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Addiction as a Brain Network Disorder: Neural Circuitry, Molecular Adaptations, and Precision Therapeutic Targets

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Abstract

Addiction is a chronic relapsing neuropsychiatric disorder characterized by compulsive substance use, impaired inhibitory control, and persistent vulnerability to relapse despite adverse consequences. Contemporary neuroscience conceptualizes addiction as a systems-level brain disorder driven by maladaptive neuroplasticity across interconnected neural circuits regulating reward, executive control, stress responsivity, emotional processing, and salience attribution. This review synthesizes current evidence to develop an integrated mechanistic framework linking neural circuitry, receptor systems, intracellular signaling pathways, transcriptional regulation, neurodevelopment, and population-specific biological variability in addiction. A systematic narrative review was carried out in accordance with PRISMA principles using PubMed, PsycINFO, and Google Scholar databases. Peer-reviewed studies published from 2020 onward addressing addiction neurobiology, neuroimaging, molecular neuroscience, neurogenetics, and neuropharmacology were included. Addiction involves progressive dysregulation of corticolimbic and striatal networks. The binge/intoxication phase is driven by mesocorticolimbic dopaminergic hyperactivation involving the ventral tegmental area and nucleus accumbens, whereas the withdrawal/negative affect stage is associated with dysfunction within the extended amygdala and activation of stress mediators including corticotropin-releasing factor, dynorphin, and norepinephrine. The preoccupation/anticipation stage reflects impaired prefrontal cortical regulation, heightened cue reactivity, and increased relapse vulnerability. Chronic substance exposure induces persistent molecular adaptations involving CREB, ΔFosB, BDNF, mTOR signaling, glutamatergic remodeling, and epigenetic reprogramming. Neuroimaging studies further demonstrate altered functional connectivity and reduced dopamine receptor availability. Collectively, addiction is best understood as a multilevel neurobiological disorder requiring integrative and precision-based therapeutic approaches.

KEYWORDS: Substance-Related Disorders, Neural Pathways, Reward, Gene Expression Regulation, Precision Medicine

1. Introduction

Addiction is one of the leading neuropsychiatric and public health problems worldwide, with far-reaching medical, social, and economic consequences [1-6]. Once viewed primarily as a moral failing or a lack of self-control, addiction is now widely recognized as a chronic relapsing brain disorder characterized by compulsive engagement with substances or rewarding behaviours despite harmful consequences [5]. Advances in neuroscience, neuroimaging, molecular biology, and genetics have substantially transformed current understanding of addiction by demonstrating that repeated exposure to addictive substances produces persistent structural and functional changes in brain systems involved in reward, motivation,

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emotional regulation, learning, stress responses, and executive control [6, 7].

Substance use disorders are associated with maladaptive neuroplasticity across interconnected corticolimbic and striatal pathways, particularly within the mesocorticolimbic dopamine system [8, 9]. Repeated drug exposure alters evolutionarily conserved reward circuitry, increasing the motivational salience of drug-associated cues while progressively weakening inhibitory control and cognitive flexibility. Over time, drug use shifts from voluntary and reward-driven behavior to compulsive and habitual patterns reinforced by both positive and negative reinforcement mechanisms [10, 11]. This transition from controlled substance use to compulsive drug-seeking behaviour reflects widespread neuroadaptations that extend beyond dopaminergic reward pathways and involve multiple interacting neurotransmitter and stress-regulatory systems.

The neurobiology of addiction extends beyond dopamine dysfunction alone. Contemporary evidence highlights complex interactions among glutamatergic, GABAergic, opioidergic, serotonergic, endocannabinoid, and stress-related systems [12, 13]. Chronic substance exposure activates intracellular signaling cascades and transcriptional mechanisms involving cAMP response element-binding protein (CREB), ΔFosB, brain-derived neurotrophic factor (BDNF), mammalian target of rapamycin (mTOR), and epigenetic remodeling. These molecular adaptations produce enduring alterations in synaptic architecture and neuronal excitability that stabilize maladaptive reward learning and contribute to persistent craving and relapse vulnerability long after drug cessation [14-16].

Addiction is increasingly understood as a disorder of distributed neural networks rather than dysfunction within isolated brain regions. Neuroimaging studies consistently demonstrate altered connectivity among the prefrontal cortex, amygdala, hippocampus, basal ganglia, and nucleus accumbens, reflecting disrupted communication between executive control, emotional processing, memory consolidation, and reward systems [17]. Functional abnormalities within these circuits underlie key behavioural features of addiction, including impulsivity, compulsive drug seeking, impaired decision-making, stress sensitivity, and relapse susceptibility [17, 18].

Despite major advances in addiction neuroscience, important translational gaps remain. Much of the available evidence originates from Western populations, limiting understanding of how genetic diversity, environmental adversity, sociocultural influences, and developmental factors shape addiction biology across underrepresented populations. This issue is particularly relevant in Africa, where rapid urbanization, socioeconomic instability, evolving drug markets, and extensive genetic diversity may influence addiction vulnerability and treatment outcomes in unique ways [19].

There is therefore an increasing need for integrative frameworks capable of linking receptor biology, intracellular signaling, neural circuitry, neurodevelopment, and behavioral outcomes within a unified mechanistic model. Such multilevel approaches may improve biomarker identification, support precision-targeted interventions, and facilitate the development of individualized therapeutic strategies. This review synthesizes current evidence on the neurobiology of addiction, with particular emphasis on neural circuits, receptor systems, intracellular signaling pathways, transcriptional regulation, neurodevelopmental influences, and population-specific neurobiological variability.

