The Neurobiology of Addiction: A Systematic Review

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Abstract

Addiction which is termed as substance use disorder is considered a neuropsychiatric disorder as recorded in DSM and ICD-10. It is characterized by relapsing, and marked by obsessive drug-seeking behaviour, persistent use despite negative effects, and long-lasting brain changes. Addiction alters how the brain interprets stress and pleasure, which has an impact on the reward system. This can result in an overpowering need to repeat activities that may initially bring relief or pleasure. The study of the neurobiological perspective of addiction has been the topic of discussion and research for the past fifty years. A systematic search of electronic databases with specified keywords and years was done on Google Scholar and PubMed/ Medline. The articles were screened based on their impact factor and h-index and fourteen researches were selected based on the inclusion criteria. The current systematic review aimed to identify and evaluate the different models and theories that explain addiction, brain structures and how neurocircuitry and molecular neurobiology are impacted due to addiction and the treatment are required. It even explores contemporary research development in association with addiction and its impact on the human brain.

Keywords: addiction, neurobiology, molecular neurobiology, reward pathway

Introduction

The common day-to-day drugs used have been integrated with human society for more than hundreds of years. For example, Opium was been utilized by various societies for medical purposes for more than 3500 years and there has been evidence that marijuana the common name for cannabis has been found to have medicinal properties and is employed in Chinese medicines. Although, these drugs have medicinal quality their periodic, consistent and frequent use lead to addiction or substance use disorder (James Sadock et al., 2018, p616). The World Health Organization (WHO) (2022) defines Substance Abuse as "the harmful or hazardous use of psychoactive substances, including alcohol and illicit drugs".

Over several years numerous terms have been employed to identify and define drug abuse for instance the term dependence is frequently utilised in two broad ways when articulating Substance Use. The first is behavioural dependencies which describe the behavioural patterns and substance-seeking activities that have pathological characteristics. The second is physical dependence which describes the physiological reactions that transpire due to frequent use of addictive substances. While terms preferred by the medical community are not pejorative, however, the layman consistently uses the term *addict* ignoring that the condition is a medical disorder. This contrast can even be considered due to the trivialisation of the word addiction and the addict by various media. Currently, the term addiction is not articulated in the medical setting and is replaced by the expression "substance use disorder". The Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-5) classifies four major diagnostic categories which include:

1. Substance Use Disorder
2. Substance Intoxication
3. Substance Withdrawal, and

4. Substance-Induced Mental Disorder (American Psychiatric Association [APA], 2013)

Furthermore, The International Classification of Mental Health and Behavioural Disorders have classified Mental and Behavioural Disorders due to Psychoactive Substance Use under the codes F10 to F19 which elaborates into categories encompassing Acute intoxication (F1x.0), Harmful use (F1x.1), Dependence syndrome (F1x.2), and Withdrawal state (F1x.3) (World Health Organization, 1992).

Substance use disorder in India

While India is one of the leading democratic countries its borders are not immune to the passage of psychoactive drugs. The location of India is between Southwest Asia (The Golden Crescent) and Southeast Asia (The Golden Triangle), highlights its vulnerability due to these two main sources of illicit opium and other narcotics drugs. The addictive characteristics are not limited to these drugs moreover can also be observed in prescribed medication that can be analgesics, anxiolytics or to treat insomnia. While these prescribed drugs come under the legal boundaries, other psychoactive substances can be categorised under the label of illegal drugs. According to 'India Today', 'Drug use in India has undergone a significant demographic and social alteration in the last decade which can further lead to devastating public health crisis.' The most frequently abused drugs in Indian demography apart from alcohol and tobacco are cannabis, opiates, and sedatives and tranquilizers. (Laha, 2016). The National Survey Report by the UN Office on Drug and Crime and the Indian Ministry of Social Justice and Empowerment recent data represented in Figure 1 reflects that Mizoram, Punjab and Manipur are the states that are most vulnerable Indian States due to their geographical location. The drug seized in the past four years was 48,209 tonnes solely in Mizoram which was reported as the highest, followed by Punjab with 39,064 tonnes of drug seized. In Punjab 2013 marked nearly half of the registered cases under the Narcotic Drug and

Psychotropic Substance Act (NDPS) and Manipur with 45,000-50,000 reported drug addicts. The report even revealed the overall composition of drug addicts at different ages to be 12% under the age of 15 years, 31% between the age of 16-25 and 56% between the age of 25-35 years. While these studies depict the grave situation that the nation is in, they even highlight how crucial it is to study divergent aspects of addiction about physiological and psychological factors and how novel techniques can be developed and utilised in future.

