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Neuroanatomical Basis of Addiction: A narrative Review

Authors : Joshua Falade[1], Oluwafemi Ajiboye[1], David Olaogun[1], Victor Anadu[1], Inaboya Momodu[1] Oluwaseun Ola[1]

Affiliations: 1. University of Medical Science Ondo, Ondo State, Nigeria.

Corresponding Author: Oluwafemi Ajiboye , Email: ajiboyeoluwafemi938@gmail.com
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Abstract

Background: The review titled "A Neuroanatomical Basis of Addiction" explores the complex neurobiological mechanisms that lead to addiction, particularly focusing on the transition from recreational use to substance use disorders. It introduces a heuristic framework that categorizes addiction into three stages: binge/intoxication, withdrawal/negative affect, and preoccupation/anticipation, each linked to specific neurocircuitries. **Aim:** The aim of the review is to elucidate the neuroanatomical underpinnings of addiction and to discuss how neuroplastic changes contribute to compulsive behaviors associated with substance use disorders. **Methodology**: The review synthesizes recent advancements in neuroimaging and neurogenetic research, examining the neurochemical pathways and microcircuits involved in addiction-related behaviors. It emphasizes the role of key brain regions, including the basal ganglia, extended amygdala, and prefrontal cortex, in the addiction process. **Results**: Findings reveal that alterations in incentive salience, emotional regulation, and executive function within these circuits drive the compulsive nature of addiction. The review highlights the significance of individual differences in neurobiology, which can inform targeted interventions. **Conclusion:** The insights gained from the neuroanatomical framework have important implications for public health policies and prevention strategies, especially amid the ongoing opioid crisis and the legalization of substances like marijuana. The review advocates for a deeper integration of neuroscience in addiction research to enhance clinical practices and recovery outcomes.

Keywords: Addiction, Neuroanatomical, Compulsive, Neuroplastic

INTRODUCTION

Drug addiction is a chronic, relapsing disorder marked by compulsive drug seeking and use, often despite harmful consequences (1). The global prevalence of addiction, particularly regarding psychoactive substances, presents significant public health challenges, as substance use disorders (SUDs) are associated with various health and social issues (2). In the U.S., around 12% of adults experience alcohol dependence, while 2-3% report dependence on illicit drugs, with notable increases during adolescence (3). Recent data indicates that approximately 12.5% of U.S. adults smoke, with rising

e-cigarette use among youth, as 12.6% of high school students reported using tobacco products in 2023 (4). Caffeine remains the most widely consumed psychoactive substance in the U.S., with about 85% of adults consuming an average of 200 mg daily (5). Additionally, the misuse of amphetamines, particularly prescription medications like Adderall, is prevalent among college students, with about 6% reporting non-medical use due to academic pressures (6,7). According to NSDUH (2023), the rising use of heroin among young adults, often as a substitute for misused prescription opioids, underscores the ongoing opioid crisis .

In Africa, drug abuse is a critical public health issue impacting social stability and economic development. Substance use disorders are notably high in South Africa, where about 13% of the population is affected, predominantly by alcohol use disorder (8). AU (2020), stated that Cannabis use is significant, along with rising trends in methamphetamine and heroin use. In Nigeria, drug abuse prevalence among secondary school students ranges from 20% to 40%, escalating to 81.1% in high-risk groups, leading to serious health issues, including mental disorders (1). Alcohol consumption has steadily increased over the years, with some countries in sub-Saharan Africa, such as South Africa and Nigeria, experiencing high rates of binge drinking (8). In South Africa, for example, over 60% of men and nearly 40% of women are reported to engage in hazardous drinking (9). The prevalence of alcohol addiction has led to a rise in related health problems, such as liver disease, mental health disorders, and an increase in accidents, violence, and road fatalities.

In addition to alcohol, the use of illicit drugs such as cannabis, heroin, and cocaine is also rising. Cannabis remains the most commonly abused drug across the continent, with significant use reported in countries like Kenya, Uganda, and Zambia (9). In some regions, such as West Africa, heroin and cocaine trafficking have surged, driven in part by the continent's role as a transit point for drugs headed to Europe and North America; this has resulted in increased local availability of these drugs, leading to a higher rate of addiction among vulnerable populations, including youth and young adults (8). The opioid crisis has also gained attention in parts of Africa. Prescription drug abuse, particularly involving opioids, is rising, especially in countries like Nigeria, where there has been a sharp increase in the misuse of tramadol and codeine (8). The economic impact of addiction is another significant concern, with costs related to healthcare, lost productivity, and law enforcement placing strain on local economies (10). The evolving substance use epidemic in Africa reflects a shift from transit points to consumer countries, influenced by rapid socioeconomic changes (11). Drug-related deaths in Africa approximate 37,000 annually, with Nigeria particularly affected (8). Overall, the transition to addiction involves complex neuroadaptations within brain regions and neurotransmitter systems (12).

