and glutamate signaling [69, 70], may augment the mesolimbic response to the drug. This supports the phenomenon of "behavioral sensitization," referring to an exacerbated drug's rewarding or motor-activating effects. Drug sensitization has been widely reported in rodents that will progressively increase locomotor activity and VTA dopamine release after they are repeatedly exposed to moderate doses of commonly abused drugs (most frequently to psychostimulants, but also to other drug types [70, 71]). But the evidence of drug sensitization in humans is more scarce [72]. In fact, there is evidence against



Mesolimbic system	Dorsal striatum	Limbic regions
Accumbens and VTA: • Changes in dendrite branching and spine density • Functional synaptic changes (LTP and/or LTD) **Accumbens:** • Reduced gray matter volume • Neurochemical alterations (lower levels of dopamine and D2 receptor expression; altered glutamate signalling) **VTA:** • Loss of dopaminergic VTA neurons (cocaine), soma reduction (cannabinoids, opioids) • Exhacerbated or decreased dopamine release	• Changes in dendrite branching and spine density • Functional synaptic changes (LTP and/or LTD) • Neurochemical alterations (lower levels of dopamine and D2 receptor expression; potentiated glutamate signalling)	**Prefrontal cortex, hippocampus, amygdala:** • Changes in dendrite branching and spine density • Functional synaptic changes (LTP and/or LTD) • Reduced gray matter volume • Neurochemical alterations (GABA and glutamate signalling) **Hippocampus:** • Reduced adult hippocampal neurogenesis

Figure 2.
A non-exhaustive list of brain structural and functional neuroadaptations induced by addictive drugs. Only the brain areas that are the focus of this review are depicted; but it should be noted that drugs affect widespread neuroplasticity in the whole brain. Neurotoxic effects (i.e., neuronal death) have been evidenced for certain drug types such as alcohol, methamphetamine, or heroin.

the drug-sensitization theory, reporting that the drug-induced dopamine response could become progressively blunted or habituated, which would then induce drug tolerance effects instead [72, 73]. Drug tolerance may ultimately lead to increased drug use, since more quantity of the substance is progressively needed to experience its effects.

In any case, escalation in drug intake is associated to a notable reduction of basal dopaminergic transmission in the accumbens and in the whole striatum, as evidenced by lower levels of endogenous striatal dopamine and reduced expression of dopamine receptors—mostly the postsynaptic D2 receptor [74–77]. This may contribute to the fact that, contrasting with the ability of drugs to stimulate the mesolimbic system, primary rewards may diminish their reinforcing value in addiction [73, 78]. Accordingly, an increased brain threshold for experiencing reward (measured by intracranial self-stimulation) and "loss of pleasure" anhedonic behaviors (e.g., reduced intake of a highly palatable food) are described in drug-withdrawn animals (reviewed in [79]). A diminished interest for non-drug rewards will impede persons with SUD to enjoy daily-life experiences or to attain

interpersonal and professional goals as they now hold a weak appeal [72]. As predicted by this "loss of reward" model, drug use may then gain motivational incentive as a compensation for the decreased sensitivity to natural rewards and the hypodopaminergic mesolimbic state [73, 78, 79].

Thereby, while in a state of overall reduced reward and motivation for non-drug experiences, the drug and its associated stimuli would increase their incentive value in addiction: drugs would be "wanted," even when they are no longer "liked" [80]. In relation to this, drug use is highly driven by "craving", an intense and uncontrollable desire for the drug that progressively increases during abstinence periods (i.e., craving incubation) and is greatly triggered or aggravated when drug-associated stimuli are presented, eliciting relapse in compulsive drug-seeking or drug-taking [55]. Current evidence suggests that the neural bases of drug craving involve the mesolimbic system but are widespread distributed through the "brain addiction circuit" (**Table 1**). As elucidated by preclinical studies, the accumbens is one of the brain regions that supports drug craving incubation and relapse, together with dorsal striatal and limbic areas (reviewed in [81]). Accordingly, functional neuroimage studies in drug users exposed to drug-associated cues have reported increased activation in either the accumbens, the dorsal striatum, or the limbic regions in correlation with the intensity of craving experienced [82–86].

3. The dorsal striatum: where goal-directed behavior becomes habit

Together with the mesolimbic system, the dorsal striatum is a key brain region to explain addiction. The dorsal striatum, composed by the caudate nucleus and putamen, is a center for sensorimotor integration. It receives excitatory inputs from the thalamus, which is a major relay for sensory signals, and extensive excitatory inputs from cortical areas that are distributed across the striatal subdivisions through the *cortico-striatal circuit* [87] (**Figure 1B**). In this regard, the *dorsomedial striatum* is mainly innervated by cognitive-related prefrontal cortical regions supporting executive functions (and thus it is mostly involved in goal-directed behavioral control), while the *dorsolateral striatum* mostly receives input from primary sensory and motor cortices (and thus seems more involved in habit learning and motor execution) [55, 88]. Furthermore, the so-called *spiraling nigrostriatal circuit* allows functional and bidirectional serial connections among the dorsal striatum and the reward centers including the accumbens and the dopaminergic neurons in the midbrain [55, 88] (**Figure 1B**).

The dorsal striatum is critical to control motor learning, motor planning, and motor execution [87] and to engage in motivated goal-directed behaviors, including those needed for survival [89]. Strikingly, hungry mice with dorsal striatal malfunction will not initiate feeding behavior even when food is placed right in front of them, nor they would explore a novel environment [89]. Considering this, the dorsal striatum is essential for instrumental learning [87, 90], but its function differs from the mesolimbic system's role. While the accumbens predicts the occurrence of a reward in the presence of reward-associated stimuli, the dorsal striatum is in charge of selecting and initiating the actions or movement patterns that are adequate to obtain such expected reward in a certain environment. However, once the reward-associated cue is repeatedly paired with an appropriate action, that results successfully rewarded, the action progressively becomes a routinary response that is automatically elicited by the associated stimulus. In other words, the action becomes a *habit* [55, 91, 92]. Compared to planned goal-directed responses, habits

are less flexible and more prone to errors since they are executed unconsciously, based on past performance, without thoughtful evaluation of the current situation. Despite this, habits are highly adaptive for normal everyday functioning, since they allow the dorsal striatum to rapidly select and perform common responses without demanding cognitive and attentional resources that may be directed elsewhere [93].