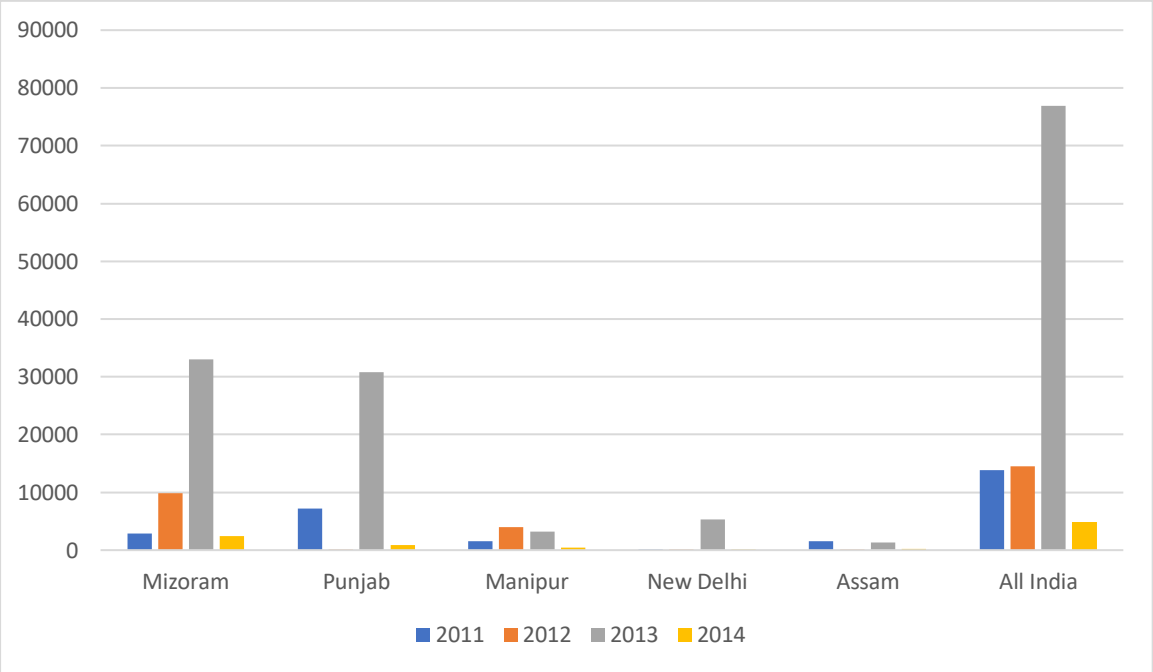


Figure 1: Lok Sabha; Figures for 2014 as of July 22, 2014, Number of cases of substance abuse disorder reported.

Methods

The research was conducted through a systematic literature search in databases: PubMed/Medline, Google Scholar and PsycINFO. The search terms that were utilized were addiction, neurobiology, neurocircuitry, substance use disorder, brain functions and pharmacology, and the search limits were published from 1996 to 2024 in English. The termed search resulted in a total of 1115 citations that were later screened and further researches were

selected that fulfilled the established inclusion criteria. The inclusion process can be seen in Fig 2.

