

REVIEW ARTICLE

The imprisoned brain: An integrated neurobiological view of substance dependence

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Abstract

Substance dependence is a complex neurobiological condition characterized by progressive dysfunction in reward processing, impulse control, and habit formation. This narrative review integrates key findings on the neural mechanisms underlying addiction, emphasizing the transition from impulsive reward-driven drug use to compulsive habitual consumption. The mesocorticolimbic dopaminergic system plays a central role in addiction, with repeated substance exposure inducing neuroadaptive changes that shift control from the nucleus accumbens to the dorsal striatum, reinforcing compulsive drug-seeking behavior. In addition, glutamatergic plasticity strengthens drug-cue associations, whereas inhibitory control deficits in the prefrontal cortex exacerbate impulsivity. Genetic and epigenetic factors modulate individual vulnerability and influence dopamine receptor expression, synaptic plasticity, and sensitivity to reinforcement. The opioid and endocannabinoid systems further contribute by disinhibiting dopamine release, amplifying craving, and increasing relapse risk. Understanding these neurobiological mechanisms highlights addiction as a condition rooted in maladaptive neural plasticity, rather than a simple failure of willpower. This perspective informs potential therapeutic strategies that target the underlying dysregulation of neurotransmitter systems and behavioral control circuits. By integrating findings from neuroimaging, molecular genetics, and behavioral neuroscience, this review provides a comprehensive framework for understanding the mechanisms sustaining addiction and the persistent challenges of relapse.

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1. Introduction

The use of psychoactive substances has been an intrinsic part of human history for millennia, documented across various cultures for religious, medicinal, and recreational purposes.¹ Global estimates suggest that nearly half of the population consumes at least one psychoactive substance at some point in their lifetime. Among the substances most frequently associated with dependence are alcohol, tobacco, and so-called “illicit drugs,” including opioids, stimulants, sedatives, and hallucinogens. Collectively, these substances represent a major cause of preventable morbidity and mortality worldwide.²

Despite the diverse pharmacodynamic mechanisms underlying each drug, their convergent effects on the mesocorticolimbic dopaminergic pathway suggest a common

neurobiological substrate responsible for both their reinforcing properties and, in the long term, their potential to drive compulsive behavior.³ Beyond dopamine, substance dependence involves profound neuroadaptive changes in the neural circuits governing learning, motivation, and inhibitory control.⁴

However, addiction cannot be reduced by neurobiological mechanisms alone. Impulsivity, compulsivity, genetic and epigenetic factors, and contextual influences such as stress and social environment all contribute to the multifactorial nature of substance use disorders.³ The interplay between environmental factors and neural plasticity further complicates the picture, reinforcing the view that addiction is not merely a consequence of drug exposure, but a complex biopsychosocial condition.¹

Given the intricate nature of addictive behavior, it is imperative to expand the focus beyond the dopaminergic system to consider the broader “reward circuitry” implicated in addiction. This includes key neurotransmitters, such as gamma-aminobutyric acid (GABA), glutamate, and serotonin, alongside neuromodulators, such as endogenous opioids and endocannabinoids.⁵ Dysregulation of these systems is believed to contribute to both the development and persistence of addictive behaviors, influencing not only hedonic processing but also executive control mechanisms.⁶

Therefore, this article aims to dissect the neurobiological foundations of substance dependence, highlighting the contemporary view that dysfunctions in reinforcement, memory, and inhibitory control mechanisms culminate in addiction. This perspective challenges reductionist interpretations of addiction as a mere “moral failure” or “lack of willpower,” advocating instead for a nuanced understanding of its underlying neurobiological and behavioral substrates.⁷

2. Methodology

This narrative review aimed to integrate and critically analyze key neurobiological, genetic, and epigenetic findings in substance dependence, emphasizing the interplay between impulsivity, compulsivity, and neural plasticity within the reward circuitry.

The literature selection encompassed studies published between 2000 and 2025, ensuring the inclusion of contemporary research aligned with the most recent discoveries while also incorporating foundational studies essential for understanding the evolution of addiction neurobiology. To achieve comprehensive coverage, a structured search was conducted across PubMed, Scopus, and the Web of Science to identify relevant publications using predefined selection criteria.

Search strategies involved specific keyword combinations and descriptors, including “substance use disorder,” “addiction neurobiology,” “dopaminergic system,” “impulsivity and compulsivity,” “reward circuit,” “epigenetics of addiction,” “genetic vulnerability in addiction,” “synaptic plasticity and substance dependence,” and “neuroimaging of addiction.” Priority was given to studies employing neuroimaging techniques, genomic analyses, and experimental models in addiction neuroscience as well as systematic reviews and meta-analyses recognized in the field.

Data analysis was conducted using an integrative approach, consolidating multiple lines of evidence into a coherent model that elucidates the mechanisms underlying the transition from recreational drug use to compulsive consumption. This review was structured to reflect the progression of neuroadaptive changes in addiction, moving from cellular and molecular mechanisms to their clinical and behavioral implications.

By avoiding an overly reductionist or purely descriptive approach, this review seeks to critically synthesize the existing literature, highlighting the multifaceted nature of addiction and its interdependence with genetic, epigenetic, and environmental factors.

3. A multifactorial phenomenon

Substance dependence, or substance use disorder, is now recognized as a multidimensional condition in which neurobiological factors interact with behavioral, genetic, and environmental influences. This disorder is characterized by neuroadaptive changes that disrupt the functionality of both the reward system and inhibitory control mechanisms, increasing an individual’s susceptibility to compulsive patterns of substance use.⁸

Many substances exhibit high addictive potential due to their rapid action on the central nervous system, whether through inhalation, intravenous administration, or oral routes with high bioavailability, or their efficient modulation of reinforcement processes within the nucleus accumbens.⁹ Neuroimaging studies have demonstrated that drugs such as cocaine, nicotine, and opioids strongly activate this region, generating potent positive reinforcement and reinforcing compulsive behaviors.⁸

On the other hand, susceptibility to substance use disorders varies significantly among individuals, shaped by personality traits (e.g., impulsivity and sensation-seeking), environmental and sociocultural contexts, and genetic factors, such as polymorphisms in dopamine receptor genes.¹⁰ Research suggests that impulsivity is a key vulnerability marker for substance use disorders, impairing an individual’s ability to regulate drug consumption.¹¹