Nevertheless, when habits involve undesired drug-seeking and drug-taking responses, they entail a core problem in drug addiction. In fact, some authors conceptualize addiction as a "shift" of behavioral control from the accumbens to the dorsal striatal regions as drug-induced neuroplasticity hijack the striatal circuits responsible for habit forming [55, 91, 92] (**Figure 2**). Similarly to what is reported for the accumbens, there is a depletion in the dorsal striatal dopaminergic signaling as evidenced by lower levels of endogenous dopamine [74, 75] and a reduced availability of the dopaminergic D2 receptors [76, 77, 94, 95]. However, in addition to structural plasticity [96], the dorsal striatal neurons may trigger concomitant synaptic changes in the presence of drugs, resulting either in LTP or LTD in response to the midbrain dopaminergic input [91, 92], together with a potentiated glutamatergic transmission attending to an increased density and synaptic facilitation of glutamate receptors [96–98]. Interestingly, while many brain regions in persons with SUDs usually show a reduced gray matter volume, the dorsal striatum has been found either reduced or hypertrophied in psychostimulant-dependent individuals [99–101]. The progressive transition of drug-seeking from a goal-directed behavior to a compulsive habit under striatal control has been elegantly modeled by animal research. At the initial phases of drug self-administration, the expression of this behavior requires the integrity of both the accumbens and the dorsal striatum [102]. But once the animal is extensively trained for drug-seeking, cue-induced drug-seeking is disrupted by interventions affecting the dorsal striatal region selectively (revised in [55]). Furthermore, animals with extended history of drug exposure will not cease drug-seeking even when this behavior is no longer "rationally" worth it (e.g., when they must endure highly aversive stimuli such as electric shocks to obtain the drug [103]), mimicking habitual drug use despite of negative consequences as found in SUD patients.

In conclusion, striatal neuroplasticity supports the progressive transformation of conscious and voluntary (i.e., goal-directed) drug-taking actions into habits (**Table 1**). Habits are an important cause of relapse as they are compulsive and uncontrollable by the individual and automatically elicited by drug-associated cues. This explains that drug-related stimuli (e.g., an alcohol bottle, a razor blade, a place where the drug was usually consumed, a drug-using companion, or even drug-associated emotions and thoughts) would trigger drug use—usually accompanied by intense craving feelings—despite of efforts to remain abstinent [55, 91, 92] (**Figure 1A**).

4. Limbic regions: the prefrontal cortex, the amygdala, and the hippocampus

4.1 Controlling behavior, memory, and mood

While the addiction theories have traditionally focused on the interaction among the mesolimbic system and the dorsal striatal regions, the limbic brain regions—such as the prefrontal cortex, the hippocampus, and the amygdala—have gained increased attention in addiction [27, 104, 105]. As exposed before, the prefrontal cortex, the hippocampus, and the amygdala are mainly glutamatergic structures all

reciprocally interconnected [33] that are closely integrated into the reward brain circuit by receiving direct dopaminergic inputs from the VTA and, conversely, by regulating accumbens and VTA activity (Section 2.1; **Figure 1B**).

The limbic system is classically defined as the brain substrate of "emotion" [106]. The limbic regions modulate the stress response, which is generally stimulated by the amygdala but suppressed by the hippocampus and the prefrontal cortex by inhibitory feedback mechanisms [107]. The amygdala also plays a pivotal role in triggering "unpleasant" emotions and responses such as anxiety and fear [108, 109], though it is also involved in positive emotions and it is activated after either appetitive or aversive stimuli, to evaluate their motivational value [110]. The limbic regions also hold cognitive functions. The prefrontal cortex has a key role in behavioral control, by guiding the dorsal striatum to select appropriate actions through the abovementioned cortico-striatal circuit [88] (Section 3) and by inhibiting or updating inappropriate behaviors (reviewed in [15]). Accordingly, the prefrontal cortex is responsible of higher cognitive process such as planning, reasoning, behavioral flexibility, or decision-making (executive functions), and it holds the "working-memory" capacity that allows to manipulate information that is stored in the short-term (reviewed in [15]). The hippocampus is involved in the acquisition, long-term storage, and further processing (extinction, retrieval, updating, etc.) of declarative memory [111]. Declarative memory includes the semantic memory (verbal information, facts, and concepts), the episodic memory (life events), as well as the spatial memory (contexts and places), so a loss of hippocampal function drives severe anterograde amnesia [111]. Moreover, the hippocampus is important for integrating events that are separated in time or space (thus being crucial for associative learning [112]), and it participates in novelty detection that contributes to recognize previously presented stimuli, allowing to lead exploration and/or cognitive resources to the novel ones [113]. Regarding the amygdala, this region also holds a role in cognition, such as in fear memories [114] or in facilitating the emotional modulation of declarative memory, since emotionally arousing experiences are more strongly consolidated and remembered than neutral ones [115] (**Table 1**).

The initial experiences with drugs would use the regular learning mechanisms in the limbic regions to be acquired and stored in memory [116]. In this way, the prefrontal cortex guides the dorsal striatum and acts as an "ON/OFF switch" for drug-seeking, deciding when this behavior should be allowed or inhibited [105]. Regarding the hippocampus and the amygdala, they interact with the prefrontal cortex and the accumbens for the learning of drug-stimuli associations; and these limbic regions collaborate for the subsequent retrieval, extinction, or reinstatement of the drug-related memories (being the reinstatement, a form of "relapse," that in preclinical models is elicited by drug-associated cues, by stress, or by a low dose of the drug—*priming*) (reviewed in [15, 27, 116]). Since the drug-related experiences are rewarding and emotionally arousing, they activate neurobiological pathways involved in the emotional enhancement of associative memory, which may potentiate their acquisition and subsequent long-term maintenance [116, 117].