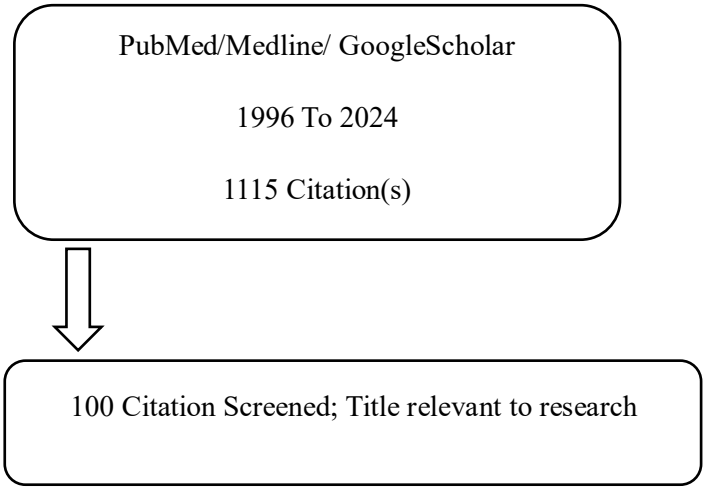
Inclusion Criteria: The research articles were screened based on their title then abstract and full-text citation and were excluded by the formulated criteria which incorporated the impact factor of the journal that should not be less than 5 and the H-index of 40 and above of the author or co-author should be fulfilled. In the case of the unrecognized and unestablished H-index of any author, the impact factor of the journal was considered the sole selection criteria. The inclusion criteria resulted in the selection of 14 articles that were thoroughly reviewed.

Exclusion Criteria: Research articles that were re-published in different journals were excluded. The Journals with less than an impact factor of five and authors with less than an h-index of 40 were excluded.

Results

Search Result

PubMed/Medline identified 115 articles, and Google Scholar 1000 articles. The combined searches yielded a total of 1115 articles. After the application of the exclusion criteria, 13 articles were selected and examined in this review.