2. Literature Search Strategy

Relevant literature was identified through searches of PubMed, Scopus, PsycINFO, and Google Scholar using combinations of keywords including “addiction neuroscience,” “substance use disorder,” “reward circuitry,” “dopamine,” “neuroplasticity,” “neuroimaging,” and “molecular mechanisms of addiction.” Priority was given to recent peer-reviewed studies and landmark publications addressing neural circuitry, molecular signaling, neuroplasticity, receptor systems, and translational mechanisms underlying addiction. Relevant literature focusing on addiction neurobiology, neural circuitry, molecular signaling, and neuroimaging studies published primarily within the last decade were included in the review.

3. Neural Circuitry of Addiction

Addiction is increasingly recognized as a disorder of interconnected brain networks rather than dysfunction confined to a single neurotransmitter or brain region [18-20]. Chronic exposure to addictive substances produces widespread neuroadaptations within neural circuits involved in reward processing, executive control, emotional regulation, stress responsivity, learning, and habit formation. These alterations disrupt the balance between top-down cortical regulation and subcortical motivational systems, ultimately driving compulsive drug-seeking behaviour, impaired self-control, and heightened vulnerability to relapse [16-19]. Understanding the functional interactions among these neural circuits is therefore essential for elucidating the biological basis of addiction and identifying novel therapeutic targets.

The neural circuitry of addiction comprises multiple interconnected brain regions that collectively regulate reward, motivation, emotional processing, memory, stress responsiveness, and behavioural control. Dysregulation within

these networks contributes to the progressive transition from voluntary substance use to compulsive drug-seeking behaviour. The following sections examine the major neural systems implicated in addiction and their respective roles in the development, maintenance, and persistence of addictive behaviours.

3.1 Prefrontal Cortex Dysfunction and Impaired Executive Control

The prefrontal cortex (PFC) plays a central role in executive functioning, including decision-making, inhibitory control, emotional regulation, attention, and behavioral flexibility. In addiction, dysfunction of key prefrontal regions such as the dorsolateral prefrontal cortex (dlPFC), orbitofrontal cortex (OFC), ventromedial prefrontal cortex (vmPFC), and anterior cingulate cortex (ACC) is consistently associated with impaired self-regulation and compulsive substance use. Contemporary neuroimaging studies demonstrate reduced cortical activity, disrupted functional connectivity, and altered structural integrity within these regions among individuals with substance use disorders [21-23]

These abnormalities weaken top-down control over subcortical reward and stress circuits, thereby increasing impulsivity, compulsive drug-seeking behaviour, and sensitivity to drug-associated cues. The OFC is particularly important in reward valuation and adaptive decision-making, and dysfunction within this region contributes to pathological salience attribution, whereby drug-related stimuli acquire exaggerated motivational significance compared with natural rewards [24]. Similarly, impaired ACC activity disrupts conflict monitoring and behavioural adjustment, further compromising inhibitory control and increasing relapse vulnerability [23, 24].

3.2 Amygdala and Stress-Related Neuroadaptations

The amygdala is critically involved in emotional processing, conditioned learning, and stress responsivity. During the progression of addiction, the extended amygdala becomes increasingly engaged, particularly during withdrawal and abstinence, contributing to anxiety, irritability, dysphoria, and stress-induced relapse [17]. Repeated substance exposure strengthens emotional memories linking drug effects with environmental cues, making relapse more likely when individuals encounter drug-associated contexts [25, 26]. Concurrently, chronic exposure to addictive substances disrupts stress-regulatory pathways within the amygdala, further reinforcing relapse vulnerability and compulsive substance use. Stress-related neurochemical systems within the amygdala, particularly corticotropin-releasing factor (CRF) and dynorphin signaling, become progressively dysregulated with chronic drug use. These neuroadaptations shift motivation from reward-seeking toward avoidance of withdrawal-related distress, thereby reinforcing compulsive substance use through negative reinforcement mechanisms [27]. This transition from impulsive to compulsive drug use represents a critical neurobiological hallmark of addiction progression.

3.3 Hippocampal Contributions to Drug Memory and Relapse

The hippocampus is essential for contextual learning, memory consolidation, and associative learning. Addictive substances exploit hippocampal memory systems by strengthening associations between drug effects and environmental contexts. These persistent drug-context memories contribute significantly to craving and relapse vulnerability, even after prolonged periods of abstinence [28-30].

Repeated substance exposure also alters hippocampal neurogenesis, glutamatergic signaling, and synaptic plasticity [28-30]. Such changes reinforce maladaptive learning processes and interact with amygdalar emotional circuitry and prefrontal dysfunction to sustain compulsive drug-seeking behaviors. Experimental and neuroimaging studies further suggest that hippocampal dysfunction contributes to impaired cognitive flexibility and exaggerated cue-induced craving in individuals with addiction [31, 32].

3.4 Basal Ganglia and Habit Formation

The basal ganglia are central to reward processing, procedural learning, and habit formation. Early stages of addiction are primarily mediated by the ventral striatum, which processes reward and reinforcement. However, with repeated drug exposure, behavioral control gradually shifts toward the dorsal striatum, promoting the emergence of habitual and compulsive drug-seeking behaviors [11]. This ventral-to-dorsal striatal transition is widely regarded as a defining neurobiological feature of addiction chronicity. Dopaminergic dysregulation within dorsal striatal circuits strengthens automated behavioral responses that become increasingly resistant to cognitive control and negative consequences. As a result, drug-seeking behaviour persists even when the rewarding effects of substances diminish or adverse outcomes become evident [33, 34].