4.2 Affective and cognitive alterations are concomitant to drug addiction

After repeated drug exposure, the limbic regions are highly vulnerable to undergo neuroplastic and/or neurodegenerative changes (**Figure 2**). A reduced gray matter volume is often found in the prefrontal cortex, hippocampus, and amygdala of chronic drug users [7, 10, 12, 59, 118], together with a dysregulated expression of genes including those involved in GABA and glutamate neurotransmission

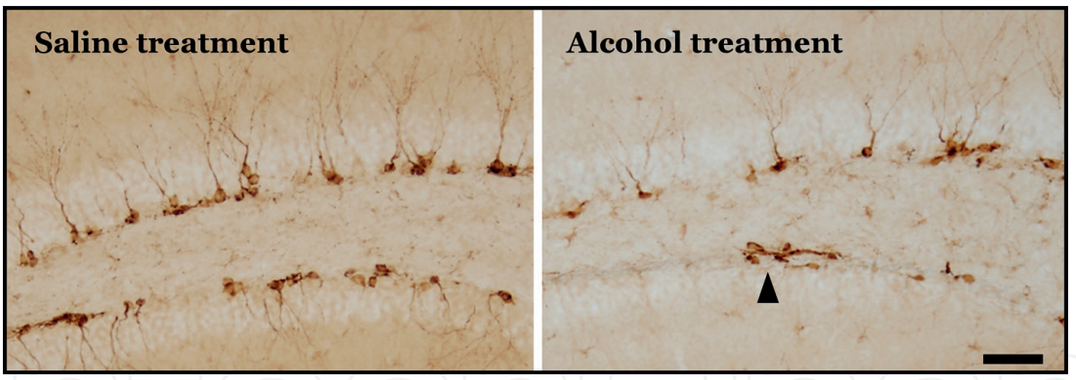


Figure 3.
Reduced adult hippocampal neurogenesis as an example of drug-induced neuroplasticity. Photographs show the hippocampus (dentate gyrus) of mice treated either with saline or ethanol for 8 days (protocol published in our previous work [22]). Young neurons expressing the immature neuron marker doublecortin were stained by immunohistochemistry. Arrow points young neurons showing horizontally disposed nuclei and underdeveloped dendritic tree in the ethanol-treated animal. Scale bar: 100 μm.

[119, 120] and alteration in LTP or LTD processes [121–124]. Particularly, alcohol is associated with severe brain damage and neurotoxicity in the limbic system [12], and sufficient exposure may precipitate severe neurocognitive syndromes such as lasting dementia [125]. Other limbic neuroadaptations induced by addictive drugs involve a reduction of adult hippocampal neurogenesis, as evidenced by a recent *postmortem* study in persons that abused alcohol [126]. The generation, maturation, and functional integration of new neurons in the adult brain—where the dentate gyrus of the hippocampus is a main neurogenic niche—has been extensively described in rodents, for which the new hippocampal neurons participate in many forms of hippocampal-dependent learning and emotional regulation [127]. While the existence and functional implications of adult hippocampal neurogenesis in humans still generate controversy [128], there is currently a wide preclinical evidence supporting that drugs of abuse modulate—mainly reduce—the adult-born hippocampal neurons (**Figure 3**), which has raised interest on the potential involvement of this neuroplastic phenomenon in addiction [27, 116, 129, 130].

Damage of the limbic regions generates the "cognitive" symptoms in drug addiction. The drug-induced neuroplasticity in prefrontal areas involved in the corticostriatal circuit contributes to the "loss of control" over drug-seeking behavior that becomes further governed by the dorsal striatal habits [105, 131, 132] (Section 3; **Table 1**). The prefrontal "disinhibition" may affect other behavioral domains, promoting impulsivity, impaired decision-making, and more involvement in risky behaviors [133] which, in turn, may contribute to further engagement in drug use (**Figure 1A**). Since the limbic regions are required for associative memory, memories for drug-stimuli associations may become engrained in addiction, being resistant to extinction and forgetting but prone to reinstatement [117, 134, 135]. Therefore, a potentiated function of the limbic regions at the initial experiences with drugs may facilitate their storage in memory; but their impoverished function after repeated drug exposure may impede these memories to be subsequently extinguished. As explained before (Sections 2 and 3), the memories for drug-stimuli associations are relevant in addiction, since they trigger drug craving and habitual drug use responses.

Furthermore, limbic system malfunction in addiction yields a variable degree of cognitive decline that may affect both prefrontal- and hippocampal-dependent domains, including attention, working memory, declarative memory, and executive functions, as evidenced in both drug-exposed animals and in persons with

SUDs (**Table 1**; reviewed in [15]). Cognitive impairment may last for months or years after ceasing drug use, and, in the most severe cases, it may be irreversible (e.g., [18, 125, 136–138]). The cognitive decline has relevant clinical implications, since it is a consistent predictor of addiction treatment dropout and relapse (reviewed in [15]). In this way, it is possible for cognitive impairment to act as an indirect indicator of the extent of malfunction of the limbic regions that are implicated in key behavioral processes that lead to drug use such as behavioral disinhibition or drug craving (**Table 1**). Another possibility is that cognitive impairment may directly compromise the follow-up of addiction treatments by burdening the acquisition of new adaptive information, such as the contents of behavioral therapies that usually require a considerable cognitive effort to be apprehended [139].

Finally, at the emotional level, malfunction of limbic regions during drug withdrawal may curse with a "negative affect" involving stress and anxiety in addition to "loss of reward" (Section 2; **Table 1**) that may trigger drug use by negative reinforcement (i.e., using drugs to escape the aversive emotional state) [78, 140] (**Figure 1A**). In fact, the stress response is frequently dysregulated in persons with SUDs [141] that are vulnerable to stressful experiences, which are a powerful cause of relapse in drug use [81, 142]. Furthermore, SUDs have a high psychiatric comorbidity (~40%) with mood and anxiety disorders [143–145]. Dual pathology complicates the treatment of drug addiction, since an integrative therapeutic approach that involves both the SUD and the comorbid psychiatric disorder may be necessary for these patients [146].

5. Conclusion

This chapter shows that addiction compromises widespread brain neuroplasticity and function, which includes—but is not limited to—key brain regions involved in learning, reward, and motivated behavior. As consequence of repeated drug exposure, probably acting in combination with pre-existing neurobiological vulnerability traits, these regions corrupt their "normal" activity and promote dysfunctional behavior that underlies the etiology and maintenance of the drug addiction disorder. Considering this, therapies directed to promote adaptive neuroplasticity that allows these brain regions to regain their original function are valuable in drug addiction. Importantly, these strategies are not limited to biomedical interventions, but they may include a wide range of behavioral approaches, such as cognitive stimulation, considering that engagement in new and appealing experiences may sculpt brain neuroplasticity, even in the presence of drugs [15]. Therefore, while addiction may be, in a way, a "brain disease," many factors should be taken into account, considering that thoughts, emotions, social, and environmental stimuli ultimately impact the brain.

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Conflict of interest

Authors declare no conflicts of interest.