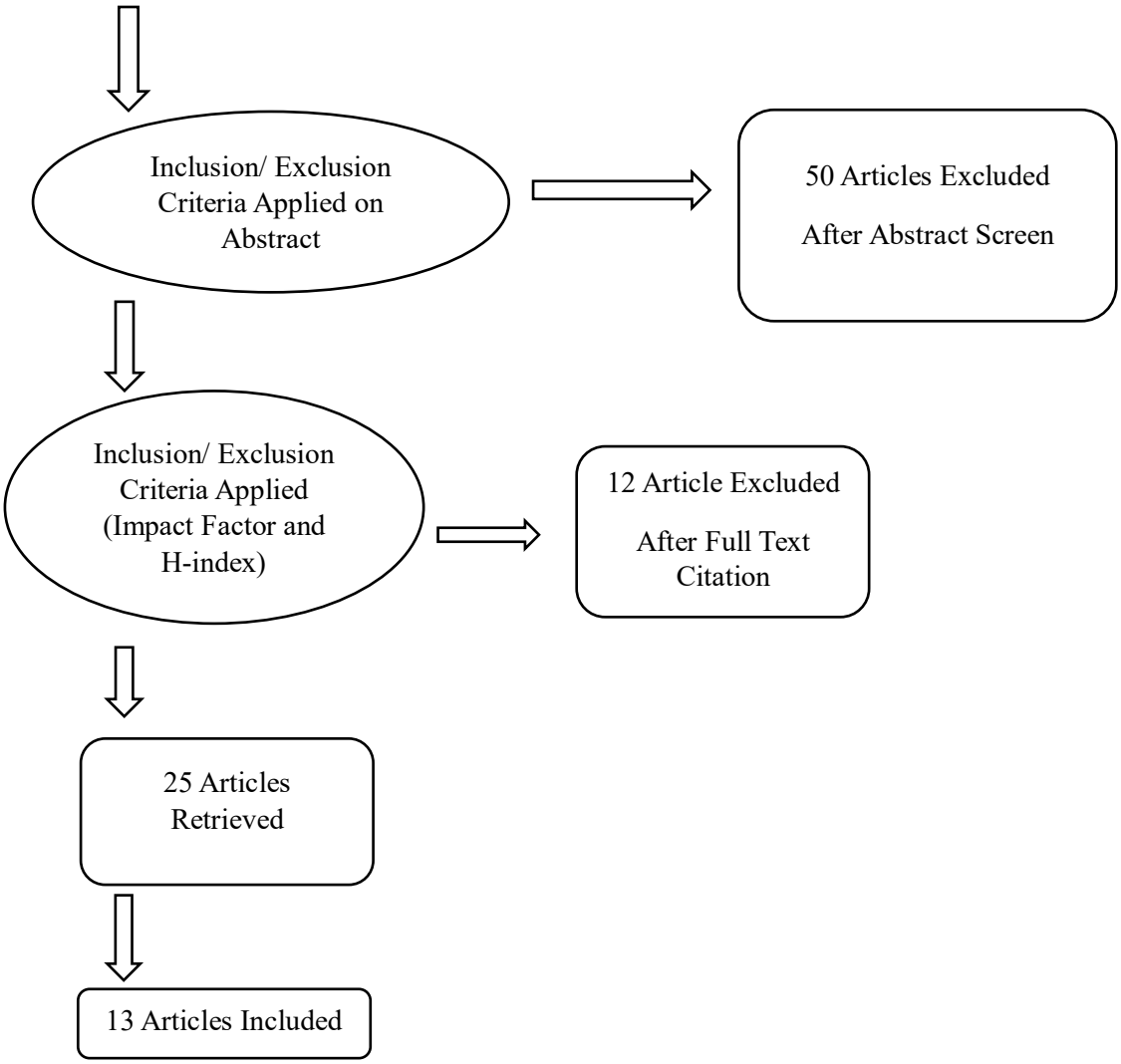


Fig.2. *Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Flow Diagram*, the detailed process of selecting articles and evaluating the association between brain and addiction

Main Result

Models of Addiction

Numerous theories are hypothesized to comprehend the phenomenon of addiction. These theories try to comprehend the underlying physiological and psychological phenomena that cause substance use disorder. Anton et al in their review paper published in 2020 review the various models and theories of addiction that can be summarized in Table 1.

Table1. Models/ theories for Addiction.

S. No	Model/ Theory	Explanation
1.	I-PACE Model	The model suggests that Interactions between personal traits and reactions to environmental stimuli lead to addictive behaviours. Early phases include emotional and mental responses to stimuli, which reinforce behaviour. Later phases exhibit heightened emotional, cognitive, and physiological reactions to stimuli associated to behaviour, leading to an increase in cravings and a loss of control. Vulnerability may rise when inhibitory control malfunctions. incorporates neuroscientific and behavioural theories about the onset and maintenance of addiction.
2.	Incentive-Sensitization Theory	The theory explains and makes a distinction between "liking" and "wanting." Drug use regularly sensitizes the dopamine system, which increases cravings in reaction to stimuli associated with drugs. People who have problems with their dopamine systems can be more vulnerable.
3.	Reward Deficiency Model	Dopaminergic dysfunctions are the root cause of addictive behaviours. People with hypodopaminergic function may resort to

		addictive behaviours to make up for reward deficits. Reward interacts with dopamine D2-like receptors and is associated to the release of dopamine in the ventral striatum.
4.	Dopamine Depletion Hypothesis	Dopaminergic system malfunctions are the root cause of addiction. Addictive habits are one way that people try to make up for dopamine deficiency. Dopamine release is controlled by intricate interactions between neurotransmitters.
5.	Dual Process Theory	Increased motivation is the root cause of addiction, which may result from reward networks' hyperreactivity to cues associated with addiction. The elevated drive could overwhelm executive control, causing people to engage in addictive behaviours even when they have detrimental effects.
6.	Tripartite Neurocognitive Model	The model explains the insula-centred interoceptive system, which converts reward impulses into individualized sensations like cravings. Cue-reactivity and desire are linked to escalated activity in reward and salience networks and decreased activity in executive-control networks.

7.	Impaired Response Inhibition and Salience Attribution (iRISA) model	It focuses on prefrontal cortex (PFC) impairment. Reaction inhibition and salience attribution deficits, as well as related brain systems, are implicated in the addiction cycle, which culminates in craving and loss of control. Deficits in self-control and response inhibition are linked to decreased activity in the memory, salience, and executive-control networks.

Antons, S., Brand, M., & Potenza, M. N. (2020) (Koob, G. F.,2011).