Early exposure to substances, socioeconomic vulnerability, and a history of trauma or chronic stress create fertile ground for the transition from experimental use to abuse and dependence.¹² Adolescents face an elevated risk of developing substance use disorders in adulthood as the developing brain remains highly susceptible to the neurotoxic effects of addictive substances.¹³

Ultimately, it is within the brain's reward system, particularly the mesolimbic pathway, that addictive drugs "hijack" neural circuits, triggering neuroadaptations that drive craving, tolerance, and relapse.¹⁴ Synaptic plasticity mediated by glutamate and dopamine plays a central role in this process, allowing repeated drug exposure to reshape responses to rewarding stimuli, while diminishing sensitivity to natural rewards.¹⁵

3.1. Impulsivity and compulsivity as behavioral axes

The two fundamental constructs for understanding the progression of substance dependence are impulsivity and compulsivity.¹⁶ Impulsivity refers to the difficulty in delaying immediate gratification in favor of long-term benefits, manifesting as rashes and poorly considered actions that override cortical inhibition. In contrast, compulsivity is characterized by repetitive engagement in a behavior despite significant negative consequences, reflecting a state in which habitual use or the need to alleviate discomfort (negative reinforcement) takes precedence over self-regulation.¹⁷

From a neurological perspective, impulsivity and compulsivity can be conceptualized as disruptions in the balance between bottom-up (subcortical, reward-, and emotion-driven) and top-down (cortical, planning-, and regulation-driven) neural processes.¹⁸ This imbalance undermines executive control, favoring maladaptive decision-making patterns that reinforce substance-seeking behavior.¹⁹

As substance use shifts from occasional experimentation to dependence, impulsive and compulsive traits become more pronounced. Impulsivity initially drives drug-seeking behavior, prioritizing immediate relief or pleasure over future consequences. Over time, this evolves into compulsivity, where substance use persists despite clear and escalating harm to the personal, relational, or professional aspects of life. This transition marks a critical shift from voluntary use to a state of diminished control, highlighting the progressive nature of addiction as a disorder of impaired behavioral regulation.²⁰ As illustrated in Figure 1, this shift is not abrupt but unfolds through distinct neuroadaptive phases – beginning with dopaminergic reinforcement and advancing through cue sensitization,

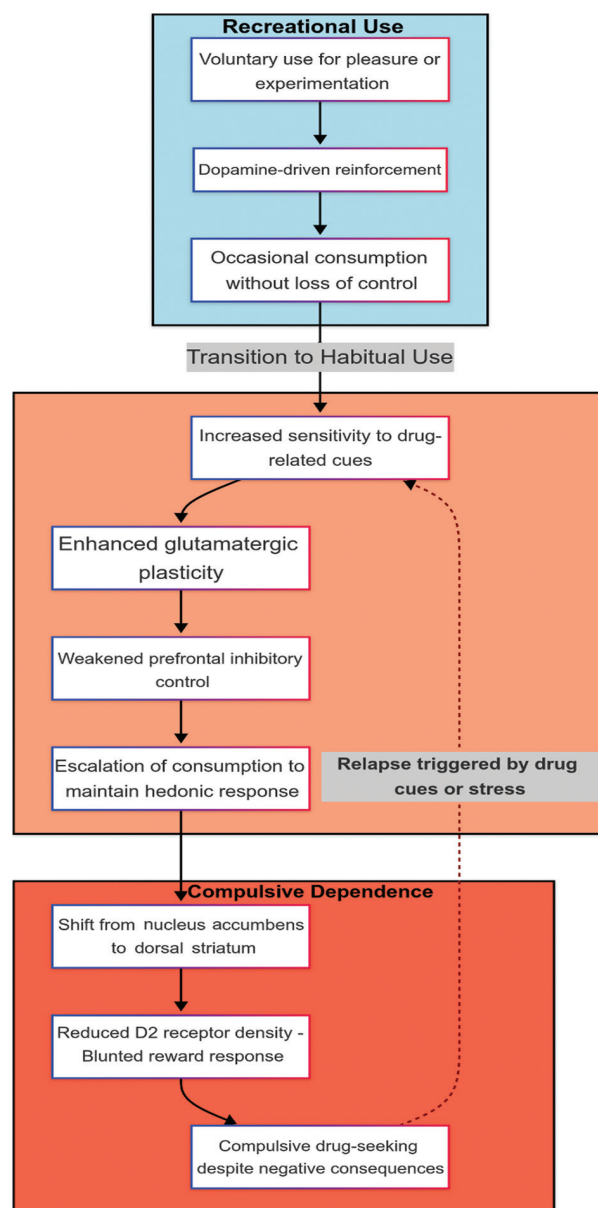


Figure 1. The neurobiological transition from recreational drug use to compulsive dependence. This schematic represents a progressive, multidimensional model of substance dependence. The figure begins with voluntary drug use reinforced by dopaminergic activity in the ventral striatum (nucleus accumbens) and transitions through neuroadaptations involving glutamatergic plasticity and impaired prefrontal inhibition. The middle section illustrates the sensitization to drug cues and the escalation of use as homeostatic hedonic thresholds shift. The lower section depicts the neurobiological shift from goal-directed to habitual behavior, associated with dorsal striatum engagement and reduced D2 receptor expression. This culminates in compulsive drug-seeking despite negative consequences. The dashed line indicates relapse pathways, emphasizing vulnerability to environmental cues and stress even after abstinence. This diagram is intended as a didactic synthesis of functional, structural, and behavioral transitions across stages of addiction.

prefrontal dysfunction, and dorsal striatum recruitment – ultimately leading to entrenched compulsivity. The figure also emphasizes the dynamic risk of relapse, even in late-stage dependence, driven by conditioned environmental triggers.