List of abbreviations and acronyms

Acb	accumbens
ACTH	acetylcholine
BLA	basolateral amygdala
D2 receptor	dopamine receptor "D2"
Dstr	dorsal striatum
GABA	γ-aminobutyric acid
Hipp	hippocampus
LTP	long-term potentiation
LTD	long-term depression
PFC	prefrontal cortex
Sep	septum
SMC	sensorimotor cortex
SUD	substance use disorder
VP	ventral pallidum
VTA	ventral tegmental area

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References

[1] GBD 2016 Alcohol Collaborators. Alcohol use and burden for 195 countries and territories, 1990-2016: A systematic analysis for the Global Burden of Disease Study 2016. Lancet. 2018;**392**:1015-1035

[2] United Nations Office on Drugs and Crime. World Drug Report 2018: United Nations publication, Sales No. E.18.XI.9; 2018

[3] Marlatt GA, Baer JS. Addictive behaviors: Etiology and treatment. Annual Review of Psychology. 1988;**39**:223-252

[4] Volkow ND, Koob GF, McLellan AT. Neurobiologic advances from the brain disease model of addiction. The New England Journal of Medicine. 2016;**374**:363-371

[5] Hammer R, Dingel M, Ostergren J, Partridge B, McCormick J, Koenig BA. Addiction: Current criticism of the brain disease paradigm. AJOB Neuroscience. 2013;**4**:27-32

[6] Levy N. Addiction is not a brain disease (and it matters). Frontiers in Psychiatry. 2013;**4**:24

[7] Battistella G, Fornari E, Annoni JM, Chtioui H, Dao K, Fabritius M, et al. Long-term effects of cannabis on brain structure. Neuropsychopharmacology. 2014;**39**:2041-2048

[8] Connolly CG, Bell RP, Foxe JJ, Garavan H. Dissociated grey matter changes with prolonged addiction and extended abstinence in cocaine users. PLoS One. 2013;**8**:e59645

[9] Ersche KD, Jones PS, Williams GB, Turton AJ, Robbins TW, Bullmore ET. Abnormal brain structure implicated in stimulant drug addiction. Science. 2012;**335**:601-604

[10] Gallinat J, Meisenzahl E, Jacobsen LK, Kalus P, Bierbrauer J, Kienast T, et al. Smoking and structural brain deficits: A volumetric MR investigation. The European Journal of Neuroscience. 2006;**24**:1744-1750

[11] Hall MG, Alhassoon OM, Stern MJ, Wollman SC, Kimmel CL, Perez-Figueroa A, et al. Gray matter abnormalities in cocaine versus methamphetamine-dependent patients: A neuroimaging meta-analysis. The American Journal of Drug and Alcohol Abuse. 2015;**41**:290-299

[12] Kril JJ, Halliday GM. Brain shrinkage in alcoholics: A decade on and what have we learned? Progress in Neurobiology. 1999;**58**:381-387

[13] Li M, Tian J, Zhang R, Qiu Y, Wen X, Ma X, et al. Abnormal cortical thickness in heroin-dependent individuals. NeuroImage. 2014;**88**:295-307

[14] Sutherland MT, McHugh MJ, Pariyadath V, Stein EA. Resting state functional connectivity in addiction: Lessons learned and a road ahead. NeuroImage. 2012;**62**:2281-2295

[15] Sampedro-Piquero P, de Guevara-Miranda DL, Pavon FJ, Serrano A, Suarez J, de Fonseca FR, et al. Neuroplastic and cognitive impairment in substance use disorders: A therapeutic potential of cognitive stimulation. Neuroscience & Biobehavioral Reviews. 2018. (In Press) DOI: 10.1016/j.neubiorev.2018.11.015

[16] Ersche KD, Williams GB, Robbins TW, Bullmore ET. Meta-analysis of structural brain abnormalities associated with stimulant drug dependence and neuroimaging of addiction vulnerability and resilience. Current Opinion in Neurobiology. 2013;**23**:615-624

[17] Homberg JR, Karel P, Verheij MM. Individual differences in cocaine addiction: Maladaptive behavioural traits. Addiction Biology. 2014;**19**:517-528

[18] Vonmoos M, Hulka LM, Preller KH, Minder F, Baumgartner MR, Quednow BB. Cognitive impairment in cocaine users is drug-induced but partially reversible: Evidence from a longitudinal study. Neuropsychopharmacology. 2014;**39**:2200-2210

[19] Belin D, Berson N, Balado E, Piazza PV, Deroche-Gamonet V. High-novelty-preference rats are predisposed to compulsive cocaine self-administration. Neuropsychopharmacology. 2011;**36**:569-579

[20] Jupp B, Caprioli D, Dalley JW. Highly impulsive rats: Modelling an endophenotype to determine the neurobiological, genetic and environmental mechanisms of addiction. Disease Models & Mechanisms. 2013;**6**:302-311

[21] Ladron de Guevara-Miranda D, Millon C, Rosell-Valle C, Perez-Fernandez M, Missiroli M, Serrano A, et al. Long-lasting memory deficits in mice withdrawn from cocaine are concomitant with neuroadaptations in hippocampal basal activity, GABAergic interneurons and adult neurogenesis. Disease Models & Mechanisms. 2017;**10**:323-336

[22] Sanchez-Marin L, Ladron de Guevara-Miranda D, Manas-Padilla MC, Alen F, Moreno-Fernandez RD, Diaz-Navarro C, et al. Systemic blockade of LPA1/3 lysophosphatidic acid receptors by ki16425 modulates the effects of ethanol on the brain and behavior. Neuropharmacology. 2018;**133**:189-201

[23] Sanchez-Marin L, Pavon FJ, Decara J, Suarez J, Gavito A, Castilla-Ortega E, et al. Effects of intermittent alcohol exposure on emotion and cognition: A potential role for the endogenous cannabinoid system and neuroinflammation. Frontiers in Behavioral Neuroscience. 2017;**11**:15

[24] Berridge KC, Robinson TE. What is the role of dopamine in reward: Hedonic impact, reward learning, or incentive salience? Brain Research. Brain Research Reviews. 1998;**28**:309-369

[25] Ikemoto S. Dopamine reward circuitry: Two projection systems from the ventral midbrain to the nucleus accumbens-olfactory tubercle complex. Brain Research Reviews. 2007;**56**:27-78

[26] Kauer JA. Learning mechanisms in addiction: Synaptic plasticity in the ventral tegmental area as a result of exposure to drugs of abuse. Annual Review of Physiology. 2004;**66**:447-475