Various models regard dopamine receptors D1, D2 and D3 as being associated with addiction however researchers have observed that D4 dopamine receptors are also associated with impulse control and no-substance addictive gambling behaviour (Antons, S., Brand, M., & Potenza, M. N.,2020)

Addiction and Brain

Addiction is a diverse concept that targets different brain structures when it comes to habit formation, while research suggests the crucial role of the mesolimbic dopamine system Wise, R. A. in his 1996 article vividly elaborated a shared mechanism for different addictions that previously thought unrelated Wise, R. A. (1996). The article reviews how different brain structures are involved in addiction, for instance, a potential involvement of dorsal pons in the brain reward system and medial forebrain activates the mesolimbic system through a cholinergic projection from the pedunculopontine nucleus. It is even observed that the pedunculopontine nucleus and the adjacent latero-dorsal tegmental nucleus release acetylcholine, which nicotine receptors on dopamine-containing neurons in the ventral tegmentum (Wise, R. A.,1996) (Koob, G. F., & Volkow, N. D,2016). Whereas studies involving

dopamine-selective neurotoxins or administration of an antagonist in the nucleus accumbens have shown significant reduction and sometimes even blocking of the reward function of self-administrated intravenous cocaine doses while it is observed that cocaine's primary reinforcing action is observed to occur in the nucleus accumbens (Darcq, E., & Kieffer, B. L.,2024) (Koob, G. F.,2011) (Koob, G. F., & Volkow, N. D.,2016) (Hyman, S. E., 2007). In a 2022 article published by Ceceli, A. O., Bradberry, C. W., & Goldstein, R. Z., a cross-species insight is provided that focuses on the dysfunction caused in PFC (pre-frontal cortex) due to addiction. It emphasizes how structural changes are seen in Gray and white matter, and inhibitory control, attention bias, cue reactivity and reward-related decision-making are also influenced by substance abuse. The study suggests significant gray matter atrophy in the ventromedial PFC and orbitofrontal cortex (vmPFC/OFC). Morphometric studies reveal that the addicted population has evidentially lower volumes of gray matter in regions associated with PFC, including anterior PFC, dorsolateral PFC, anterior cingulate cortex, inferior frontal gyrus and ventrolateral PFC as compared to the non-addicted population (Ceceli, A. O., Bradberry, C. W., & Goldstein, R. Z,2022) (Koob, G. F.,2011) Koob, G. F., & Volkow, N. D. (2016). The profound changes in the volume of gray matter, may predict sustained abstinence in individuals who are recovering from substance use disorder, with evidence suggesting that individuals who relapse have a significantly lower baseline volume of gray matter in comparison to those who sustain abstinence. The consistency of the water molecule's diffusion along the neural white matter pathway is termed Fractional anisotropy. A lower measure of FA indicates the incoherence and inconsistent diffusion of water molecules along the direction associated with demyelination and reduced axonal integrity and this lower fractional anisotropy is observed in individuals diagnosed with substance use disorder (Ceceli, A. O., Bradberry, C. W., & Goldstein, R. Z,2022) (Koob, G. F.,2011) (Koob, G. F., & Volkow, N. D.,2016) (Hyman, S. E., 2007). The lower measures of FA in different brain structures can be seen in Table 2 below

Table 2 Substance and brain structures

S. No	Substance abuse	Brain structures with lower levels of FA
1.	Tobacco	The anterior corpus callosum, anterior cingulum white matter, pathways associated with nucleus accumbens, habenula, and motor cortex to PFC
2.	Alcohol	Fronto-cingular pathways
3.	Cannabis	Frontal and frontotemporal pathways, especially connected to the orbitofrontal cortex for example forceps minor
4.	Cocaine	Genu of corpus callosum

PFC prefrontal cortex.