3.2. The brain's reward system as a biological axis

Historically, explanations for psychoactive substance use were often rooted in theories of “subconscious instincts” or “moral weakness,” reflecting a limited understanding of the neurobiological substrates involved. However, pioneering research challenged this perspective by demonstrating that primates could learn to perform tasks to obtain opioids, suggesting that drug consumption was not merely an inevitable instinct, but rather a behavior governed by reinforcement mechanisms, contradicting simplistic innate response models.²¹

A seminal breakthrough occurred in 1954 when James Olds and Peter Milner implanted electrodes in specific brain regions of rats and observed that the animals compulsively pressed a lever to receive electrical stimulation in what they identified as the septal area.²² This finding, known as intracranial self-stimulation, provided the first concrete evidence of a neural reward system, revealing that stimulation of certain brain regions could override even vital survival behaviors, such as eating and drinking.²³

Subsequent research established that these reward-related regions are primarily centered on the mesolimbic dopaminergic pathway, originating in the ventral tegmental area (VTA) and projecting to the nucleus accumbens.²⁴ Over the following decades, this concept of a “reward circuit” was solidified through studies demonstrating that virtually all drugs of abuse – regardless of their initial pharmacological mechanism – ultimately converge on dopamine release in the mesolimbic pathway.²⁵

Thus, substance dependence can be understood as a hijacking of neural circuits originally evolved to reinforce behaviors essential for survival, such as feeding, reproduction, and pursuit of well-being.²⁶ Therefore, the compulsive nature of addiction arises from the maladaptive engagement of a system designed to optimize adaptive behaviors, emphasizing the profound neurobiological underpinnings of substance use disorders.

4. Dopaminergic convergence

The realization that drugs with distinct pharmacological mechanisms ultimately converge to enhance dopamine release in limbic brain regions has been pivotal in shaping contemporary models of substance dependence.²⁷ This convergence lies in the mesocorticolimbic circuit,

featuring a network of pathways that originate from dopaminergic cell bodies in the VTA and project to the nucleus accumbens, prefrontal cortex, and other limbic structures.²⁸ This system, which is crucial for attributing value to experiences and reinforcing adaptive behaviors, is hijacked by psychoactive substances that exploit the same neurochemical pathways evolved to mediate natural reward-seeking behaviors.²⁴

As discussed in the previous section, Olds and Milner demonstrated that rodents preferred to electrically stimulate certain reinforcement-related brain regions, particularly those near the medial forebrain bundle, even at the expense of vital behaviors such as eating and resting.²² Subsequent studies clarified that dopaminergic activity triggered by such self-stimulation was the primary driver of this compulsive behavior.²⁹ Similarly, substances such as cocaine, opioids, nicotine, and alcohol elevate dopamine levels in the nucleus accumbens through various mechanisms, including blocking dopamine reuptake, inducing excessive neurotransmitter release, and inhibiting GABAergic interneurons that modulate dopaminergic firing in the VTA.³⁰

Although these substances act through distinct initial targets, with opioids binding to μ -opioid receptors, stimulants blocking dopamine transporters, and cannabinoids activating CB1 receptors, their final physiological effects converge with the enhancement of dopaminergic transmission. This results in heightened hedonic salience of drug-related cues and contexts, reinforcing compulsive substance use and driving the neuroadaptive changes that underlie addiction.³¹ [Figure 2](#) offers a conceptual simplification of this interplay, illustrating how glutamatergic excitation, GABAergic disinhibition, and opioid modulation converge on the dopaminergic system. Rather than presenting an exhaustive neurochemical map, the figure provides a didactic synthesis of how these systems interact functionally to reinforce craving, emotional dysregulation, and compulsive drug-seeking behaviors.

In this context, dopamine is now widely recognized as a primary modulator of motivational processes, including reward expectations, associative learning, and outcome prediction.³² In the nucleus accumbens, dopamine release reinforces the perception that a given stimulus or action, such as consuming a psychoactive substance, possesses high value and should be repeated.²⁴ Over time, dopaminergic activity becomes conditioned to cues and contexts that precede the attainment of the reward, such that mere exposure to objects, locations, or individuals associated with drug use is sufficient to elicit an intense urge to consume, a phenomenon referred to as craving.³³