[27] Castilla-Ortega E, Serrano A, Blanco E, Araos P, Suarez J, Pavon FJ, et al. A place for the hippocampus in the cocaine addiction circuit: Potential roles for adult hippocampal neurogenesis. Neuroscience and Biobehavioral Reviews. 2016;**66**:15-32

[28] Floresco SB, Todd CL, Grace AA. Glutamatergic afferents from the hippocampus to the nucleus accumbens regulate activity of ventral tegmental area dopamine neurons. The Journal of Neuroscience. 2001;**21**:4915-4922

[29] Rahman S, McBride WJ. Feedback control of mesolimbic somatodendritic dopamine release in rat brain. Journal of Neurochemistry. 2000;**74**:684-692

[30] Faget L, Osakada F, Duan J, Ressler R, Johnson AB, Proudfoot JA, et al. Afferent inputs to neurotransmitter-defined cell types in the ventral tegmental area. Cell Reports. 2016;**15**:2796-2808

[31] Haber SN, Fudge JL, McFarland NR. Striatonigrostriatal pathways in primates form an ascending spiral

from the shell to the dorsolateral striatum. The Journal of Neuroscience. 2000;**20**:2369-2382

[32] Geisler S, Wise RA. Functional implications of glutamatergic projections to the ventral tegmental area. Reviews in the Neurosciences. 2008;**19**:227-244

[33] Jin J, Maren S. Prefrontal-hippocampal interactions in memory and emotion. Frontiers in Systems Neuroscience. 2015;**9**:170

[34] Schultz W, Dayan P, Montague PR. A neural substrate of prediction and reward. Science. 1997;**275**:1593-1599

[35] Bunzeck N, Doeller CF, Dolan RJ, Duzel E. Contextual interaction between novelty and reward processing within the mesolimbic system. Human Brain Mapping. 2012;**33**:1309-1324

[36] Menon V, Levitin DJ. The rewards of music listening: Response and physiological connectivity of the mesolimbic system. NeuroImage. 2005;**28**:175-184

[37] Cooper JC, Knutson B. Valence and salience contribute to nucleus accumbens activation. NeuroImage. 2008;**39**:538-547

[38] Rinaldi A, Oliverio A, Mele A. Spatial memory, plasticity and nucleus accumbens. Reviews in the Neurosciences. 2012;**23**:527-541

[39] Nelson AJ, Thur KE, Marsden CA, Cassaday HJ. Dissociable roles of dopamine within the core and medial shell of the nucleus accumbens in memory for objects and place. Behavioral Neuroscience. 2010;**124**:789-799

[40] Fadok JP, Darvas M, Dickerson TM, Palmiter RD. Long-term memory for pavlovian fear conditioning requires dopamine in the nucleus accumbens and basolateral amygdala. PLoS One. 2010;**5**:e12751

[41] Hernandez PJ, Sadeghian K, Kelley AE. Early consolidation of instrumental learning requires protein synthesis in the nucleus accumbens. Nature Neuroscience. 2002;**5**:1327-1331

[42] Alcaro A, Huber R, Panksepp J. Behavioral functions of the mesolimbic dopaminergic system: An affective neuroethological perspective. Brain Research Reviews. 2007;**56**:283-321

[43] Day JJ, Carelli RM. The nucleus accumbens and Pavlovian reward learning. The Neuroscientist. 2007;**13**:148-159

[44] Bennett BA, Hollingsworth CK, Martin RS, Harp JJ. Methamphetamine-induced alterations in dopamine transporter function. Brain Research. 1998;**782**:219-227

[45] Brodie MS, Dunwiddie TV. Cocaine effects in the ventral tegmental area: Evidence for an indirect dopaminergic mechanism of action. Naunyn-Schmiedeberg's Archives of Pharmacology. 1990;**342**:660-665

[46] Brodie MS, Pesold C, Appel SB. Ethanol directly excites dopaminergic ventral tegmental area reward neurons. Alcoholism, Clinical and Experimental Research. 1999;**23**:1848-1852

[47] French ED. delta9-Tetrahydrocannabinol excites rat VTA dopamine neurons through activation of cannabinoid CB1 but not opioid receptors. Neuroscience Letters. 1997;**226**:159-162

[48] Liu L, Zhao-Shea R, McIntosh JM, Gardner PD, Tapper AR. Nicotine persistently activates ventral tegmental area dopaminergic neurons via nicotinic acetylcholine receptors containing

alpha4 and alpha6 subunits. Molecular Pharmacology. 2012;**81**:541-548

[49] Uramura K, Yada T, Muroya S, Shioda S, Shiratani T, Takigawa M. Methamphetamine induces cytosolic Ca^{2+} oscillations in the VTA dopamine neurons. Neuroreport. 2000;**11**:1057-1061

[50] Johnson SW, North RA. Opioids excite dopamine neurons by hyperpolarization of local interneurons. The Journal of Neuroscience. 1992;**12**:483-488

[51] Steffensen SC, Taylor SR, Horton ML, Barber EN, Lyle LT, Stobbs SH, et al. Cocaine disinhibits dopamine neurons in the ventral tegmental area via use-dependent blockade of GABA neuron voltage-sensitive sodium channels. The European Journal of Neuroscience. 2008;**28**:2028-2040

[52] Drevets WC, Gautier C, Price JC, Kupfer DJ, Kinahan PE, Grace AA, et al. Amphetamine-induced dopamine release in human ventral striatum correlates with euphoria. Biological Psychiatry. 2001;**49**:81-96

[53] Boye SM, Grant RJ, Clarke PB. Disruption of dopaminergic neurotransmission in nucleus accumbens core inhibits the locomotor stimulant effects of nicotine and D-amphetamine in rats. Neuropharmacology. 2001;**40**:792-805

[54] Sellings LH, McQuade LE, Clarke PB. Evidence for multiple sites within rat ventral striatum mediating cocaine-conditioned place preference and locomotor activation. The Journal of Pharmacology and Experimental Therapeutics. 2006;**317**:1178-1187

[55] Everitt BJ. Neural and psychological mechanisms underlying compulsive drug seeking habits and drug memories—Indications for novel treatments of addiction. The European Journal of Neuroscience. 2014;**40**:2163-2182

[56] Corrigall WA, Franklin KB, Coen KM, Clarke PB. The mesolimbic dopaminergic system is implicated in the reinforcing effects of nicotine. Psychopharmacology (Berl). 1992;**107**:285-289