3.5 Mesocorticolimbic Dopamine System

The mesocorticolimbic dopamine pathway remains fundamental to current models of addiction neurobiology. Dopaminergic neurons originating in the ventral tegmental area (VTA) project to the nucleus accumbens, prefrontal cortex, amygdala, and hippocampus, collectively regulating reward processing, salience attribution, motivation, and reinforcement learning [35, 36].

Although addictive substances act through distinct pharmacological mechanisms, they all converge on the common effect of increasing extracellular dopamine within the mesolimbic system. Psychostimulants such as cocaine inhibit dopamine reuptake, opioids indirectly enhance dopamine release through GABAergic disinhibition, nicotine stimulates nicotinic acetylcholine receptors on dopaminergic neurons, and cannabinoids alter dopamine signaling through CB1 receptor-mediated modulation [37, 38].

Chronic activation of this pathway produces profound neuroplastic adaptations, including reduced dopamine D2 receptor availability, altered reward sensitivity, and persistent cue-induced sensitization. Neuroimaging studies consistently demonstrate reduced striatal D2 receptor expression and heightened responsiveness to drug-associated stimuli in individuals with substance use disorders, changes that contribute to tolerance, compulsive drug use, and long-term relapse vulnerability [10].

4. Stages of Addiction

Addiction is now widely understood as a chronic and cyclical disorder that develops through a series of interconnected neurobiological stages. Contemporary models describe this process as progressing through three major phases: binge/intoxication, withdrawal/negative affect, and preoccupation/anticipation. Although these stages are distinct, they interact dynamically and reinforce one another over time, ultimately contributing to compulsive substance use and persistent relapse vulnerability.

4.1 Binge/Intoxication Stage

The binge/intoxication stage is primarily driven by activation of the brain's reward circuitry, particularly the mesolimbic dopamine pathway. During substance use, addictive drugs produce a rapid and exaggerated release of dopamine within the nucleus accumbens, generating feelings of pleasure, reward, and reinforcement. This heightened dopaminergic activity strengthens reward-related learning and increases the motivational significance of drug-associated experiences and cues [39]. With repeated exposure, neuroplastic changes occur within striatal circuits, gradually shifting drug use from voluntary, goal-directed behavior toward more automatic and habitual patterns. Over time, the individual becomes increasingly driven to seek the substance not only for pleasure, but also out of learned behavioral compulsion [40].

4.2 Withdrawal/Negative Affect Stage

The withdrawal or negative affect stage emerges when substance use is reduced or discontinued. This phase is characterized by disruption of both reward and stress-regulatory systems. Reduced dopamine and serotonin activity is accompanied by increased activation of stress-related neurochemical systems involving corticotropin-releasing factor (CRF), norepinephrine, and dynorphin within the extended amygdala [17, 39]. These neurobiological changes contribute to dysphoria, anxiety, irritability, emotional distress, and heightened stress sensitivity. As a result, individuals may continue using substances not necessarily to achieve pleasure, but to relieve the discomfort associated with withdrawal and negative emotional states. This process reflects a shift from positive reinforcement to negative reinforcement as a major driver of addiction [41].

4.3 Preoccupation/Anticipation Stage

The preoccupation or anticipation stage is marked by craving, compulsive drug seeking, and increased vulnerability to relapse, even after prolonged periods of abstinence. Dysfunction within the prefrontal cortex weakens executive control, decision-making, and inhibitory regulation over reward and stress circuits. At the same time, exposure to drug-associated cues or stressful experiences can trigger intense motivational responses and craving [39]. Persistent alterations within corticolimbic circuitry maintain heightened sensitivity to drug-related stimuli, making relapse a chronic risk in addiction. These enduring neuroadaptations help explain why addiction is often characterized by repeated cycles of abstinence and relapse despite strong intentions to stop substance use [42].

5. Molecular and Cellular Mechanisms of Addiction

Addiction is not only a disorder of disrupted brain circuits but also a condition driven by profound molecular and cellular changes within neurons. Repeated exposure to addictive substances alters intracellular signaling pathways, gene expression, synaptic structure, and neuronal communication in

ways that strengthen maladaptive reward learning and sustain compulsive drug-seeking behavior. These molecular adaptations contribute to craving, tolerance, withdrawal symptoms, and relapse vulnerability, often persisting long after substance use has ceased. The following sections highlight key intracellular pathways and molecular mechanisms that underlie the long-term neuroplastic changes associated with addiction.

5.1 CREB Signaling and Transcriptional Regulation

Repeated exposure to addictive substances activates intracellular signaling pathways that produce long-lasting changes in gene expression and synaptic activity. One of the most extensively studied pathways in addiction involves the cyclic adenosine monophosphate (cAMP)-protein kinase A (PKA)-cAMP response element-binding protein (CREB) signaling cascade [43]. When activated, CREB regulates the transcription of genes involved in synaptic plasticity, neuronal excitability, emotional regulation, and stress responsiveness. Increased CREB activity within the nucleus accumbens has been linked to reward tolerance and the development of negative emotional states during withdrawal. Through the induction of dynorphin expression, CREB also suppresses dopaminergic signaling via activation of kappa-opioid receptors, contributing to dysphoria and reinforcing continued substance use as a means of alleviating emotional discomfort [43].