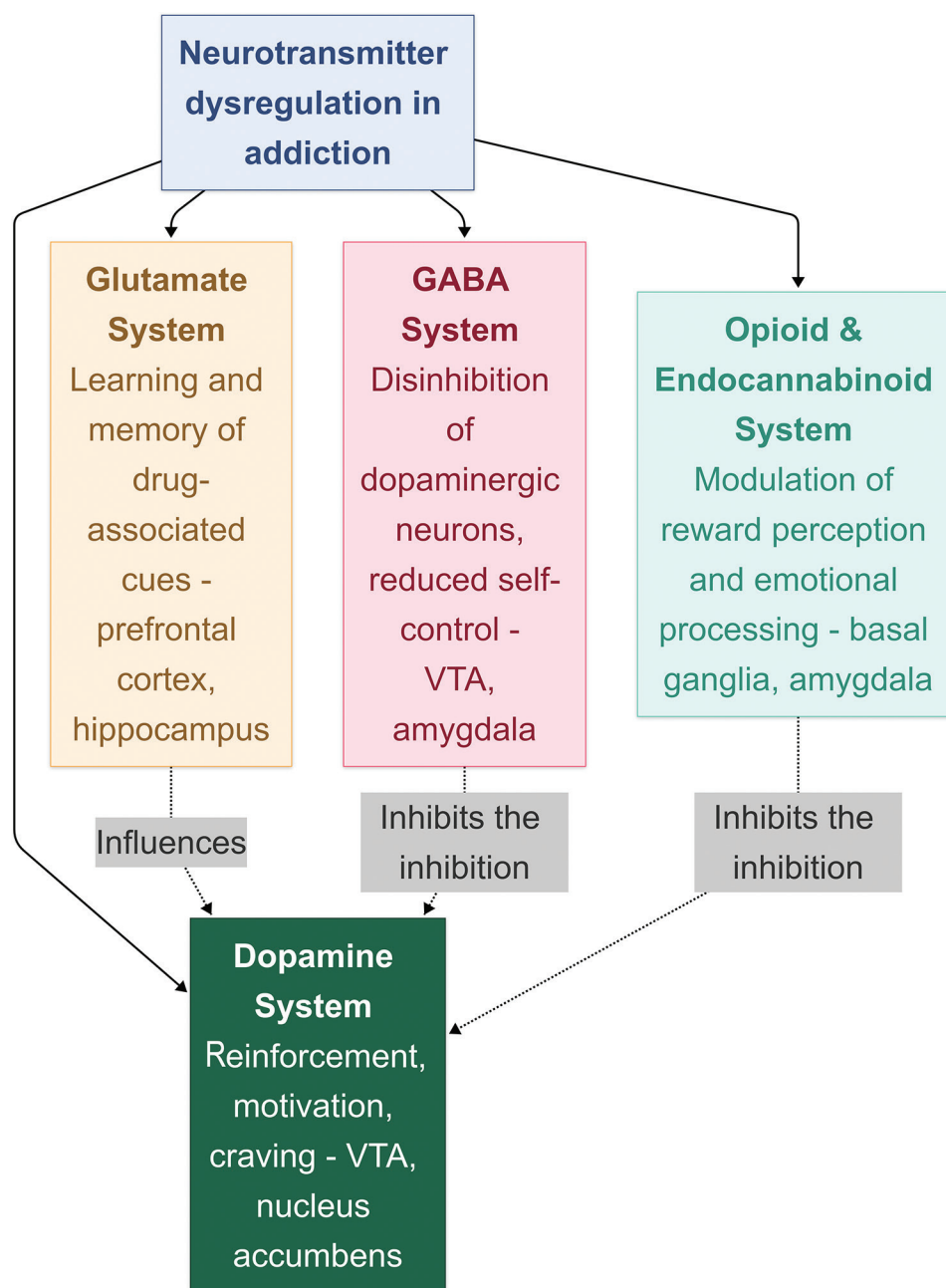


Figure 2. Neurotransmitter dysregulation in addiction. This diagram illustrates the interdependent roles of key neurotransmitter systems in sustaining substance dependence. The glutamatergic system contributes to the encoding and retrieval of drug-associated memories, primarily within the prefrontal cortex and hippocampus, and potentiates dopaminergic signaling. The GABAergic system, through disinhibition of dopaminergic neurons in the VTA and amygdala, contributes to loss of self-regulation. The opioid and endocannabinoid systems modulate affective and hedonic responses, influencing basal ganglia and amygdalar circuits. The dopamine system integrates these influences to mediate reinforcement, craving, and compulsive motivation. Arrows denote stimulatory or inhibitory effects across systems. This figure is a heuristic tool intended to conceptually unify molecular, behavioral, and circuit-level findings discussed in the text.

Abbreviations: GABA: Gamma-aminobutyric acid; VTA: Ventral tegmental area.

This conditioning process shifts the dopaminergic peak from the moment of actual drug consumption to the time of anticipation of its availability. With repeated substance use, the excitatory dopaminergic response associated

with natural reinforcers, such as food, social bonding, or personal achievements, is progressively eclipsed by disproportionate and repetitive hyperstimulation induced by psychoactive substances. This leads to anhedonia, a

diminished ability to derive pleasure from non-drug-related stimuli, further reinforcing the cycle of compulsive substance use.³⁴

The effects of dopamine are mediated by receptor subtypes, classified into two main families: D1-like receptors (D1 and D5) and D2-like receptors (D2, D3, and D4). The primary distinction between these families lies in their intracellular signaling pathways: D1 and D5 receptors, coupled to Gs proteins, increase cyclic AMP (cAMP) levels, thereby facilitating neuronal excitability, whereas D2, D3, and D4 receptors, coupled to Gi proteins, suppress cAMP production and tend to decrease neuronal excitability. However, the functional outcome depends on the neuronal type and synaptic context.³⁵ In the nucleus accumbens, dopaminergic projections interact with medium spiny neurons, whose activity is highly sensitive to these receptor populations, shaping the processes of reinforcement, habit formation, and learning of compulsive behaviors.³⁶

This intricate arrangement explains why chronic dopamine elevation can lead to seemingly paradoxical effects, such as the need for progressively higher doses of a substance to achieve the same euphoric response (tolerance) while simultaneously increasing sensitivity to conditioned stimuli that trigger drug-seeking behavior (sensitization).³⁷ In the advanced stages of dependence, a reduction in D2 dopamine receptor density is observed in striatal regions, likely as a compensatory downregulation in response to frequent and excessive dopamine surges.³⁸ This receptor downregulation correlates clinically with increased compulsivity and a diminished capacity to experience pleasure from everyday activities (anhedonia), reinforcing the vicious cycle that perpetuates continued drug use.²⁷

Despite the diverse pharmacological mechanisms employed by different drug classes, they all ultimately converge on modulating dopamine transmission within the mesocorticolimbic circuit. Psychostimulants such as cocaine and methamphetamine inhibit dopamine reuptake or induce its massive release, resulting in intense and abrupt peaks in the nucleus accumbens.³⁹ Opioids, including morphine and heroin, primarily target μ -opioid receptors on GABAergic interneurons, suppressing inhibitory control over dopaminergic cells, thereby disinhibiting dopamine release.³⁷ Alcohol and benzodiazepines, by enhancing GABAergic transmission, similarly lead to the disinhibition of dopaminergic neurons in the VTA, amplifying reward signaling.⁴⁰ In contrast, cannabinoid derivatives act on CB1 receptors, modulating the release of excitatory and inhibitory neurotransmitters, ultimately

increasing dopamine levels in the nucleus accumbens and altering memory formation and temporal perception.⁴¹

The multifaceted nature of substance use, involving distinct neurochemical pathways, reinforces the robustness of the common final pathway hypothesis: while the “gateway” varies – whether through opioid receptors, dopamine transporters, GABA-A receptors, CB1 receptors, or nicotinic receptors – the ultimate outcome is typically an increase in dopamine release within limbic structures. With chronic use, this dopaminergic surge triggers neuroadaptive mechanisms that exacerbate both impulsivity and compulsivity, further reinforcing drug-seeking behavior.⁴² This convergence arises because most substances of abuse, regardless of their initial pharmacological targets, ultimately modulate the mesolimbic dopaminergic system.⁴³