[57] Pettit HO, Ettenberg A, Bloom FE, Koob GF. Destruction of dopamine in the nucleus accumbens selectively attenuates cocaine but not heroin self-administration in rats. Psychopharmacology. 1984;**84**:167-173

[58] Spyraki C, Fibiger HC, Phillips AG. Attenuation of heroin reward in rats by disruption of the mesolimbic dopamine system. Psychopharmacology. 1983;**79**:278-283

[59] Makris N, Oscar-Berman M, Jaffin SK, Hodge SM, Kennedy DN, Caviness VS, et al. Decreased volume of the brain reward system in alcoholism. Biological Psychiatry. 2008;**64**:192-202

[60] Schuch-Goi SB, Goi PD, Bermudez M, Fara LS, Kessler FP, Pechansky F, et al. Accumbens volumes are reduced among crack-cocaine users. Neuroscience Letters. 2017;**645**:86-89

[61] Little KY, Ramssen E, Welchko R, Volberg V, Roland CJ, Cassin B. Decreased brain dopamine cell numbers in human cocaine users. Psychiatry Research. 2009;**168**:173-180

[62] Peterson VL, McCool BA, Hamilton DA. Effects of ethanol exposure and withdrawal on dendritic morphology and spine density in the nucleus accumbens core and shell. Brain Research. 2015;**1594**:125-135

[63] Robinson TE, Kolb B. Structural plasticity associated with exposure to drugs of abuse. Neuropharmacology. 2004;**47**(Suppl 1):33-46

[64] Spiga S, Lintas A, Migliore M, Diana M. Altered architecture and functional consequences of the mesolimbic dopamine system in cannabis dependence. Addiction Biology. 2010;**15**:266-276

[65] Collo G, Cavalleri L, Spano P. Structural plasticity in mesencephalic dopaminergic neurons produced by drugs of abuse: Critical role of BDNF and dopamine. Frontiers in Pharmacology. 2014;**5**:259

[66] Sklair-Tavron L, Shi WX, Lane SB, Harris HW, Bunney BS, Nestler EJ. Chronic morphine induces visible changes in the morphology of mesolimbic dopamine neurons. Proceedings of the National Academy of Sciences of the United States of America. 1996;**93**:11202-11207

[67] Argilli E, Sibley DR, Malenka RC, England PM, Bonci A. Mechanism and time course of cocaine-induced long-term potentiation in the ventral tegmental area. The Journal of Neuroscience. 2008;**28**:9092-9100

[68] Shen H, Kalivas PW. Reduced LTP and LTD in prefrontal cortex synapses in the nucleus accumbens after heroin self-administration. The International Journal of Neuropsychopharmacology. 2013;**16**:1165-1167

[69] Self DW. Regulation of drug-taking and -seeking behaviors by neuroadaptations in the mesolimbic dopamine system. Neuropharmacology. 2004;**47**(Suppl 1):242-255

[70] Steketee JD, Kalivas PW. Drug wanting: Behavioral sensitization and relapse to drug-seeking behavior. Pharmacological Reviews. 2011;**63**:348-365

[71] Trujillo KA, Kubota KS, Warmoth KP. Continuous administration of opioids produces locomotor sensitization. Pharmacology, Biochemistry, and Behavior. 2004;**79**:661-669

[72] Leyton M. Conditioned and sensitized responses to stimulant drugs in humans. Progress in Neuro-Psychopharmacology & Biological Psychiatry. 2007;**31**:1601-1613

[73] Volkow ND, Wang GJ, Fowler JS, Tomasi D, Telang F, Baler R. Addiction: Decreased reward sensitivity and increased expectation sensitivity conspire to overwhelm the brain's control circuit. BioEssays. 2010;**32**:748-755

[74] Kish SJ, Kalasinsky KS, Derkach P, Schmunk GA, Guttman M, Ang L, et al. Striatal dopaminergic and serotonergic markers in human heroin users. Neuropsychopharmacology. 2001;**24**:561-567

[75] Martinez D, Greene K, Broft A, Kumar D, Liu F, Narendran R, et al. Lower level of endogenous dopamine in patients with cocaine dependence: Findings from PET imaging of D(2)/D(3) receptors following acute dopamine depletion. The American Journal of Psychiatry. 2009;**166**:1170-1177

[76] Martinez D, Saccone PA, Liu F, Slifstein M, Orlowska D, Grassetti A, et al. Deficits in dopamine D(2) receptors and presynaptic dopamine in heroin dependence: Commonalities and differences with other types of addiction. Biological Psychiatry. 2012;**71**:192-198

[77] Volkow ND, Wang GJ, Fowler JS, Logan J, Hitzemann R, Ding YS, et al. Decreases in dopamine receptors but not in dopamine transporters in alcoholics. Alcoholism, Clinical and Experimental Research. 1996;**20**:1594-1598

[78] Koob GF. Addiction is a reward deficit and stress surfeit disorder. Frontiers in Psychiatry. 2013;**4**:72

[79] Ahmed SH. Imbalance between drug and non-drug reward availability: A major risk factor for addiction. European Journal of Pharmacology. 2005;**526**:9-20

[80] Berridge KC, Robinson TE. Liking, wanting, and the incentive-sensitization theory of addiction. The American Psychologist. 2016;**71**:670-679

[81] Bossert JM, Marchant NJ, Calu DJ, Shaham Y. The reinstatement model of drug relapse: Recent neurobiological findings, emerging research topics, and translational research. Psychopharmacology. 2013;**229**:453-476

[82] Childress AR, Mozley PD, McElgin W, Fitzgerald J, Reivich M, O'Brien CP. Limbic activation during cue-induced cocaine craving. The American Journal of Psychiatry. 1999;**156**:11-18

[83] Fotros A, Casey KF, Larcher K, Verhaeghe JA, Cox SM, Gravel P, et al. Cocaine cue-induced dopamine release in amygdala and hippocampus: A high-resolution PET [(1)(8)F]fallypride study in cocaine dependent participants. Neuropsychopharmacology. 2013;**38**:1780-1788

[84] Garavan H, Pankiewicz J, Bloom A, Cho JK, Sperry L, Ross TJ, et al. Cue-induced cocaine craving: Neuroanatomical specificity for drug users and drug stimuli. The American Journal of Psychiatry. 2000;**157**:1789-1798

[85] Huang Y, Mohan A, De Ridder D, Sunaert S, Vanneste S. The neural correlates of the unified percept of alcohol-related craving: A fMRI and EEG study. Scientific Reports. 2018;**8**:923