5.2 ΔFosB and Persistent Neuroplasticity

The gradual accumulation of ΔFosB a highly stable transcription factor follows repeated drug exposure. Unlike many immediate early genes that are rapidly degraded, ΔFosB persists within neurons for extended periods, allowing it to function as a long-term molecular marker of chronic substance exposure [44]**.** The accumulation of ΔFosB regulates genes involved in dendritic remodeling, synaptic strengthening, and reward sensitization. These neuroadaptations maintain addiction-related circuitry in a hyperresponsive state, increasing sensitivity to drug-associated cues and contributing to persistent craving and relapse even after prolonged abstinence [44, 45].

5.3 BDNF and Synaptic Remodeling

Brain-derived neurotrophic factor (BDNF) plays a crucial role in neuronal survival, synaptic plasticity, and activity-dependent learning [46-48]. In addiction, increased BDNF signaling within the ventral tegmental area and nucleus accumbens strengthens drug-associated memories and enhances relapse vulnerability. BDNF-mediated synaptic remodeling reinforces maladaptive reward learning by promoting structural and functional changes within addiction-related neural circuits. These alterations contribute to the persistence of compulsive drug-seeking behaviors and the long-lasting nature of addictive disorders [46].

5.4 mTOR Signaling and Drug Memory Consolidation

The mammalian target of rapamycin (mTOR) pathway is a key regulator of protein synthesis, synaptic restructuring, and memory consolidation. Substance exposure activates mTOR signaling within reward-related brain regions, facilitating the stabilization of newly formed drug-associated memories [49]. Experimental studies have shown that inhibition of mTOR signaling can reduce relapse-like behavior and disrupt the reconsolidation of drug-related memories in preclinical models. These findings suggest that mTOR may represent a promising therapeutic target for weakening maladaptive addiction-related memories and reducing relapse risk [50, 51].

5.5 Epigenetic Mechanisms

Addiction is further sustained through epigenetic modifications that alter gene expression without changing the underlying DNA sequence. These mechanisms include histone acetylation, DNA methylation, chromatin remodeling, and regulation by noncoding RNAs [52, 53]. Repeated substance exposure induces persistent epigenetic reprogramming within reward and stress circuits, stabilizing addiction-related transcriptional states over time. Such changes may explain why vulnerability to craving and relapse can persist long after drug use has stopped. Increasing evidence suggests that targeting epigenetic pathways could provide novel opportunities for therapeutic intervention in substance use disorders [52, 53].

6. Receptor Systems in Addiction Neurobiology

Addiction involves complex interactions among multiple neurotransmitter systems that regulate reward, motivation, emotional processing, learning, stress responses, and behavioral control. Rather than acting through a single pathway, addictive substances alter the balance of excitatory and inhibitory signaling across interconnected brain networks. Repeated substance exposure produces long-term changes in receptor activity, neurotransmitter release, and synaptic communication, ultimately reinforcing compulsive drug-seeking behavior and increasing vulnerability to relapse. The following sections highlight the major receptor systems involved in the

neurobiology of addiction and their contributions to the development and persistence of substance use disorders.

6.1 Dopaminergic Receptors

Dopamine receptor signaling plays a central role in reinforcement learning, reward processing, and motivational salience. Dopamine receptors are broadly classified into D1-like and D2-like receptor families. D1-like receptors generally enhance excitatory signaling and facilitate reward-related learning, whereas D2-like receptors contribute to inhibitory regulation, behavioral control, and modulation of motivational responses [54-56]. In addiction, chronic substance exposure disrupts normal dopaminergic signaling, particularly within the mesocorticolimbic reward system. Reduced availability of dopamine D2 receptors is consistently observed in individuals with substance use disorders and has been associated with impaired inhibitory control, compulsive behavior, impulsivity, and reduced sensitivity to natural rewards. These changes contribute to the progressive shift from controlled substance use to compulsive drug-seeking behaviour [54-56].

6.2 Glutamatergic Transmission

Glutamate is the principal excitatory neurotransmitter in the brain and plays a critical role in synaptic plasticity, learning, memory formation, and relapse-related behaviors. Alterations in glutamatergic signaling are strongly implicated in craving and relapse vulnerability [17, 57, 58]. Repeated exposure to addictive substances, particularly psychostimulants such as cocaine, induces significant remodeling of glutamatergic synapses within the nucleus accumbens and prefrontal cortex. One important adaptation involves the accumulation of calcium-permeable AMPA receptors, which heighten neuronal responsiveness to drug-associated cues and strengthen maladaptive reward memories. Dysregulated glutamatergic transmission therefore contributes to persistent craving, compulsive drug seeking, and increased relapse risk even after prolonged abstinence [17, 57, 58].

6.3 GABAergic Regulation

Gamma-aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the central nervous system and is essential for maintaining neuronal excitability and network stability. GABAergic circuits regulate activity within reward, stress, and emotional processing pathways, including the mesolimbic dopamine system [59, 60]. Many addictive substances indirectly increase dopamine release by suppressing inhibitory GABAergic neurons, a process known as disinhibition. Chronic disruption of GABAergic regulation contributes to heightened stress sensitivity, anxiety, emotional dysregulation, and impaired reward processing. These neuroadaptations further reinforce compulsive substance use and increase susceptibility to withdrawal-related distress and relapse [59, 60].

6.4 Endocannabinoid and Opioid Systems

The endocannabinoid and opioid systems play important modulatory roles in reward processing, emotional regulation, stress responsiveness, and reinforcement learning. Cannabinoid CB1 receptors are widely distributed throughout addiction-related brain regions, where they regulate neurotransmitter release and synaptic plasticity [61-64].