Justification

Advances in neuroscience have provided significant insights into the neuroanatomical basis of addiction, which can be conceptualized within a three-stage framework: binge/intoxication, withdrawal/ negative affect, and preoccupation/ anticipation (craving) (13). However there is paucity review on it recent findings, this review focus on recent findings in neuroanatomical basis of drug addiction, it is important to note that understanding the neuroanatomical basis of addiction may plays important roles in targeted development treatments that address the root causes of addictive behaviors, providing knowledge of neuroanatomical factors that can help tailor interventions to individual differences in brain structure and function, understanding how addiction alters brain structure and function which can aid in the early identification of individuals at risk.

Aim: To elucidate the neuroanatomical mechanisms underlying addiction by examining the major brain regions and circuits

involved in the addiction cycle. This review also aims to integrate findings from recent neuroimaging studies to provide a comprehensive understanding of how these neuroanatomical structures interact during the stages of addiction, from binge/intoxication to withdrawal and preoccupation/anticipation.

METHODOLOGY

Literature Search Strategy: A systematic search was conducted in major academic databases, including PubMed, Google Scholar, and PsycINFO. Keywords used in the search included "neuroanatomy of addiction," "brain structures and addiction," "neuroimaging addiction," and "addiction neuroscience." The search was limited to articles published between 2020 and with a focus on peer-reviewed journal articles.

Inclusion and Exclusion Criteria: Inclusion Criteria: The following studies were included (a) comprehensive reviews, (b) focused on the neuroanatomical aspects of addiction, (c) utilized neuroimaging and anatomical analysis, and (d) were published in English.

Exclusion Criteria: The following studies were excluded (a) not directly related to neuroanatomical structures (e.g.) behavioral studies without neuroimaging data, (b) lacked a clear focus on addiction (c) reviews with limited discussion on neuroanatomy (d) Manuscript with great discrepancies from others

Data Extraction and Synthesis: From the selected studies, relevant data were extracted, including information on brain structures implicated in addiction (e.g., the nucleus accumbens, amygdala, prefrontal cortex), methodological approaches (e.g., fMRI, PET scans), and key findings related to the role of these structures in addiction. The data were then categorized based on the brain regions and their functional roles in addiction processes.

Analysis: A qualitative synthesis of the extracted data was performed to identify common themes and discrepancies across studies. The review emphasizes key brain structures and their connections, highlighting their contributions to addiction mechanisms. Differences in findings among studies were discussed to provide a nuanced understanding of the current state of neuroanatomical research in addiction.

RESULTS

Heuristic framework categorizing addiction

The heuristic framework categorizing addiction into three stages which are binge/intoxication, withdrawal/negative affect, and preoccupation/anticipation provides a valuable lens through which to understand the neuroanatomical underpinnings of substance use disorders (SUDs). Each stage is associated with distinct neurobiological processes and brain regions, illustrating how addiction evolves and manifests in individuals.

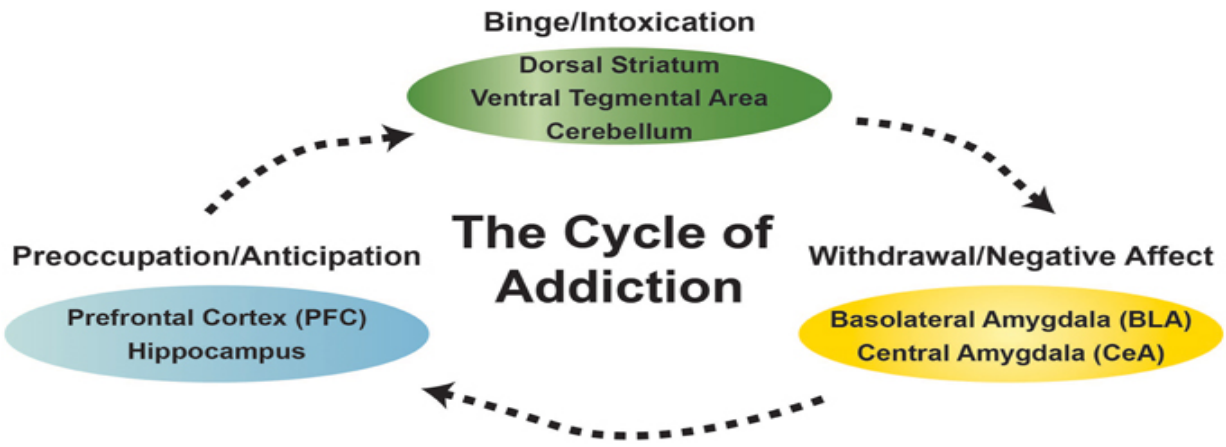

Figure 1: Diagram illustrating the behavioral states and key brain regions related to the addiction cycle (14).

a) Binge/Intoxication

In the binge/intoxication stage, individuals consume substances to experience their rewarding effects. This stage is primarily associated with the basal ganglia, particularly the nucleus accumbens (NAc), which is a critical component of the brain's reward circuitry. The Nucleus accumbens is heavily influenced by dopaminergic projections from the ventral tegmental area (VTA). When a substance is consumed, it leads to a surge of dopamine in the NAc, reinforcing the behavior and creating a strong association between the substance and pleasurable experiences. Repeated exposure results in long-lasting changes in synaptic strength and connectivity within the reward circuitry, which can enhance the incentive salience of drug-related cues; this means that cues associated with drug use become more appealing and can trigger cravings even long after the drug is no longer present (15).