[86] Li Q, Wang Y, Zhang Y, Li W, Yang W, Zhu J, et al. Craving correlates with mesolimbic responses to heroin-related cues in short-term abstinence from heroin: An event-related fMRI study. Brain Research. 2012;**1469**:63-72

[87] Graybiel AM, Aosaki T, Flaherty AW, Kimura M. The basal ganglia and adaptive motor control. Science. 1994;**265**:1826-1831

[88] Haber SN. Corticostriatal circuitry. Dialogues in Clinical Neuroscience. 2016;**18**:7-21

[89] Palmiter RD. Dopamine signaling in the dorsal striatum is essential for motivated behaviors: Lessons from dopamine-deficient mice. Annals of the New York Academy of Sciences. 2008;**1129**:35-46

[90] O'Doherty J, Dayan P, Schultz J, Deichmann R, Friston K, Dolan RJ. Dissociable roles of ventral and dorsal striatum in instrumental conditioning. Science. 2004;**304**:452-454

[91] Belin D, Everitt BJ. Cocaine seeking habits depend upon dopamine-dependent serial connectivity linking the ventral with the dorsal striatum. Neuron. 2008;**57**:432-441

[92] Gerdeman GL, Partridge JG, Lupica CR, Lovinger DM. It could be habit forming: Drugs of abuse and striatal synaptic plasticity. Trends in Neurosciences. 2003;**26**:184-192

[93] Malvaez MW, K.M. Regulation of habit formation in the dorsal striatum. Current Opinion in Behavioral Sciences. 2018;**20**:67-74

[94] Martinez D, Broft A, Foltin RW, Slifstein M, Hwang DR, Huang Y, et al. Cocaine dependence and d2 receptor availability in the functional subdivisions of the striatum: Relationship with cocaine-seeking behavior. Neuropsychopharmacology. 2004;**29**:1190-1202

[95] Volkow ND, Chang L, Wang GJ, Fowler JS, Franceschi D, Sedler M, et al. Loss of dopamine transporters in methamphetamine abusers recovers

with protracted abstinence. The Journal of Neuroscience. 2001;**21**:9414-9418

[96] Jedynak JP, Uslaner JM, Esteban JA, Robinson TE. Methamphetamine-induced structural plasticity in the dorsal striatum. The European Journal of Neuroscience. 2007;**25**:847-853

[97] Cuzon Carlson VC, Seabold GK, Helms CM, Garg N, Odagiri M, Rau AR, et al. Synaptic and morphological neuroadaptations in the putamen associated with long-term, relapsing alcohol drinking in primates. Neuropsychopharmacology. 2011;**36**:2513-2528

[98] Parikh V, Naughton SX, Shi X, Kelley LK, Yegla B, Tallarida CS, et al. Cocaine-induced neuroadaptations in the dorsal striatum: Glutamate dynamics and behavioral sensitization. Neurochemistry International. 2014;**75**:54-65

[99] Barros-Loscertales A, Garavan H, Bustamante JC, Ventura-Campos N, Llopis JJ, Belloch V, et al. Reduced striatal volume in cocaine-dependent patients. NeuroImage. 2011;**56**:1021-1026

[100] Chang L, Alicata D, Ernst T, Volkow N. Structural and metabolic brain changes in the striatum associated with methamphetamine abuse. Addiction. 2007;**102**(Suppl 1):16-32

[101] Jacobsen LK, Giedd JN, Gottschalk C, Kosten TR, Krystal JH. Quantitative morphology of the caudate and putamen in patients with cocaine dependence. The American Journal of Psychiatry. 2001;**158**:486-489

[102] Suto N, Wise RA, Vezina P. Dorsal as well as ventral striatal lesions affect levels of intravenous cocaine and morphine self-administration in rats. Neuroscience Letters. 2011;**493**:29-32

[103] Pelloux Y, Everitt BJ, Dickinson A. Compulsive drug seeking by rats under punishment: Effects of drug taking history. Psychopharmacology. 2007;**194**:127-137

[104] Koob GF. Brain stress systems in the amygdala and addiction. Brain Research. 2009;**1293**:61-75

[105] Peters J, Pattij T, De Vries TJ. Targeting cocaine versus heroin memories: Divergent roles within ventromedial prefrontal cortex. Trends in Pharmacological Sciences. 2013;**34**:689-695

[106] Rajmohan V, Mohandas E. The limbic system. Indian Journal of Psychiatry. 2007;**49**:132-139

[107] Herman JP, McKlveen JM, Solomon MB, Carvalho-Netto E, Myers B. Neural regulation of the stress response: Glucocorticoid feedback mechanisms. Brazilian Journal of Medical and Biological Research. 2012;**45**:292-298

[108] Davis M, Walker DL, Miles L, Grillon C. Phasic vs sustained fear in rats and humans: Role of the extended amygdala in fear vs anxiety. Neuropsychopharmacology. 2010;**35**:105-135

[109] Martijena ID, Molina VA. The influence of stress on fear memory processes. Brazilian Journal of Medical and Biological Research. 2012;**45**:308-313

[110] Zald DH. The human amygdala and the emotional evaluation of sensory stimuli. Brain Research. Brain Research Reviews. 2003;**41**:88-123

[111] Squire LR. Memory and the hippocampus: A synthesis from findings with rats, monkeys, and humans. Psychological Review. 1992;**99**:195-231

[112] Mayes A, Montaldi D, Migo E. Associative memory and the medial temporal lobes. Trends in Cognitive Sciences. 2007;**11**:126-135

[113] Knight R. Contribution of human hippocampal region to novelty detection. Nature. 1996;**383**:256-259

[114] Phillips RG, LeDoux JE. Differential contribution of amygdala and hippocampus to cued and contextual fear conditioning. Behavioral Neuroscience. 1992;**106**:274-285

[115] McGaugh JL. The amygdala modulates the consolidation of memories of emotionally arousing experiences. Annual Review of Neuroscience. 2004;**27**:1-28

[116] Castilla-Ortega E, Ladron de Guevara-Miranda D, Serrano A, Pavon FJ, Suarez J, Rodriguez de Fonseca F, et al. The impact of cocaine on adult hippocampal neurogenesis: Potential neurobiological mechanisms and contributions to maladaptive cognition in cocaine addiction disorder. Biochemical Pharmacology. 2017;**141**:100-117

[117] Torregrossa MM, Corlett PR, Taylor JR. Aberrant learning and memory in addiction. Neurobiology of Learning and Memory. 2011;**96**:609-623