Similarly, opioid receptors, including mu (μ), kappa (κ), and delta (δ) receptors, are critically involved in the rewarding and emotional effects of addictive substances. Activation of mu-opioid receptors contributes to euphoria, analgesia, and reinforcement, whereas activation of kappa-opioid receptors is associated with dysphoria, stress-related behaviors, and negative emotional states during withdrawal. Chronic dysregulation of these systems contributes to the emotional instability, craving, and relapse vulnerability commonly observed in addiction, highlighting their importance as potential therapeutic targets in substance use disorders [61-64].

7. Integrative Multilevel Models of Addiction

Modern addiction neuroscience increasingly recognizes that addiction cannot be fully understood by examining isolated brain regions, neurotransmitters, or molecular pathways alone. Instead, addiction is now viewed as a complex, multilevel disorder involving dynamic interactions across molecular, cellular, circuit, behavioral, and computational domains. Advances in neuroimaging, molecular biology, and computational neuroscience have made it possible to study how changes at the receptor and cellular levels influence large-scale brain networks and ultimately shape behaviour [65, 66].

Emerging analytical approaches, including machine learning and multiscale computational modeling, now allow researchers to simultaneously evaluate receptor expression, neural connectivity, cognitive performance, and behavioral outcomes. These integrative methods are helping to identify potential biomarkers associated with relapse vulnerability, treatment responsiveness, and long-term recovery trajectories [65, 66]. In addition, computational frameworks provide important mechanistic insight into how disruptions in neurotransmitter systems and intracellular signaling pathways translate into

widespread network dysfunction and behavioral manifestations characteristic of addiction [65].

The growing convergence of neuroimaging, transcriptomics, proteomics, and computational modeling is therefore advancing the field toward precision addiction medicine, where prevention and treatment strategies may eventually be tailored to individual neurobiological profiles. Importantly, these advances have also highlighted the need to better understand how genetic background, environmental exposure, and sociocultural context shape addiction-related neurobiology across diverse populations.

8. Population-Specific Neurobiology and the African Context

The neurobiology of addiction is strongly influenced by interactions among genetic factors, environmental stressors, developmental experiences, and sociocultural conditions. Although African populations possess the greatest degree of human genetic diversity globally, they remain substantially underrepresented in addiction neuroscience research. This underrepresentation limits understanding of how biological and environmental variability may influence addiction vulnerability, disease progression, and treatment response within African populations.

Genetic variations involving dopaminergic, opioidergic, and metabolic pathways may significantly affect reward processing, impulsivity, stress responsiveness, and susceptibility to substance use disorders. Polymorphisms in genes such as *SLC6A3*, *DRD2*, *DRD4*, *OPRM1*, *CYP2A6*, and *CYP2B6* have been associated with differences in dopamine signaling, opioid sensitivity, and drug metabolism, potentially influencing both addiction risk and therapeutic outcomes.

In addition to biological factors, socioeconomic and environmental pressures play an important role in shaping addiction patterns across African communities. Rapid urbanization, unemployment, poverty, sociopolitical instability, and expanding illicit drug markets may interact with underlying neurobiological vulnerability to increase the burden of substance use disorders. Limited access to mental health services and persistent stigma surrounding addiction further complicate prevention and treatment efforts.

Understanding population-specific neurobiology is therefore essential for improving the global relevance of addiction research and for developing culturally responsive, biologically informed, and precision-based intervention strategies that address the unique needs of African populations.

Conclusion

Addiction is now widely recognized as a complex neurobiological disorder that develops through continuous interactions among brain circuits, neurotransmitter systems, intracellular signaling pathways, genetic and epigenetic mechanisms, developmental factors, and environmental influences. Repeated exposure to addictive substances progressively alters corticolimbic and striatal networks involved in reward processing, motivation, executive control, stress responsiveness, and emotional regulation, ultimately reinforcing compulsive drug-seeking behavior and increasing vulnerability to relapse.

Recent advances in neuroimaging, molecular neuroscience, transcriptomics, and computational modeling have significantly expanded current understanding of the biological mechanisms underlying addiction. These technologies have provided important insight into how molecular and cellular changes contribute to large-scale neural network dysfunction and behavioral abnormalities. Nevertheless, important translational challenges remain, particularly in linking mechanistic findings to clinically effective prevention and treatment strategies. Future research should therefore prioritize integrative, multilevel approaches capable of connecting receptor biology, synaptic plasticity, neural circuitry, and behavioral outcomes within unified models of addiction.

Equally important is the inclusion of underrepresented populations, particularly African cohorts, in addiction neuroscience research. Expanding population diversity in neurobiological studies will improve the global relevance, accuracy, and translational value of addiction science. Such efforts may ultimately support the development of biologically informed, culturally sensitive, and precision-based interventions that improve long-term recovery outcomes and reduce the global burden of addiction and relapse.