To avoid reductionist interpretations of the role of dopamine, it is essential to acknowledge that multiple neurotransmitters contribute to the plasticity underlying addictive behaviors. Glutamate, the principal excitatory neurotransmitter in the central nervous system, plays a fundamental role in associative learning within the prefrontal cortex and the nucleus accumbens, reinforcing memory traces that link drug use to specific environments and affective states.⁵ Thus, glutamatergic modulation intensifies craving and relapse susceptibility, as even subtle environmental cues can trigger robust synaptic responses and reactivate drug-seeking behaviors.⁴⁴

In addition, GABA, the predominant inhibitory neurotransmitter in the brain, acts as a regulatory brake for dopaminergic firing. Substances that potentiate GABAergic activity or disrupt inhibitory interneurons in the VTA facilitate increased dopamine release into the ventral striatum, reinforcing compulsive patterns of use.³ Meanwhile, serotonin, although less extensively studied in the context of reinforcement, modulates impulsivity and mood regulation, directly influencing an individual's likelihood of engaging in substance use as a means of managing negative emotional states.⁴⁵

Finally, endogenous opioids and endocannabinoids serve as crucial regulatory agents that can either inhibit or facilitate dopamine release through pre- and post-synaptic mechanisms. For instance, the endocannabinoid system modulates not only dopaminergic signaling but also emotional responses associated with drug use, directly shaping learning and memory processes related to addiction.⁴⁶ Understanding the interplay between these systems is fundamental to a comprehensive neurobiological framework of addiction as they collectively shape the progression from initial substance exposure to compulsive dependence.

5. Genetic and epigenetic factors in vulnerability to addiction

The body of evidence presented thus far reinforces the understanding that the reward circuit, anchored in the mesocorticolimbic dopaminergic pathway, is central to neurobiological alterations that drive loss of control and compulsive drug use.⁴⁷ However, individual susceptibility to these changes varies considerably, highlighting the critical role of genetic, epigenetic, and environmental interactions in shaping addiction vulnerability.⁴⁸ Genetic predisposition models have proposed that polymorphisms in genes encoding dopamine receptors or transporters may render certain individuals particularly prone to developing compulsive drug-seeking behaviors more rapidly or engaging in more intense patterns of substance use.⁴⁹ [Table 1](#) highlights the key findings in this domain.

Not all individuals who encounter highly addictive substances inevitably progress to compulsive or substance use disorders. The search for explanations regarding these variations in susceptibility has led to the identification of genetic factors that influence dopaminergic neurotransmission, synaptic plasticity, and more recently, epigenetic processes that modify gene expression without altering the DNA sequence.⁵⁰ Epigenetic regulation can modulate the expression of addiction-related genes, inducing changes in synaptic plasticity that increase an individual's vulnerability to substance use disorders.⁵¹

Family studies, particularly those involving twin cohorts, suggest that the heritability of substance use disorders can reach substantial levels, although estimates vary depending on drug type and sociocultural context. Current evidence indicates that approximately 40 – 60% of addiction risk can be attributed to genetic factors.⁵² However, unlike well-characterized monogenic diseases, addiction follows a highly polygenic model, involving dozens or even hundreds of genetic variants dispersed throughout the genome. When combined, these variants incrementally increase susceptibility to various substances, emphasizing the complex and multifactorial nature of vulnerability to addiction.⁵³

A significant portion of this polygenic framework includes genes associated with the dopaminergic pathway. Mutations or polymorphisms in *DRD2*, *DRD4*, and *DAT1* and components of intracellular signaling cascades can subtly alter reinforcement sensitivity, predisposing certain individuals to perceive drug-related stimuli as particularly rewarding.⁵⁴ In parallel, variations in genes encoding metabolic enzymes, such as those in the cytochrome P450 family, influence the rate at which various substances are metabolized, thereby modulating the intensity of drug effects and development of tolerance.⁵⁵ These multiple genetic influences act synergistically, forming an underlying risk that facilitates the transition from causal substance use to chronic dependence.⁵⁶

Studies integrating genome-wide association studies with clinical data have further underscored the multifactorial nature of addiction vulnerability. Polymorphisms in genes encoding components of the endogenous opioid system, such as *OPRM1*, have been linked to an increased risk of heroin or alcohol dependence depending on how they modulate euphoric and analgesic responses on initial substance exposure.⁵⁷ Beyond *OPRM1*, several genome-wide association studies (GWASs) have identified additional genetic loci associated with substance dependence. For example, variants in *DRD2* and *SLC6A3* – both implicated in dopaminergic transmission – as well as in *BDNF*, which modulates synaptic plasticity, have been repeatedly associated with vulnerability to addiction-related behaviors.⁵⁸⁻⁶⁰ These associations reinforce the complex and polygenic nature of addiction and suggest potential molecular targets for future interventions. Although no single genetic marker can precisely predict who will develop addiction, it is increasingly evident that the presence or absence of specific genetic variants can shape an individual's susceptibility and clinical trajectory.⁶¹

One frequently cited concept in the literature is the reward-deficiency hypothesis. According to this model, individuals with reduced expression or diminished sensitivity of D2 dopamine receptors due to variants in *DRD2* or regulatory regions may experience diminished satisfaction from everyday activities, leading to a state of

Table 1. Genetic and epigenetic contributions to addiction vulnerability

Factor	Mechanism	Impact on addiction susceptibility
<i>DRD2</i> (D2 dopamine receptor) polymorphisms	Reduced receptor density	Increased impulsivity, blunted response to natural rewards
<i>DAT1</i> (dopamine transporter) variants	Altered dopamine reuptake	Affects intensity of drug effects and craving
Epigenetic modifications (DNA methylation, histone acetylation)	Changes in gene expression without DNA sequence alterations	Can induce long-term adaptations in reward circuits
<i>OPRM1</i> (μ-opioid receptor) variants	Modulates opioid system response	Affects sensitivity to opioids and risk of addiction

Notes: This table presents the key genetic polymorphisms and epigenetic modifications associated with an increased addiction risk. These factors influence dopamine signaling, craving intensity, and long-term neuroadaptations that reinforce compulsive drug use.