The initial use of substances activates the mesolimbic dopamine pathway, resulting in positive reinforcement. This stage is characterized by impulsivity, where the immediate rewards of substance use overshadow potential negative consequences. Research indicates that acute exposure to various drugs, such as cocaine and opioids, significantly increases dopamine levels in the NAc, contributing to the euphoric effects experienced during intoxication (16).

b) Withdrawal/Negative Affect

The withdrawal/negative affect stage occurs when the substance is no longer available, leading to a negative emotional state characterized by dysphoria, anxiety, and irritability. This stage is primarily associated with the extended amygdala, which plays a crucial role in stress responses.The extended amygdala includes structures such as the central nucleus of the amygdala and the bed nucleus of the stria terminalis. These areas are involved in the regulation of stress and negative emotions.

Chronic substance use leads to neuroadaptive changes in these brain regions, resulting in heightened sensitivity to stress and negative affect during withdrawal. The anti-reward system becomes activated, driving individuals to seek substances again to alleviate withdrawal symptoms. This shift from positive reinforcement to negative reinforcement illustrates how the motivation for substance use changes over time, as individuals begin using substances to escape negative feelings rather than to achieve pleasure (16).

c) Preoccupation/Anticipation

In the preoccupation/anticipation stage, individuals experience intense cravings for the

substance, often triggered by environmental cues associated with past use. This stage is primarily linked to the prefrontal cortex (PFC), which is responsible for higher cognitive functions such as decision-making and impulse control.

The PFC interacts with the NAc and other limbic structures to regulate craving and drug-seeking behavior. Dysregulation in this circuitry can lead to compulsive drug-seeking behaviors.

The anticipation of substance use is associated with changes in executive control and inhibitory control, leading to impaired decision-making. Neuroimaging studies have shown that cues associated with drug use can activate the PFC and NAc, reinforcing the cycle of addiction. The transition from impulsivity to compulsivity is evident in this stage, where individuals may prioritize drug-seeking behavior over other life responsibilities (16). The heuristic framework of addiction stages provides a comprehensive understanding of how neuroanatomy and neurobiology contribute to the development and maintenance of substance use disorders. By delineating the specific brain regions and mechanisms involved in each stage binge/intoxication, withdrawal/negative affect, and preoccupation/anticipation researchers and clinicians can better target interventions and treatments aimed at breaking the cycle of addiction. This understanding is crucial for developing effective strategies to prevent and treat substance use disorders.

Recent advancements in neuroimaging and neurogenetic research have significantly enhanced our understanding of the neurochemical pathways and microcircuits that mediate addiction-related behaviors.

Neuroimaging in Addiction

The recent advancements in neuroimaging and neurogenetic research have provided valuable insights into the neuroanatomical basis of addiction, with significant implications for public health policies and prevention strategies. Neuroimaging studies have revealed the impact of opioid use on brain circuits involved in reward, motivation, and impulse control. These findings underscore the highly addictive nature of opioids and the need for targeted interventions (17). By identifying specific neurobiological markers associated with opioid addiction, such as reduced dopamine receptor availability, neuroimaging can help in early identification of individuals at risk and guide personalized treatment approaches (18). Neuroimaging can also be used to monitor the effectiveness of opioid addiction treatments, such as medication-assisted therapies, by assessing changes in brain function over time (18). As more states legalize marijuana, neuroimaging research can provide important insights into the potential long-term effects of cannabis use on brain development, particularly in adolescents (18). Studies have shown that early initiation of drug use, including marijuana, is strongly correlated with the likelihood of developing substance use disorders later in life (17). Neuroimaging can help identify vulnerable populations and guide prevention efforts. Neuroimaging can also be used to assess the impact of different strains and potencies of marijuana on brain function, informing public health policies regarding product regulation and age restrictions (17). Neuroimaging research can help identify specific brain circuits and genetic factors that contribute to addiction vulnerability, allowing for targeted prevention efforts (18). By understanding the neurobiological mechanisms underlying the transition from recreational use to addiction, prevention strategies can be tailored to address the specific needs of individuals at different stages of the addiction cycle (17).

Neuroimaging Techniques in Addiction

FMRI and PET are indispensable tools in addiction research. While they each possess unique advantages such as fMRI's superior spatial resolution and PET's sensitivity for neurotransmitter detection they collectively enhance our comprehensive understanding of how addiction reshapes brain function (18). As research progresses towards bridging clinical application with neuroscientific

findings, these imaging technologies hold promise for developing targeted interventions that could significantly improve treatment outcome for individuals struggling with substance use disorder.

a) Functional Magnetic Resonance Imaging (fMRI)

Functional Magnetic Resonance Imaging (fMRI) uses the blood-oxygen-level-dependent (BOLD) signal to indirectly measure neuronal activity in the brain over time (19). This noninvasive neuroimaging technique enables researchers to objectively assess neural signatures of subjective states associated with addiction, such as craving, withdrawal, effort, and reward processing (19).