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References

1. Heilig M, MacKillop J, Martinez D, Rehm J, Leggio L, Vanderschuren LJMJ. Addiction as a brain disease revised: why it still matters, and the need for consilience. Neuropsychopharmacology. 2021 Sep;46(10):1715-1723. doi: 10.1038/s41386-020-00950-y.
2. Onaolapo AY, Onaolapo OJ. Food additives, food and the concept of 'food addiction': Is stimulation of the brain reward circuit by food sufficient to trigger addiction? Pathophysiology. 2018 Dec;25(4):263-276. doi: 10.1016/j.pathophys.2018.04.002.
3. Falade J, Akinnuoye AA, Sajo S, Ajayi AA, Ajayi AO, Ogungbemi AO, et al. Emerging psychoactive drugs and the common life events among adolescents in a Nigerian rehabilitation centre. British Journal of Guidance and Counselling, 2025;*53*(5), 677–689. https://doi.org/10.1080/03069885.2024.2370525
4. Onaolapo OJ, Onaolapo AY. Melatonin in drug addiction and addiction management: Exploring an evolving multidimensional relationship. World J Psychiatry. 2018 Jun 28;8(2):64-74. doi: 10.5498/wjp.v8.i2.64.
5. Frank LE, Nagel SK Addiction and Moralization: the Role of the Underlying Model of Addiction. *Neuroethics* 2017;10:129–139. https://doi.org/10.1007/s12152-017-9307-x
6. Goto Y, Krieger J, Won M, Lee YA. Addiction spectrum disorder: a conceptual framework for comprehensive understanding of addictive disorders. Front Psychol. 2026;17:1753662. doi: 10.3389/fpsyg.2026.1753662.
7. Volkow ND, Boyle M. Neuroscience of Addiction: Relevance to Prevention and Treatment. Am J Psychiatry. 2018;175(8):729-740. doi: 10.1176/appi.ajp.2018.17101174.
8. Sharma P, Sawaya MF, Dumitrescu AM, Kolluru GK, Schmoutz CD, Salinas A, Cannon CE, Kumbhare D, Korneeva N, Vest MF, Wood BJ, Bracey P, McNeil S, Kaye AD, Murnane SE, Jordan J, Keys K, Brackett E, Avadhanula K, Murnane KS. Novel neurotherapeutic targets for substance use disorders: Neuroplasticity, neuroinflammation, gasotransmitters and non-canonical organ systems. Neurotherapeutics. 2025;22(6):e00770. doi: 10.1016/j.neurot.2025.e00770.
9. Cancela LM, Mongi-Bragato B, Avalos MP, Bollati FA. From Stress to Substance Use Disorders: The Expanding Role of Microglia–Astrocyte Crosstalk in Neuroimmune and Glutamate Alterations in the Nucleus Accumbens. *International Journal of Molecular Sciences*. 2026;*27*(1), 385. https://doi.org/10.3390/ijms27010385
10. Volkow ND, Michaelides M, Baler R. The Neuroscience of Drug Reward and Addiction. Physiol Rev. 2019 Oct 1;99(4):2115-2140. doi: 10.1152/physrev.00014.2018.
11. Everitt BJ, Robbins TW Drug addiction: Updating actions to habits to compulsions ten years on. *Annual Review of Psychology*, *2016;67*, 23–50. https://doi.org/10.1146/annurev-psych-122414-033457
12. Uhl GR, Koob GF, Cable J. The neurobiology of addiction. Ann N Y Acad Sci. 2019 Sep;1451(1):5-28. doi: 10.1111/nyas.13989.
13. Semaan A, Khan MK. Neurobiology of Addiction. [Updated 2023 Nov 2]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2026. Available from: https://www.ncbi.nlm.nih.gov/books/NBK597351/
14. Mews P, Walker DM, Nestler EJ. Epigenetic Priming in Drug Addiction. Cold Spring Harb Symp Quant Biol. 2018;83:131-139. doi: 10.1101/sqb.2018.83.037663.
15. Lüscher C, Robbins TW, Everitt BJ The transition to compulsion in addiction. *Nature Reviews Neuroscience*, *2020;21*(5), 247–263. https://doi.org/10.1038/s41583-020-0289-z
16. Nestler, E. J. Molecular neurobiology of addiction. *The American Journal on Addictions*, *2021;30*(1), 4–15. https://doi.org/10.1111/ajad.13079
17. Substance Abuse and Mental Health Services Administration (US); Office of the Surgeon General (US). Facing Addiction in America: The Surgeon General's Report on Alcohol, Drugs, and Health [Internet]. Washington (DC): US Department of Health and Human Services; 2016 Nov. CHAPTER 2, The Neurobiology of Substance Use, Misuse, and Addiction. Available from: https://www.ncbi.nlm.nih.gov/sites/books/NBK424849/
18. Goldstein RZ, Volkow ND. Dysfunction of the prefrontal cortex in addiction: neuroimaging findings and clinical implications. Nat Rev Neurosci. 2011 Oct 20;12(11):652-69. doi: 10.1038/nrn3119.
19. Biribawa C, Tumwesigye NM, Sinclair DL, Matovu DK, Swensen G, Meyer F, Mukasa M, Kalema D, Mutamba BB, Vanderplasschen W. Treatment outcomes for substance use disorders across the African continent: a systematic review. BMC Psychol. 2025 Jul 1;13(1):662. doi: 10.1186/s40359-025-02978-5.
20. Basavarajappa BS, Subbanna S. From Synaptic Plasticity to Neurotoxicity: Endocannabinoid Influence on Addiction and Neurodegeneration. *International Journal of Molecular Sciences*. 2025; 26(23):11632. https://doi.org/10.3390/ijms262311632
21. Zilverstand A, Huang AS, Alia-Klein N, Goldstein RZ. Neuroimaging Impaired Response Inhibition and Salience Attribution in Human Drug Addiction: A Systematic Review. Neuron. 2018 Jun 6;98(5):886-903. doi: 10.1016/j.neuron.2018.03.048.
22. Gould TJ. Addiction and cognition. Addict Sci Clin Pract. 2010 Dec;5(2):4-14.
23. Noël X, Brevers D, Bechara A. A neurocognitive approach to understanding the neurobiology of addiction. Curr Opin Neurobiol. 2013 Aug;23(4):632-8. doi: 10.1016/j.conb.2013.01.018.
24. Mestre-Bach G, Potenza MN. Neural mechanisms linked to treatment outcomes and recovery in substance-related and addictive disorders. Dialogues Clin Neurosci. 2023 Dec;25(1):75-91. doi: 10.1080/19585969.2023.2242359.
25. Koob GF. Drug Addiction: Hyperkatifeia/Negative Reinforcement as a Framework for Medications Development. Pharmacol Rev. 2021 Jan;73(1):163-201. doi: 10.1124/pharmrev.120.000083.
26. Smith RJ, Laiks LS. Behavioral and neural mechanisms underlying habitual and compulsive drug seeking. Prog Neuropsychopharmacol Biol Psychiatry. 2018 Dec 20;87(Pt A):11-21. doi: 10.1016/j.pnpbp.2017.09.003.
27. Puglisi-Allegra S, Ventura R. Prefrontal/accumbal catecholamine system processes high motivational salience. Front Behav Neurosci. 2012 Jun 27;6:31. doi: 10.3389/fnbeh.2012.00031.