chronic hypodopaminergia.⁶² In an effort to compensate for this underactivation of the reward circuit, such individuals may seek substances or behaviors capable of producing a more pronounced dopaminergic surge, thereby increasing their risk of addiction.⁶³

Thus, predisposition toward impulsive behavior may also be interpreted as a consequence of an underlying deficit in the ability to derive pleasure or motivation from everyday experiences.⁶⁴ Although the Reward Deficiency Hypothesis does not fully account for all cases of addiction, it offers a compelling framework to explain the correlation between genetic variations that influence dopamine levels and the tendency to seek more intense forms of reinforcement.⁶²

While classical genetics focuses on changes in DNA sequences, epigenetics refers to heritable modifications in gene expression that do not alter genomic sequences. These modifications include DNA methylation, histone acetylation or methylation, and post-transcriptional regulation mediated by miRNAs.⁴⁸ Such epigenetic changes may be triggered by external factors such as exposure to psychosocial stressors or chronic use of psychoactive substances.⁵² The persistence of substance dependence and difficulty in reversing addictive behaviors may be linked to stable epigenetic modifications in dopaminergic and glutamatergic circuits, which reinforce reward-associated memories while impairing the restoration of pre-addiction homeostasis.⁶⁵

In animal models, repeated exposure to substances such as cocaine or alcohol induced epigenetic modifications in medium spiny neurons of the nucleus accumbens, altering the expression of genes linked to synaptic plasticity.⁵² Similar changes have been observed in genes encoding dopamine receptors, cytoskeletal components, and transcriptional regulators, reinforcing the heightened excitability in response to drug-associated cues.⁴⁸ In humans, although detailed investigations are more challenging due to ethical and logistical constraints, studies suggest that chronic drug users exhibit variations in genomic promoter methylation, indicating that prolonged substance use may lead to long-lasting transcriptional remodeling.⁵⁰

These findings offer insights into why some individuals, even after prolonged periods of abstinence, continue to experience intense cravings and heightened vulnerability to environmental triggers. The persistence of epigenetic signatures in key reward circuit regions may function as cellular memory of prior substance use, such that even small drug re-exposures potentially reactivate reinforcement-related neural networks.⁶⁶ While this epigenetic plasticity presents a significant barrier to spontaneous recovery, it also introduces potential therapeutic targets aimed

at modulating gene expression, although many such strategies remain in the experimental stages.⁶⁷

The epigenetic landscape of addiction further aligns with the notion that substance dependence is not an isolated event but rather a process deeply influenced by trauma, chronic stress, and socio-environmental conditions. Studies on early life adversity have revealed that experiences such as physical abuse, neglect, and family instability are associated with earlier onset and more severe patterns of addiction.⁶⁸ This link extends beyond psychological and behavioral components, potentially involving epigenetic modifications in genes regulating the hypothalamic-pituitary-adrenal axis, which modulates stress responses.⁶⁹ The interplay between genetic vulnerabilities, epigenetic modifications, and developmental stressors may result in heightened neural sensitivity to drug reinforcement, ultimately fostering more compulsive and destructive patterns of substance use.⁷⁰

However, it is essential to emphasize that the presence of genetic or epigenetic variants influencing addiction vulnerability does not determine outcomes in an inevitable or deterministic manner. Environmental factors, whether protective or stress-inducing, act as critical modulators that shape the likelihood of addiction-related phenotypes.⁴⁷ Thus, individuals carrying *DRD2* polymorphisms may never develop substance use disorders if they are exposed to supportive environments or have psychological and socioeconomic resources that allow them to channel their reinforcement needs into creative, athletic, or professional pursuits.⁷¹ Conversely, individuals without genetic predispositions may still develop severe patterns of addiction when exposed to high-risk environments, such as lack of familial support or early exposure to highly addictive substances.⁷²

Genetic predisposition can shape the intensity of the dopaminergic response to each drug exposure, the strength of the memory imprint associated with drug-induced euphoria, and the extent to which excitatory and inhibitory pathways adapt to repeated stimulation.⁵⁶ The cumulative effect of these factors results in a high “exit cost,” making cessation increasingly difficult once the organism has physiologically and potentially epigenetically adapted to the constant presence of the substance.⁷³ Therefore, the propensity for compulsive behavior is the product of pre-existing molecular biases combined with synaptic circuits that reinforce the repetition of substance use, further entrenching addictive patterns.⁷⁴

6. An integrated view

Neurobiological changes associated with addiction involve multiple brain regions and neurotransmitter

systems, leading to impaired control and compulsive drug-seeking behavior. These changes are summarized in Table 2. Contrary to classical models that attribute drug use to “moral weakness,” or view it as the mere consequence of static pharmacological reinforcement, the contemporary integrative perspective recognizes that genetic and epigenetic factors actively shape dopaminergic circuitry, modulate the excitability threshold of the nucleus accumbens, and influence sensitivity to reward and punishment signals.⁴⁸ Within this framework, the importance of environmental and cultural factors becomes even more pronounced as life experiences, stress exposure, and substance availability function as modulators of this biologically predisposed landscape, potentially triggering or mitigating addiction risk.⁵⁰

This modern framework conceptualizes substance dependence as a condition that rarely follows a homogeneous trajectory. Rather, it exists in a spectrum where distinct genetic predispositions and environmental influences produce highly variable clinical outcomes.⁵² Advances in neuroscience have been instrumental in dispelling reductionist views, reinforcing the notion that while the initial decision to consume a drug may be voluntary to some extent, the progression to compulsive use involves a cascade of deep biological adaptations shaped by inherited genetic variants and acquired epigenetic modifications.⁶⁶

In the early stages of drug exposure, dopaminergic activation in the nucleus accumbens projects to the prefrontal cortex and limbic areas, reinforcing the positive association (positive reinforcement) and memory of drug-induced euphoria.⁶⁵ This process is mediated by dopamine release and synaptic plasticity, involving key neurotransmitters such as glutamate and GABA.⁵¹ At this stage, drug use is primarily impulsive and driven by intense immediate rewards and the pursuit of pleasurable sensations. The experience of euphoria or emotional relief

serves as the dominant conscious motivation for continued consumption.⁶⁷

With repeated substance use, the neural circuitry undergoes reorganization, shifting from reliance on the nucleus accumbens, which is primarily associated with motivation, to the dorsal striatum, a region implicated in habit formation and automatic behavioral sequences.⁷⁵ This transition reflects the gradual establishment of behavioral patterns that occur almost automatically and are triggered by environmental cues or emotional states linked to drug use. Concurrently, a reduction in D2 dopamine receptors within the ventral striatum results in diminished sensitivity to natural rewards, further intensifying the drive for highly dopaminergic stimuli such as drug consumption.⁷⁶ At this stage, compulsivity becomes deeply entrenched, and drug-seeking behavior persists despite clear negative consequences across multiple domains of life.