Functional Magnetic Resonance Imaging (fMRI) has become a vital tool in understanding the neurobiological underpinnings of addiction. By measuring brain activity through changes in blood flow, fMRI provides insights into how various substances and behaviors associated with addiction affect brain function and structure (17).

Functional Magnetic Resonance Imaging (fMRI) has been instrumental in studying brain activity related to addiction by measuring blood flow changes in the brain. This technique has revealed alterations in brain circuits associated with reward processing, impulse control, and decision-making in individuals with substance use disorders (SUDs) (17).

fMRI studies have shown that addiction is often accompanied by disruptions in functional connectivity between brain networks. For example, individuals with Internet gaming disorder exhibit altered connectivity within the default mode network (DMN) and inhibitory control network (ICN), which may explain difficulties in regulating gaming behavior (18). Similarly, alterations in the connectivity of reward-related networks have been documented across various substance use disorders, highlighting common neurobiological pathways involved in addiction (20). Functional Magnetic Resonance Imaging (fMRI) has significantly advanced our understanding of the anatomical and functional changes associated with addiction. By mapping brain activity related to cravings, decision-making, and emotional responses, fMRI continues to inform both research and clinical practices aimed at addressing addictive behaviors effectively. The integration of fMRI findings into therapeutic strategies holds promise for enhancing recovery outcomes for individuals affected by addiction.

Studies using fMRI have shown that individuals with addiction exhibit altered activation patterns in the prefrontal cortex, nucleus accumbens, and other regions involved in the reward system, indicating how these changes contribute to compulsive drug-seeking behavior and impaired executive function (17).

b) Positron Emission Tomography (PET)

Positron Emission Tomography (PET) is a powerful image technique that plays a significant role in elucidating the neurobiological mechanisms of addiction. PET enables the visualization of metabolic processes and neurotransmitter activity in the brain, enhancing our understanding of how substances like drugs and alcohol influence brain function and behavior. It has been particularly valuable in studying dopamine (DA) in drug addiction, allowing for the assessment of presynaptic and postsynaptic dopamine receptor functions, especially concerning substances like heroin. This includes measuring dopamine synthesis, transport, and receptor binding, which are vital for understanding drug reinforcement and addiction vulnerability (20). Research indicates that individuals with a history of addiction often exhibit reduced dopamine receptor availability, leading to a diminished capacity to experience pleasure from natural rewards (21). This reduction in dopaminergic signaling can increase the incentive salience of drug-related stimuli, which contributes to compulsive behaviors associated with

addiction (17). PET is also employed to investigate neurotransmitter systems related to alcohol abuse, examining biochemical changes in alcoholism, such as serotonin signaling, which may be linked to aggressive behaviors in alcohol-dependent individuals (22). The technique can identify neurobiological markers associated with addiction vulnerability, facilitating the development of targeted treatment strategies and their monitoring over time (22). Moreover, PET supports drug development by providing insights into how new treatments impact brain metabolism and neurotransmitter dynamics, crucial for optimizing dosing regimens and evaluating therapeutic efficacy (22). Recent advancements in imaging technology have enabled the combination of PET with other modalities like CT and MRI, enhancing the anatomical context of functional data and allowing for a more comprehensive understanding of addiction-related brain changes (23).

c) Emerging Techniques

Novel neuroimaging technologies, such as three-dimensional arterial spin labeling magnetic resonance imaging (3D aMRI) and diffusion imaging, are expected to provide deeper insights into the microcircuits involved in addiction. These advancements may enhance our understanding of the structural and functional changes in the brain that accompany substance use and withdrawal (21).

Neurogenetic review

a) Genetic Vulnerability

Neurogenetic studies have revealed specific genetic variants that increase susceptibility to addiction, particularly those related to dopamine signaling pathways. These genetic variations are associated with individual differences in reward sensitivity and impulsivity, both critical factors in the development of substance use disorders (SUDs) (11). This understanding of genetic underpinnings can aid in identifying individuals at higher risk for addiction and in creating personalized treatment strategies. Heritability estimates for various addictions vary significantly, ranging from 39% for hallucinogen use to as high as 72% for cocaine addiction, indicating a substantial genetic component across different substances (24). Opioid addiction has a heritability estimate of approximately 50%. Despite identifying several genetic variants linked to opioid addiction, a comprehensive understanding of all contributing genetic factors remains challenging, often referred to as the "missing heritability" problem (25).

b) Specific Genes Identified

Certain genes have been consistently linked to addiction vulnerability. Notable examples include:

- *OPRM1:* This gene, associated with opioid receptors, has been one of the most studied in relation to opioid addiction.
- *ADH1B and ALDH2:* These genes are linked to alcohol metabolism and have implications for alcohol-related behaviors and risks (25).
- *CHRNA5:* Variants in this gene are associated with nicotine dependence and smoking behaviors (25).

c) Gene-Environment Interactions

The development of addictions is not solely determined by genetics; it is significantly influenced by environmental factors. The interplay between genetic predispositions and environmental exposures (such as stressors or availability of substances) is critical in understanding addiction risk (17).

d) Recent Advances in Research Methods

Large-scale Genome-Wide Association Studies (GWAS) have identified numerous genetic loci associated with substance use disorders, enhancing our understanding of the genetic architecture underlying addiction. These studies reveal that many genes contribute small effects rather than a few

genes having large impacts (24). There is a growing emphasis on functional studies that explore how specific genetic variants affect biological pathways related to addiction. For example, research on the A118G variant of OPRM1 has provided insights into how this variant influences opioid response and addiction risk (25).

Understanding genetic vulnerabilities can inform personalized treatment approaches in addiction medicine. By identifying individuals at higher genetic risk, targeted prevention strategies can be developed, potentially improving outcomes for those susceptible to substance use disorders. While significant progress has been made in identifying genetic factors associated with addiction. Ongoing research is essential to fully elucidate the complex interplay between genetics and environmental influences on addictive behaviors. Future studies are expected to focus on larger populations and consider comorbid conditions to refine our understanding of these dynamics (24).

e) Gene-Environment Interactions

Research has also focused on how environmental factors interact with genetic predispositions to influence addiction risk. For instance, family history of substance use disorder and parental impulsivity have been shown to differentially affect neural responses during risky decision-making tasks, highlighting the complex interplay between genetics and environment in addiction (21).

Neurochemical Pathways and Microcircuits

a) Dopaminergic Pathways

The mesolimbic dopamine pathway, particularly the connection between the VTA and the NAc, is central to the reward and reinforcement mechanisms in addiction. Neuroimaging studies have demonstrated that chronic substance use leads to neuroadaptive changes in this pathway, resulting in altered dopamine signaling and increased craving for drugs (17). These neurochemical changes contribute to the compulsive behaviors characteristic of addiction, as individuals become increasingly focused on obtaining and using substances to achieve the desired effects.

b) Corticostriatal Circuits

The corticostriatal circuitry, which includes connections between the prefrontal cortex and the striatum, plays a critical role in decision-making and impulse control. Neuroimaging findings indicate that dysfunctions in this circuitry are associated with impaired executive function and increased impulsivity in individuals with addiction (21). These changes can lead to a diminished ability to regulate drug-seeking behavior and an increased likelihood of relapse.

Neuroembryology basis of addiction

Understanding the neuroembryological basis of addiction is essential to identify vulnerabilities, comprehend underlying mechanisms, and inform therapeutic approaches in addiction. Early brain development is a critical period where genetic and environmental factors can significantly influence an individual's susceptibility to addiction. By investigating how specific brain structures develop and how external factors such as drugs, stress, or trauma can alter this development, researchers can pinpoint vulnerabilities that predispose individuals to addictive behaviors later in life. The diencephalon, a key brain structure involved in addiction, regulates essential functions such as emotion, motivation, and reward processing. It includes the thalamus, hypothalamus, subthalamic nucleus, and epithalamus, each playing a unique role in addiction neurobiology (26). The thalamus functions as a major relay station for sensory and motor signals, integrating information from various sensory modalities and transmitting it to the appropriate cortical areas, making it pivotal in reward circuitry and the experience of pleasure and craving (28, 29). The subthalamic nucleus, part of the

basal ganglia, is associated with regulating impulsivity and decision-making; its dysfunction may contribute to compulsive behaviors often seen in addiction (30, 31). Conversely, the epithalamus processes aversive stimuli and is thought to be involved in the negative emotional states linked to addiction, such as withdrawal and depression (32). The human brain undergoes significant changes during development, particularly in childhood and adolescence, characterized by heightened neuroplasticity, which makes the brain more responsive to environmental stimuli (33, 34). The prefrontal cortex, responsible for decision-making, impulse control, and emotion regulation, matures later than the limbic system, which governs reward and pleasure (35). This developmental mismatch can increase the likelihood of addiction among adolescents, as the desire for immediate rewards may outweigh their ability to evaluate long-term consequences (36). Research indicates that early exposure to addictive substances can disrupt normal brain development, with substances like alcohol and drugs altering the trajectory of brain maturation, leading to enduring changes in structure and function (37, 38). Studies have demonstrated that adolescents who use substances exhibit alterations in the prefrontal cortex and limbic system, impairing judgment and increasing the likelihood of continued substance use (38).