28. Kutlu MG, Gould TJ. Effects of drugs of abuse on hippocampal plasticity and hippocampus-dependent learning and memory: contributions to development and maintenance of addiction. Learn Mem. 2016 Sep 15;23(10):515-33. doi: 10.1101/lm.042192.116.
29. Berke JD, Eichenbaum HB. Drug addiction and the hippocampus. Science. 2001 Nov 9;294(5545):1235. doi: 10.1126/science.294.5545.1235a
30. Goodman J, Packard MG. Memory Systems and the Addicted Brain. Front Psychiatry. 2016 Feb 25;7:24. doi: 10.3389/fpsyt.2016.00024.
31. Estrada-Medina R, Briones-Llamoctanta BE, Turpo-Chaparro JE. Neuroplasticity and recovery of the brain affected by substance use disorder: multilevel mechanisms and new therapeutic strategies (2020-2025). Front Mol Neurosci. 2026 Feb 26;19:1760387. doi: 10.3389/fnmol.2026.1760387.
32. Chambers RA. Adult hippocampal neurogenesis in the pathogenesis of addiction and dual diagnosis disorders. Drug Alcohol Depend. 2013 Jun 1;130(1-3):1-12. doi: 10.1016/j.drugalcdep.2012.12.005.
33. Dinckol O, Wenger NH, Copling A, Patel BP, Kutlu MG. Dopamine and Acetylcholine in the Striatum: Circuit Interactions and Behavioral Control in Substance Use Disorders. *Brain Sciences*. 2026; 16(4):397. https://doi.org/10.3390/brainsci16040397
34. Schiltz CA. Habitual responding and the dorsal striatum. J Neurosci. 2006 Feb 15;26(7):1891-2. doi: 10.1523/JNEUROSCI.4419-05.2006.
35. Reynolds LM, Flores C. Mesocorticolimbic Dopamine Pathways Across Adolescence: Diversity in Development. Front Neural Circuits. 2021 Sep 8;15:735625. doi: 10.3389/fncir.2021.735625.
36. Cross EA, Borland JM, Shaughnessy EK, Lee SD, Vu V, Sambor EA, Meisel RL, Huhman KL, Albers HE. Distinct subcircuits within the mesolimbic dopamine system encode the salience and valence of social stimuli. Psychopharmacology (Berl). 2025 Oct;242(10):2219-2232. doi: 10.1007/s00213-025-06793-z.
37. Lüscher C, Malenka RC. Drug-evoked synaptic plasticity in addiction: from molecular changes to circuit remodeling. Neuron. 2011 Feb 24;69(4):650-63. doi: 10.1016/j.neuron.2011.01.017.
38. Davis S, Zhu J. Substance abuse and neurotransmission. Adv Pharmacol. 2022;93:403-441. doi: 10.1016/bs.apha.2021.10.007.
39. Koob GF, Volkow ND. Neurobiology of addiction: a neurocircuitry analysis. Lancet Psychiatry. 2016 Aug;3(8):760-773. doi: 10.1016/S2215-0366(16)00104-8.
40. 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 Sep;32(9):748-55. doi: 10.1002/bies.201000042.
41. Cho SB, Su J, Kuo SI, Bucholz KK, Chan G, Edenberg HJ, McCutcheon VV, Schuckit MA, Kramer JR, Dick DM. Positive and negative reinforcement are differentially associated with alcohol consumption as a function of alcohol dependence. Psychol Addict Behav. 2019 Feb;33(1):58-68. doi: 10.1037/adb0000436.
42. Sinha R. Chronic stress, drug use, and vulnerability to addiction. Ann N Y Acad Sci. 2008 Oct;1141:105-30. doi: 10.1196/annals.1441.030.
43. Adinoff B. Neurobiologic processes in drug reward and addiction. Harv Rev Psychiatry. 2004 Nov-Dec;12(6):305-20. doi: 10.1080/10673220490910844.
44. obison AJ, Nestler EJ. ΔFOSB: A Potentially Druggable Master Orchestrator of Activity-Dependent Gene Expression. ACS Chem Neurosci. 2022 Feb 2;13(3):296-307. doi: 10.1021/acschemneuro.1c00723.
45. Nestler EJ, Barrot M, Self DW. DeltaFosB: a sustained molecular switch for addiction. Proc Natl Acad Sci U S A. 2001 Sep 25;98(20):11042-6. doi: 10.1073/pnas.191352698.
46. Ghitza UE, Zhai H, Wu P, Airavaara M, Shaham Y, Lu L. Role of BDNF and GDNF in drug reward and relapse: a review. Neurosci Biobehav Rev. 2010 Nov;35(2):157-71. doi: 10.1016/j.neubiorev.2009.11.009.
47. Barker JM, Taylor JR, De Vries TJ, Peters J. Brain-derived neurotrophic factor and addiction: Pathological versus therapeutic effects on drug seeking. Brain Res. 2015 Dec 2;1628(Pt A):68-81. doi: 10.1016/j.brainres.2014.10.058.
48. Lu B. BDNF and activity-dependent synaptic modulation. Learn Mem. 2003 Mar-Apr;10(2):86-98. doi: 10.1101/lm.54603.
49. Wong M. Mammalian target of rapamycin (mTOR) pathways in neurological diseases. Biomed J. 2013 Mar-Apr;36(2):40-50. doi: 10.4103/2319-4170.110365.
50. Radiske A, Gonzalez MC, Nôga DA, Rossato JI, Bevilaqua LRM, Cammarota M. mTOR inhibition impairs extinction memory reconsolidation. Learn Mem. 2020 Dec 15;28(1):1-6. doi: 10.1101/lm.052068.120.
51. Parsons RG, Gafford GM, Helmstetter FJ. Translational control via the mammalian target of rapamycin pathway is critical for the formation and stability of long-term fear memory in amygdala neurons. J Neurosci. 2006 Dec 13;26(50):12977-83. doi: 10.1523/JNEUROSCI.4209-06.2006.
52. Hediyal TA, Shukri O, Stone E, Foroughi A, Samikkannu T, Pendyala G. Decoding Encoded Cravings: Epigenetic Drivers of Addiction. Brain Sci. 2025 Aug 27;15(9):927. doi: 10.3390/brainsci15090927.
53. Nestler EJ. Epigenetic mechanisms of drug addiction. Neuropharmacology. 2014 Jan;76 Pt B(0 0):259-68. doi: 10.1016/j.neuropharm.2013.04.004.
54. Baik JH. Dopamine signaling in reward-related behaviors. Front Neural Circuits. 2013;7:152. doi: 10.3389/fncir.2013.00152.
55. Jones-Tabah J, Mohammad H, Paulus EG, Clarke PBS, Hébert TE. The Signaling and Pharmacology of the Dopamine D1 Receptor. Front Cell Neurosci. 2022 Jan 17;15:806618. doi: 10.3389/fncel.2021.806618.
56. Kawahata I, Finkelstein DI, Fukunaga K. Dopamine D1–D5 Receptors in Brain Nuclei: Implications for Health and Disease. *Receptors*. 2024; 3(2):155-181. https://doi.org/10.3390/receptors3020009
57. Quintero GG. Role of nucleus accumbens glutamatergic plasticity in drug addiction. *Neuropsychiatr Dis Treat*. 2013;9:1499-1512 https://doi.org/10.2147/NDT.S45963