Stronger attention bias before and during interactions with drug cues and temptations suggests a disturbance of attentional allocation and drug pursuit. Attention bias and heightened sensitivity to drug cues in the PFC reflect the intensity of substance abuse. It was shown that stimulant-addicted people made more poor decisions than opiate-addicted people when asked to complete the Cambridge Risk Task. (Ceceli, A. O., Bradberry, C. W., & Goldstein, R. Z,2022) (Koob, G. F.,2011) Koob, G. F., & Volkow, N. D. (2016) (Hyman, S. E., 2007). Neuroimaging techniques are used to comprehend these brain reactions and are essential for creating fMRI biomarkers to pinpoint the reasons behind drug relapse in the early stages of abstinence and for treating addiction. A shared fMRI signature among cognitive domains may be the goal of cognitive and/or pharmaceutical interventions, especially if different brain biomarkers could predict treatment responses and successful and unsuccessful abstinence (Suckling, J., & Nestor, L. J.,2017).

The usefulness of imaging in addiction research is supported by the few studies that use fMRI to predict relapse and treatment response. An important study using decision-making tasks on methamphetamine users discovered that activity patterns in the temporal cortex, posterior cingulate, and insular cortex could accurately predict the likelihood of relapse (94% for relapse and 90% for non-relapse) (Hyman, S. E., 2007). In a different long-term study on the neural responses to reinforcement learning, it was found that after a year of abstinence, those who relapsed showed increased prefrontal activation during learning but decreased striatal, insular, and frontal activation in response to feedback. The problem of reverse inference, which entails assigning particular functional relevance to fMRI activations based on the known distribution of neurotransmitters and receptors, is mostly ignored in fMRI studies. One such illustration is attributing dopamine deficits to decreased BOLD signals in dopamine-rich brain regions (such as the nucleus accumbens) in response to non-drug rewards (like money) in addiction populations. Nevertheless, the underlying neurochemistry of a functioning process or how addiction-related disorders modify this neurochemistry are not readily discernible from fMRI (Suckling, J., & Nestor, L. J.,2017).

This restriction might be overcome by the creation of MRI and PET imaging devices that work together. Although research on PET-MRI is still in its infancy, it may eventually demonstrate that concurrent and collocated decreases in dopamine release are the cause of BOLD signal reductions in response to non-drug incentives. According to preliminary PET-MRI research, these complementing methods can provide fresh perspectives on the structural and functional architecture of the brain (Suckling, J., & Nestor, L. J.,2017).

Addiction and Gender Difference

The study conducted by Becker in 2016 demonstrated gender differences when it comes to addiction. In the study, it was found that in both human participants and laboratory rats' trials, women tend to become addicted more quickly than males. The primary reason for this

discrepancy is the impact of ovarian hormones, specifically oestradiol, which increases the rate of medication acquisition. Compared to male rats, female rats learn to administer medications on their own faster and are more motivated to do so, even when they follow reinforcement regimens that get harder to follow every time. Women are more likely than men to face more severe withdrawal symptoms while trying to stop using drugs like cocaine or amphetamines. These symptoms include elevated negative affect and stress reactions (Becker, J. B.,2016).

During withdrawal, female smokers also report having stronger cravings. On the other hand, when it comes to alcohol withdrawal, men usually have more severe symptoms. These results imply that hormonal variables, especially oestradiol, are important for both the development of drug-taking behaviour and the desire to use drugs. Additionally, gender-specific methods of addiction therapy is necessary, as evidenced by the disparities in cravings and withdrawal symptoms across the sexes throughout periods of abstinence (Becker, J. B.,2016).

It has been demonstrated that oestradiol increases the behavioural response of female rats to stimulants such as amphetamine and cocaine, resulting in increased rotational behaviour, motility, and stereotypy. Oestradiol also increases the induction, amplification, motivation, and resumption of drug-taking behaviour in these rats. The activity of oestradiol in the dorsal lateral striatum (DLS), where it amplifies the rise in dopamine (DA) brought on by stimulants such as amphetamine and cocaine, mediates these effects. A major factor in the enhancement of sex differences in the reaction to drugs such as cocaine is oestradiol. Dopamine (DA) response in the nucleus accumbens (NAc) in drug-naive rats naturally differs by sex; after cocaine administration, ovariectomized (OVX) females show a lower increase in DA than castrated males. But not in the NAc, oestrogen administration of female OVX rats increases triggered DA release in the dorsal lateral striatum (DLS). The balance between these two brain regions varies depending on the sex as a result. There is a tendency for increased DA release in the

DLS and decreased DA release in the NAc when drug-taking behaviour becomes habitual. It is proposed that a factor underpinning sex variations in addiction is this change in brain activity. The sex-specific patterns seen in addiction are essentially a result of the interaction between oestradiol, DA release in various brain areas, and the change from drug-naive to habitual drug-taking behaviour (Becker, J. B.,2016).