Genetic and Epigenetic Factors in Diencephalic Development

The development of the diencephalon is influenced by a variety of genes and signaling pathways that orchestrate the patterning and differentiation of neuronal populations. Several key genetic families are involved, including:

a) Sonic Hedgehog (Shh)

Sonic Hedgehog (Shh) signaling is crucial for the regionalization of the diencephalon, particularly in establishing boundaries between different brain compartments, with the zona limitans intrathalamica (ZLI) being a key producer of Shh (39, 40). This pathway plays a significant role in specifying neuronal subtypes and forming functional neural circuits. Emerging research highlights the connection between Shh signaling and addiction, suggesting that disruptions in Shh during neurodevelopment may increase susceptibility to substance use disorders (41). Shh is involved in regulating dopaminergic neurons, which are integral to the brain's reward pathways. Studies indicate that Shh influences the proliferation and differentiation of dopaminergic progenitors, potentially shaping responses to rewarding stimuli, including drugs of abuse (41). In addition to its developmental roles, Shh signaling remains active in the adult brain, contributing to neuroplasticity the brain's capacity to adapt and reorganize. This adaptability is crucial for learning and memory related to drug use, and dysregulation of Shh in adults may lead to maladaptive changes associated with addiction (41). Given its influence on neurodevelopment and dopaminergic signaling, Shh represents a promising therapeutic target for addiction treatment. Modulating Shh signaling could help restore normal neurodevelopmental and neuroplastic processes, potentially mitigating addiction-related behaviors and improving outcomes for individuals with substance use disorders.

b) Fibroblast Growth Factors (FGFs)

FGFs are involved in the growth and differentiation of neural progenitor cells (42). They play a role in establishing the midbrain-hindbrain boundary and are crucial for the proper formation of the diencephalon (43). Specific FGFs, such as FGF8, have been shown to be essential for the development of the thalamic and pretectal regions (44). Recent studies have indicated that FGFs, particularly FGF2, are implicated in the neurobiological responses to drugs of abuse. For instance, research has shown that escalated self-administration of substances like oxycodone is associated with changes in FGF signaling pathways (45). This suggests that FGFs may contribute to the

neuroadaptive changes that occur during the development of addiction and withdrawal. FGFs are also linked to neuroplastic changes that occur during withdrawal from addictive substances (46, 47). The expression of FGFs and their receptors may be altered in response to drug exposure, affecting the brain's ability to adapt to the absence of the drug; this dysregulation can contribute to withdrawal symptoms and the risk of relapse (46).

c) Homeobox Genes

Homeobox genes, including those in the Iroquois and HOX gene families, are crucial for the spatial and temporal regulation of diencephalic development. They play a significant role in defining regional identities and differentiating specific neuronal populations within the diencephalon (48). The HOX gene family, in particular, is essential for the development of the central nervous system (CNS) and specifies regional identity along the anterior-posterior axis of the brain (49). These genes regulate the proliferation, migration, and differentiation of neural progenitor cells, establishing the fundamental architecture of the brain (49, 50). Disruptions or mutations in homeobox genes during brain development can result in structural and functional abnormalities in brain regions linked to addiction, such as the prefrontal cortex, amygdala, and ventral tegmental area (50). Notably, homeobox genes like Pitx3 and Lmx1a are critical for the development and maintenance of dopaminergic neurons, which are vital for the brain's reward and motivation pathways associated with addiction (50). In addition to their developmental roles, homeobox genes are expressed in the adult brain and contribute to neuroplasticity, the brain's capacity to adapt in response to experiences. Neuroplasticity is fundamental to addiction, facilitating the strengthening of drug-related memories and the formation of compulsive behaviors (50). Homeobox genes, including the Dlx and Msx families, have been implicated in regulating synaptic plasticity and dendritic spine formation in adults, with disruptions in these processes potentially contributing to maladaptive changes associated with addiction (48). Given their critical roles in brain development and function, homeobox genes are considered potential therapeutic targets for treating addiction. Modulating the expression or activity of specific homeobox genes may help restore normal brain structure and function, prevent the development of addiction in vulnerable populations, and enhance the effectiveness of existing addiction treatments by targeting neuroplasticity (50).

Key brain region involved in addiction

Addiction primarily affects the brain's reward circuitry, which includes the mesolimbic dopamine system, the prefrontal cortex, and the amygdala. The mesolimbic dopamine system, particularly the nucleus accumbens, plays a crucial role in the experience of pleasure and reward. The prefrontal cortex is involved in decision-making, impulse control, and executive function. The amygdala is associated with emotional responses and stress regulation.

Nucleus Accumbens (NAc): This region is critical to the brain's reward circuitry. Studies have shown that activation in the NAc correlates with craving and the euphoric effects of drugs such as cocaine and methamphetamine. For instance, cocaine-induced euphoria has been linked to increased activity in the NAc, while craving persists as this area remains activated after the initial high subsides (51).

The NAc is integral to the processing of rewards and reinforcement. It receives glutamatergic inputs from several brain regions, including the prefrontal cortex and amygdala, which are involved in evaluating environmental cues and making decisions related to reward-seeking behavior. When an individual engages with an addictive substance or behavior, the NAc is activated, reinforcing the behavior through a dopamine-mediated reward pathway (52).