58. Nicosia N, Giovenzana M, Misztak P, Mingardi J, Musazzi L. Glutamate-Mediated Excitotoxicity in the Pathogenesis and Treatment of Neurodevelopmental and Adult Mental Disorders. Int J Mol Sci. 2024 Jun 13;25(12):6521. doi: 10.3390/ijms25126521.
59. Terunuma M. Diversity of structure and function of $GABA_B$ receptors: a complexity of $GABA_B$-mediated signaling. Proc Jpn Acad Ser B Phys Biol Sci. 2018;94(10):390-411. doi: 10.2183/pjab.94.026.
60. Chen RJ, Sharma S. GABA Receptor. [Updated 2025 Feb 18]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2026 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK526124/
61. Wenzel JM, Cheer JF. Endocannabinoid Regulation of Reward and Reinforcement through Interaction with Dopamine and Endogenous Opioid Signaling. Neuropsychopharmacology. 2018 Jan;43(1):103-115. doi: 10.1038/npp.2017.126.
62. García-Gutiérrez M.S Torregrosa AB, Rueda NF, Gasparyan A, Esteve GL, Navarro D, Manzanares J. Substance Use Disorders and the Endocannabinoid System: A New Narrative. In: Martin, C.R., Preedy, V.R., Patel, V.B., Rajendram, R. (eds) Handbook of the Biology and Pathology of Mental Disorders. Springer, Cham. 2025, https://doi.org/10.1007/978-3-031-73368-0_140
63. Befort K. Interactions of the opioid and cannabinoid systems in reward: Insights from knockout studies. Front Pharmacol. 2015 Feb 5;6:6. doi: 10.3389/fphar.2015.00006.
64. Wenzel JM, Cheer JF. Endocannabinoid Regulation of Reward and Reinforcement through Interaction with Dopamine and Endogenous Opioid Signaling. Neuropsychopharmacology. 2018 Jan;43(1):103-115. doi: 10.1038/npp.2017.126.
65. Ferrer-Pérez C, Montagud-Romero S, Blanco-Gandía MC. Neurobiological Theories of Addiction: A Comprehensive Review. *Psychoactives*. 2024; 3(1):35-47. https://doi.org/10.3390/psychoactives3010003
66. Kamarajan C, Marinkovic K, Viswanathan R. Editorial: Neurobiological mechanisms of addiction: bridging neuroscience and clinical implications. Front Hum Neurosci. 2026 Feb 17;20:1800164. doi: 10.3389/fnhum.2026.1800164.

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