The shift in behavioral control toward the dorsal striatum, which is also interconnected with the motor cortex and associative regions, facilitates repetitive execution of substance use behaviors. As a result, drug-seeking becomes progressively less dependent on conscious decision-making or rational deliberation, becoming instead more closely linked to sensorimotor or contextual “triggers.”⁷⁷ This functional transition between striatal subregions is now regarded as one of the most influential findings in addiction neuroscience, reinforcing the notion that chronic substance use transitions from a volitional act to a deeply ingrained neural “program” governing habitual behavior.⁷⁸

Throughout this progression from nucleus accumbens-driven control to dorsal striatum dominance, the prefrontal cortex plays a dual role, while it is essential for decision-making and inhibitory control and is simultaneously reshaped by dopaminergic and glutamatergic projections that encode drug-seeking behavior. In particular, the ventromedial and orbitofrontal regions of the prefrontal

Table 2. Key neuroadaptations in substance dependence

Brain region	Function in normal state	Alterations in addiction	Primary neurotransmitter involved
Prefrontal cortex	Executive control, impulse regulation	Weakened inhibitory control, impaired decision-making	Glutamate
Nucleus accumbens	Reward processing, reinforcement	Heightened response to drug cues, blunted response to natural rewards	Dopamine
Dorsal striatum	Habit formation, action selection	Transition from goal-directed to compulsive drug-seeking	Opioids
Amygdala	Emotional processing, threat detection	Heightened stress response, increased craving	GABA
Hippocampus	Contextual memory, learning	Strengthened drug-cue associations, increased relapse risk	Glutamate

Notes: This table summarizes the main brain regions affected by addiction, highlighting their functional changes and the associated neurotransmitter systems. These adaptations contribute to impaired impulse control, compulsive drug-seeking, and heightened sensitivity to drug-related cues.

Abbreviation: GABA: Gamma-aminobutyric acid.

cortex integrate value-based information and long-term consequences, modulating behavior in alignment with future-oriented goals.⁷⁹ However, in individuals with chronic drug exposure, these regions exhibit reduced activation and impaired ability to suppress subcortical impulses, further compromising self-regulation and reinforcing compulsive drug seeking.⁸⁰

Functional neuroimaging studies (functional magnetic resonance imaging, positron emission tomography) in chronic stimulants and opioid users have revealed significant alterations in prefrontal cortex responsivity to drug-related stimuli. These findings suggest that heightened dopaminergic signaling in these contexts may effectively override decision-making and planning capacities, shifting cognitive control toward compulsive behaviors.⁸¹ Synaptic plasticity within cortico-striatal circuits facilitates the consolidation of signaling pathways that prioritize drug-related cues, making it increasingly difficult to redirect motivation toward alternative goals.⁸² Moreover, postmortem and neuroimaging studies have demonstrated significant volume reductions and decreased neuronal density in specific brain regions of individuals with heroin dependence, notably in the prefrontal cortex and basal ganglia. These findings suggest that chronic opioid use may result in neurodegenerative-like changes.^{83,84}

Simultaneously, the loss of D2 dopamine receptors in striatal regions exacerbates the cognitive-affective ambivalence experienced by individuals with substance dependence, who fully recognize the harmful nature of their behavior yet unable to suppress it.⁷⁶ In this sense, impulsivity and compulsivity are not merely personality traits, but behavioral manifestations of profound neurobiological reorganization, reflecting a disruption in communication between subcortical reinforcement systems and the prefrontal cortex, which under normal circumstances would impose stronger inhibitory control over impulsive actions.⁸⁵

While the dorsal striatum and prefrontal cortex play central roles in addiction, other key regions, notably the amygdala and hippocampus, also contribute to the encoding and retrieval of substance-related memory. The amygdala processes the emotional salience of stimuli, assigning affective valence to drug-related experiences, whereas the hippocampus encodes the contextual information associated with substance use.¹⁸ This architecture explains why individuals with substance dependence often experience intense cravings when revisiting environments where they previously used drugs or upon re-establishing contact with individuals linked to their former consumption patterns.⁸⁶

Moreover, there is evidence that the amygdala extends glutamatergic projections to the nucleus accumbens and

prefrontal cortex, signaling the affective significance of environmental triggers.⁸⁷ Simultaneously, the hippocampus contextualizes these experiences, ensuring that specific scenes, objects, or settings elicit a strong episodic recall of prior substance use, leading to conditioned dopaminergic responses.⁸⁸ These mechanisms provide a neurobiological basis for the high relapse rates observed in individuals who, after sustaining abstinence in controlled environments, return to prior contexts rich in substance-associated cues, triggering renewed drug-seeking behavior.⁸⁹

7. Craving and relapse

In the context of substance dependence, craving emerges as the subjective manifestation of an underlying physiological alteration: the brain's reward system becomes preemptively responsive to cues and memories associated with substance use, triggering an urgent desire for dopaminergic rewards that past consumption has historically provided.⁹⁰ This intense urge is, therefore, a symptom of dysregulated neural networks, which, through hyperconnectivity, pathologically prioritize drug-seeking behavior over other motivational processes.⁹¹

From the perspective of these neural circuits, relapse represents the reactivation of previously established dysfunctional dopaminergic and glutamatergic pathways.⁹² Even after sustained abstinence, the memory of reinforcement and synaptic plasticity associated with drug-seeking remain dormant, often preserved by epigenetic adaptations that allow for rapid reactivation of prior neural configurations when the substance is reintroduced or when environmental triggers resurface.⁹³ Craving episodes can be elicited by both external stimuli (e.g., objects, locations, and social contacts) and internal states (e.g., anxiety, depressive mood, and boredom), each capable of reinitiating reward circuit activation within seconds.⁹⁴