Research has shown that activation of the NAc correlates with craving for drugs. For instance, studies have indicated that cocaine-related cues can trigger significant NAc activation, which persists even after the euphoric effects of the drug have diminished. This suggests that the NAc plays a crucial role in maintaining cravings and may contribute to relapse vulnerability by encoding memories associated with drug use (53). Chronic exposure to addictive substances leads to neuroadaptive changes within the NAc. These changes can affect synaptic plasticity, resulting in altered neurotransmission that underlies compulsive drug-seeking behaviors. For example, studies have demonstrated that repeated drug use can lead to decreased levels of glutamate in the NAc, which is associated with diminished pleasure-seeking behaviors and increased compulsivity (54)

Anterior Cingulate Cortex (ACC): The ACC is involved in emotional processing and decision-making. Research indicates that individuals with substance use disorders exhibit altered activation patterns in the ACC when exposed to drug-related cues, suggesting a compromised ability to regulate emotional responses to these cues (53).

Prefrontal Cortex (PFC): The PFC plays a crucial role in executive functions, including impulse control and decision-making. Chronic substance abuse has been associated with reduced activity in this area, which may contribute to impaired judgment and increased susceptibility to addiction (55).

Insula: This region is implicated in interoceptive awareness and emotional regulation. Altered connectivity of the insula has been observed in individuals with addictions, indicating its role in craving and relapse (56).

Real-time fMRI neurofeedback has emerged as a promising intervention for reducing cravings by allowing individuals to modulate their brain activity consciously (21).

Role of Receptors in Addiction

a) Dopamine receptors

Five types of dopamine receptors D1, D2, D3, D4, and D5 and their roles in addiction has been identified in previous researches, Rampino et al (2021) also categorized them into two subclasses: D-1 like (D1, D5) and D-2 like (D2, D3, D4) receptors. D1-like receptors enhance the activity of protein kinase A, leading to increased cAMP levels and impacting learning, memory, and the reward system (57, 58) D2-like receptors, conversely, inhibit adenylate cyclase, reducing cAMP synthesis. Neurophysiologically, addiction is characterized by a decrease in dopamine D2 receptors, indicating a hypo-dopaminergic state, with the Taq1A (rs1800497) polymorphism linked to lower D2 receptor density and increased addiction risk (59).

The role of antipsychotics in treating certain conditions like alcoholism, may worsen symptoms in stimulant users (59). Dopamine's role in substance use disorders is evolving, with research showing that increased dopamine levels correlate with the intensity of drug-induced highs (60). For instance, studies using methylphenidate (MPH) have shown varying dopamine responses in individuals, with those on cocaine demonstrating lower highs from MPH compared to controls (60). Interestingly, addictive substances may not significantly increase dopamine release in addicts compared to non-addicted individuals. Dopamine surges in response to drug-related stimuli have been observed, indicating a shift in how drug rewards are processed, with dopamine phasic firing contributing to cravings and compulsive behavior (61). Reduced D2 receptor activity in key brain regions related to emotion regulation and decision-making has been linked to obsessive behaviors in addicts. Animal studies suggest that increasing D2 receptor expression in the nucleus accumbens can decrease drug consumption (62). In humans, aerobic exercise has been shown to upregulate striatal D2 and D3 receptors in methamphetamine users, although its effects

on cravings and drug use are yet to be fully understood (63). Furthermore, D2 receptors require lower dopamine concentrations for activation compared to D1 receptors (64, 65). Dopamine neurons in the ventral tegmental area (VTA) typically exhibit tonic firing, leading to a stable flow of dopamine to the prefrontal cortex, while phasic firing occurs in response to significant rewards or adverse events, resulting in transient dopamine spikes necessary for the full rewarding effects of dopamine (66, 67, 68). Drugs of abuse often mimic these spikes, activating both D1 and D2 receptors and contributing to addictive behaviors (69, 70).

b) Opiod receptors

Opioid receptors, which are G protein-coupled receptors located in the brain, spinal cord, skin, and gastrointestinal tract, play a critical role in mediating the effects of opioids. These receptors can lead to sedation, analgesia, euphoria, and respiratory depression upon activation (71). Opioids are among the most potent drugs of abuse, primarily affecting the μ, κ, and δ receptor subtypes. Activation of μ-opioid receptors (MORs) is especially linked to analgesia and euphoria, but it also carries risks of respiratory depression and overdose (72). Each opioid receptor subtype has distinct roles and distribution in the brain. MORs are concentrated in regions such as the periaqueductal gray and thalamus, and their activation contributes to physical dependency and compulsive drug use, driven by changes in decision-making and cognitive function (73, 74, 75). The rapid development of tolerance leads users to increase consumption, while withdrawal symptoms such as bone pain and anxiety can be severe, compounding the cycle of addiction (73). Medications for treating substance use disorders (SUDs) include full agonists like methadone, partial agonists like buprenorphine, and antagonists like naloxone and naltrexone. Methadone's longer half-life can help reduce cravings and withdrawal symptoms, thereby aiding recovery (76, 73, 77). Buprenorphine offers a lower risk of respiratory depression compared to methadone. Antagonists, such as naloxone, can counteract opioid overdose by blocking receptor activation (73).