[118] Orikabe L, Yamasue H, Inoue H, Takayanagi Y, Mozue Y, Sudo Y, et al. Reduced amygdala and hippocampal volumes in patients with methamphetamine psychosis. Schizophrenia Research. 2011;**132**:183-189

[119] Enoch MA, Zhou Z, Kimura M, Mash DC, Yuan Q, Goldman D. GABAergic gene expression in postmortem hippocampus from alcoholics and cocaine addicts; corresponding findings in alcohol-naive P and NP rats. PLoS One. 2012;**7**:e29369

[120] Liu J, Lewohl JM, Harris RA, Iyer VR, Dodd PR, Randall PK, et al. Patterns of gene expression in the frontal cortex discriminate alcoholic from nonalcoholic individuals. Neuropsychopharmacology. 2006;**31**:1574-1582

[121] Fu Y, Pollandt S, Liu J, Krishnan B, Genzer K, Orozco-Cabal L, et al. Long-term potentiation (LTP) in the central amygdala (CeA) is enhanced after prolonged withdrawal from chronic cocaine and requires CRF1 receptors. Journal of Neurophysiology. 2007;**97**:937-941

[122] Huang CC, Lin HJ, Hsu KS. Repeated cocaine administration promotes long-term potentiation induction in rat medial prefrontal cortex. Cerebral Cortex. 2007;**17**:1877-1888

[123] Huang YC, Wang SJ, Chiou LC, Gean PW. Mediation of amphetamine-induced long-term depression of synaptic transmission by CB1 cannabinoid receptors in the rat amygdala. The Journal of Neuroscience. 2003;**23**:10311-10320

[124] Izumi Y, Nagashima K, Murayama K, Zorumski CF. Acute effects of ethanol on hippocampal long-term potentiation and long-term depression are mediated by different mechanisms. Neuroscience. 2005;**136**:509-517

[125] Brust JC. Ethanol and cognition: Indirect effects, neurotoxicity and neuroprotection: A review. International Journal of Environmental Research and Public Health. 2010;**7**:1540-1557

[126] Le Maitre TW, Dhanabalan G, Bogdanovic N, Alkass K, Druid H. Effects of alcohol abuse on proliferating cells, stem/progenitor cells, and immature neurons in the adult human hippocampus. Neuropsychopharmacology. 2018;**43**:690-699

[127] Castilla-Ortega E, Pedraza C, Estivill-Torrus G, Santin LJ. When is adult hippocampal neurogenesis necessary for learning? Evidence

from animal research. Reviews in the Neurosciences. 2011;**22**:267-283

[128] Sorrells SF, Paredes MF, Cebrian-Silla A, Sandoval K, Qi D, Kelley KW, et al. Human hippocampal neurogenesis drops sharply in children to undetectable levels in adults. Nature. 2018;**555**:377-381

[129] Chambers RA. Adult hippocampal neurogenesis in the pathogenesis of addiction and dual diagnosis disorders. Drug and Alcohol Dependence. 2013;**130**:1-12

[130] Jun H, Mohammed Qasim Hussaini S, Rigby MJ, Jang MH. Functional role of adult hippocampal neurogenesis as a therapeutic strategy for mental disorders. Neural Plasticity. 2012;**2012**:854285

[131] Jentsch JD, Taylor JR. Impulsivity resulting from frontostriatal dysfunction in drug abuse: Implications for the control of behavior by reward-related stimuli. Psychopharmacology (Berl). 1999;**146**:373-390

[132] Renteria R, Baltz ET, Gremel CM. Chronic alcohol exposure disrupts top-down control over basal ganglia action selection to produce habits. Nature Communications. 2018;**9**:211

[133] de Wit H. Impulsivity as a determinant and consequence of drug use: A review of underlying processes. Addiction Biology. 2009;**14**:22-31

[134] Cleva RMG, J.T. Neuroanatomical structures underlying the extinction of drug-seeking behavior. The Open Addiction Journal. 2010;**3**:63-75

[135] Hyman SE. Addiction: A disease of learning and memory. The American Journal of Psychiatry. 2005;**162**:1414-1422

[136] Darke S, Sims J, McDonald S, Wickes W. Cognitive impairment among methadone maintenance patients. Addiction. 2000;**95**:687-695

[137] Dean AC, Groman SM, Morales AM, London ED. An evaluation of the evidence that methamphetamine abuse causes cognitive decline in humans. Neuropsychopharmacology. 2013;**38**:259-274

[138] Shrivastava A, Johnston M, Tsuang M. Cannabis use and cognitive dysfunction. Indian Journal of Psychiatry. 2011;**53**:187-191

[139] Perry CJ, Lawrence AJ. Addiction, cognitive decline and therapy: Seeking ways to escape a vicious cycle. Genes, Brain, and Behavior. 2017;**16**:205-218

[140] Baker TB, Piper ME, McCarthy DE, Majeskie MR, Fiore MC. Addiction motivation reformulated: An affective processing model of negative reinforcement. Psychological Review. 2004;**111**:33-51

[141] Lovallo WR. Cortisol secretion patterns in addiction and addiction risk. International Journal of Psychophysiology. 2006;**59**:195-202

[142] Sinha R. The role of stress in addiction relapse. Current Psychiatry Reports. 2007;**9**:388-395

[143] Garcia-Marchena N, Araos PF, Barrios V, Sanchez-Marin L, Chowen JA, Pedraz M, et al. Plasma chemokines in patients with alcohol use disorders: Association of CCL11 (Eotaxin-1) with psychiatric comorbidity. Frontiers in Psychiatry. 2016;**7**:214

[144] Merikangas KR, Mehta RL, Molnar BE, Walters EE, Swendsen JD, Aguilar-Gaziola S, et al. Comorbidity of substance use disorders with mood and anxiety disorders: Results of the international consortium in psychiatric epidemiology. Addictive Behaviors. 1998;**23**:893-907

[145] Pedraz M, Araos P, Garcia-Marchena N, Serrano A, Romero-Sanchiz P, Suarez J, et al. Sex differences in psychiatric comorbidity and plasma biomarkers for cocaine addiction in abstinent cocaine-addicted subjects in outpatient settings. Frontiers in Psychiatry. 2015;**6**:17

[146] Kelly TM, Daley DC. Integrated treatment of substance use and psychiatric disorders. Social Work in Public Health. 2013;**28**:388-406