The progression from substance use to dependence is often conceptualized as a three-stage cycle, comprising (i) intoxication/binge, (ii) withdrawal/negative affect, and (iii) anticipation/craving.³ Each phase correlates with distinct neurobiological changes across key brain structures, including the ventral striatum, extended amygdala, and prefrontal cortex, respectively.⁹⁵ During intoxication, the individual experiences intense positive reinforcement, driven by elevated dopaminergic signaling. As the substance is metabolized, withdrawal symptoms emerge, producing physical and psychological distress that fosters negative reinforcement, wherein continued use serves to alleviate discomfort.⁹⁶ Finally, the anticipation phase is characterized by craving, which propels drug-seeking behavior even after prolonged abstinence, underscoring

the persistence of associative learning mechanisms that sustain long-term vulnerability to relapse.⁹⁷

Each of these three addiction phases is governed by distinct neural mechanisms: the ventral striatum and nucleus accumbens are predominant during intoxication, the extended amygdala sustains the state of hyperexcitability characteristic of withdrawal, and the prefrontal cortex, along with the hippocampus and amygdala, plays a central role in the anticipatory craving phase.⁷⁷ Although this model represents a simplified framework, it effectively captures the dynamic interplay of neural networks throughout addiction, demonstrating that with each completed cycle, the underlying neural connections are strengthened, progressively reducing the likelihood of a spontaneous return to pre-addiction homeostasis.⁹⁸

A network-based perspective emphasizes that addiction is not a unitary condition or simply the result of excessive dopaminergic reinforcement. Rather, it emerges as a pathological communication pattern between neural modules governing motivation, associative learning, and habitual behavior.⁹⁹ When dopamine levels surge, glutamatergic synapses reorganize, and long-lasting contextual memory traces are formed, the prefrontal cortex gradually loses its capacity to impose inhibitory control over subcortical impulses.¹⁰⁰ As previously discussed, genetic and epigenetic factors further modulate resilience to these changes, rendering some individuals more vulnerable to these neuroadaptive processes.¹⁰¹

This network-driven perspective also explains why simple substance cessation is rarely sufficient to resolve addiction; the circuitry remains primed to respond to conditioned cues and seek dopaminergic relief when faced with emotional distress or adverse experiences.¹⁰² Thus, addiction represents a profound reorganization of neural networks, manifesting behaviorally as impulsivity, compulsivity, and elevated risk of relapse.¹⁰³

Considering the role of dopamine and D2 receptors, genetic predispositions, and epigenetic adaptations, it is evident that multiple regulatory levels contribute to the emergence and persistence of addiction. Over the course of chronic substance use, the mesolimbic pathway shifts its emphasis toward the dorsal striatum, accelerating habit formation.⁷ Concurrently, prefrontal regions responsible for inhibition and consequence evaluation progressively weaken, reducing their ability to counteract subcortical motivation-driven behaviors.¹⁰⁴ Meanwhile, synaptic plasticity in the amygdala and hippocampus consolidates affective and contextual memories of drug use, such that re-exposure to the prior environment, or even its mere recollection, reactivates the entrenched dopaminergic response patterns.¹⁰⁵

8. Bridging the pillars

While each of the four dimensions explored – impulsivity and compulsivity, dopaminergic dysfunction, reward system plasticity, and genetic vulnerability – offers discrete explanatory power, their strength lies in interaction. Addiction, in this framework, results not from a single neurochemical imbalance or structural anomaly, but from a systems-level interplay that mirrors the complexity of human behavior itself. Impulsivity predisposes the brain to initiate substance use; compulsivity then sustains it as prefrontal control wanes. This loss of control is potentiated by dopaminergic alterations, which reinforce reward-seeking even in the face of negative consequences. Meanwhile, genetic polymorphisms and epigenetic shifts modulate baseline susceptibility, influencing how the other domains express themselves behaviorally and neurochemically.

Rather than envisioning these elements as parallel lines, this framework invites us to imagine a feedback loop – circular and self-reinforcing – where molecular, behavioral, and environmental factors coalesce. It is precisely this loop that “imprisons” the brain, making addiction a dynamic and evolving pathology.

9. Limitations and scope

This narrative review is intended to synthesize current neurobiological knowledge on substance dependence through an integrative and pedagogical framework. Unlike systematic reviews or meta-analyses, it does not aim to address a specific clinical question or evaluate intervention outcomes quantitatively. Instead, it offers a logical overview of diverse but interrelated domains of evidence that are often dispersed across primary literature.

The scope is inherently limited by the exclusion of non-English publications and databases beyond PubMed, Scopus, and Web of Science, which may introduce language or indexing bias. While these choices were made to ensure methodological consistency and access to peer-reviewed data, we acknowledge that important contributions in other languages may have been missed.

In addition, the figures and schematic representations showed here are simplified heuristics rather than exhaustive depictions of neural circuitry or molecular pathways. Finally, the integrated view proposed here is conceptual and didactic in nature; it is not intended as a diagnostic or therapeutic protocol, but as a tool for fostering interdisciplinary understanding and guiding future research.

10. Conclusion

In synthesizing current neurobiological findings under the metaphor of “the imprisoned brain,” this review underscores

the need to reframe addiction not as a mere consequence of weak willpower or deviance, but as a multidimensional neurological condition shaped by impulsivity, reward circuitry dysregulation, dopaminergic imbalance, and genetic vulnerability. These mechanisms are not isolated but mutually reinforcing, constituting a pathophysiological cycle that perpetuates compulsive drug-seeking behavior. Recognizing these interactions offers a more humane and scientifically grounded approach to prevention, diagnosis, and treatment. Although a deeper understanding of these neurobiological mechanisms alone is insufficient to formulate comprehensive clinical interventions, it paves the way for future investigations at the intersection of neurology, basic neuroscience, and behavioral sciences. Advances in brain imaging technologies, population genetics, and mapping of epigenetic signatures will likely continue to unravel the intricate network of maladaptive positive feedback loops that define addiction.

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