Understanding the mechanisms of opioids and their effects on neurochemical systems is essential for addressing substance use disorders. Kappa opioid receptors (KORs) and delta opioid receptors (DORs) have distinct effects; KORs can induce dysphoria and sedation, while DORs may provide anxiolytic effects (78). Despite their clinical utility for pain management, opioids' high potential for addiction necessitates ongoing research into safer alternatives. One promising avenue involves G protein-biased opioid agonists, which selectively activate certain signaling pathways while minimizing adverse effects (79). This comprehensive examination of opioid receptors and their pharmacology underscores the complex interplay between effective pain management and the risk of addiction, highlighting the need for innovative therapeutic strategies.

c) GABA (γ-aminobutyric acid) receptors

The primary inhibitory neurotransmitter, GABA, controls anxiety and fear under normal circumstances. Addiction, sadness, anxiety, schizophrenia, and sleep disorders have all been associated with a reduction in brain GABA (80). A decreased activation in the GABAA receptor induces tolerance when exposed to chronic doses of alcohol, while the GABAB receptor is involved in adjunct treatments to aid in the initiation of abstinence, maintenance of abstinence, and prevention of cue-related relapse in some addictions (81, 82).

d) Glutamate receptors

The most important excitatory neurotransmitter, glutamate plays a function in emotions, learning and memory, synaptic plasticity, and cognition. Numerous neuropsychiatric conditions, such as addiction disorder, bipolar disorder, anxiety, depression, and schizophrenia, have been linked to glutamatergic dysfunction (83, 84). The brain's responsiveness to drugs is enhanced by chronic substance use, which causes plastic alterations in the glutamatergic

response in the striatum (85, 86). Ketamine and esketamine are antagonist of the N-methyl-D-aspartate (NMDA) glutamate receptor. Preliminary data suggest that ketamine can prolonged abstinence from alcohol and heroin as well as reduce the craving for cocaine, but ketamine itself may lead to addiction if used ill-advisedly exceeding the therapeutically dose (87).

Conclusion

In conclusion, this narrative review highlights the intricate neuroanatomical underpinnings of addiction and the critical role of neuroplastic changes in fostering compulsive behaviors associated with substance use disorders. The findings underscore the importance of understanding the neurochemical pathways and microcircuits involved in addiction, particularly within key brain regions such as the basal ganglia, extended amygdala, and prefrontal cortex. These regions are not only central to the addiction process but also reflect individual differences in neurobiology that can inform targeted interventions. The synthesis of recent advancements in neuroimaging and neurogenetic research enhances our understanding of how alterations in incentive salience, emotional regulation, and executive function contribute to the compulsive nature of addiction. As the review suggests, recognizing these neurobiological changes is vital for developing effective treatment strategies tailored to individual vulnerabilities. Moreover, the exploration of genetic factors influencing addiction susceptibility opens new avenues for research into personalized medicine approaches. By identifying specific genetic markers associated with addiction risk, future studies could lead to more precise interventions that address both behavioral and biological aspects of substance use disorders. Overall, this review not only consolidates current knowledge on the neuroanatomical basis of addiction but also sets a foundation for future research aimed at unraveling the complex interplay between genetic predispositions and environmental influences in the development and maintenance of addictive behaviors. As we advance our understanding of these mechanisms, we move closer to improving prevention and treatment strategies for those affected by addiction.

Recommendation

Clinicians should incorporate findings from neuroanatomical and neurobiological research into their treatment protocols. Understanding the specific neurocircuitries involved in addiction can inform more effective, individualized treatment plans that address the unique neurobiological profiles of patients. Given the identified stages of addiction (binge/intoxication, withdrawal/negative affect, preoccupation/anticipation), interventions should be tailored to address the specific challenges associated with each stage. For example, therapies focusing on emotional regulation may be particularly beneficial during the withdrawal phase, while cognitive-behavioral strategies could be emphasized during the preoccupation stage. Future research should adopt a multidisciplinary approach that combines neuroscience, psychology, genetics, and social sciences to create a more comprehensive understanding of addiction. Collaborative studies can help elucidate how genetic predispositions interact with environmental influences to shape addictive behaviors. By implementing these recommendations, stakeholders can improve understanding, prevention, and treatment outcomes related to addiction, ultimately contributing to better public health strategies in addressing this complex issue.

Limitation

Dependence on existing literature in this review can present several challenges. One significant issue is the potential for incomplete or biased coverage. If the available studies on a topic are limited in scope or exhibit inherent biases, the review will inevitably reflect these limitations, potentially leading to skewed conclusions. Another concern is publication bias, wherein studies with positive or statistically significant results are more likely to be published and cited. This

overrepresentation of positive findings can distort the overall review ultimately affecting the comprehensiveness and objectivity of the review.

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