Addiction and Molecular Mechanism

A transcription factor known as CREB binds to particular DNA sequences known as CRE sites to control the expression of different genes. Phosphorylation of Ser-133 is a crucial step in CRE-mediated transcription, activating it. Numerous signalling pathways, such as the cAMP route, calcium signalling, ERK pathway, PI3K/Akt pathway, and stress-induced signalling cascades, have an impact on CREB activation. After becoming active, CREB attaches itself to DNA and draws in CBP, a protein that helps break chromatin to start gene transcription. Because it is located downstream of the cAMP pathway, which is increased in response to long-term drug exposure, CREB is significant in the context of drug addiction. It is believed that this overexpression is a compensation mechanism for the inhibitory effects of opioids and other medications. Depending on the precise brain regions involved, different aspects of addiction are impacted by the activation of the cAMP pathway (Chao, J., & Nestler, E. J. 2004).

Prolonged use of substances such as cocaine, alcohol, and opiates stimulate the cAMP pathway in the Nucleus Accumbens (NAc), a particular area of the brain. As a result, the protein CREB, which controls the expression of genes, is activated. Research has indicated that elevating CREB activity in the NAc reduces the pleasurable impacts of natural rewards like sucrose as well as medications like cocaine and opiates. However, inhibiting CREB activity increases the benefit of the medication. Furthermore, feelings of dysphoria during early drug withdrawal may be attributed to activation of the cAMP pathway and CREB in the NAc. While inhibiting

CREB's activity produces antidepressant-like effects, overexpressing it in the NAc causes reactions that resemble depression. Numerous genes involved in reward processing and emotional reactions are controlled by CREB in the NAc (Chao, J., & Nestler, E. J. 2004).

Genes that activate rapidly in response to stimuli are known as immediate early genes. The immediate early gene families of the Fos and Jun are particularly interesting in addiction research. Transcription factors that control the expression of other genes are encoded by these genes. Proteins from the Fos family, such as c-Fos, FosB, and Fos-related antigens 1 and 2 (Fra-1 and -2), combine with transcription factors from the Jun family to control the expression of certain genes (Chao, J., & Nestler, E. J. 2004).

1FosB, a particular variation of FosB, exhibits distinct behaviour from other Fos proteins. 1FosB is constant for a considerable amount of time, even weeks after exposure to drugs of abuse, in contrast to other Fos proteins that rapidly revert to their normal levels after being activated. Given its extended existence, 1FosB might have a longer-term function in the dominance of the expression of genes linked to addiction. The expression of 1FosB is induced by long-term drug exposure to substances including as cocaine, amphetamine, opiates, nicotine, ethanol, and phencyclidine. This is especially true in brain regions associated with addiction, such as the dorsal striatum and Nucleus Accumbens (Chao, J., & Nestler, E. J. 2004).

Addiction and Treatment

According to Lingford-Hughes & Nutt, addiction treatment differs according to the substance abuse. In their published article in 2003, they elaborated on the dopamine pathway and how different drug substitution therapy approaches or antagonists/ blockers can be utilised as a treatment.

The dopamine Pathway

Reward: Dopaminergic stimulation of the nucleus accumbens is linked to the rewarding effects of medicines. Research on humans and animals has demonstrated that with the absence of dopamine D2 receptors, substances like alcohol and morphine lose their rewarding qualities. Studies using neuroimaging have also shown a correlation between elevated brain dopamine levels and drug-induced emotions of pleasure and euphoria.

Anticipation*:* Dopamine plays a critical role in predicting drug usage. Studies have indicated that cues linked to drug use, rather than the substance itself, cause an increase in dopamine activity. Decreased dopamine function during withdrawal can have negative effects, such as dysphoria, when drugs are not accessible, which may encourage people to look for drugs to get over these emotions.

Withdrawal*:* When using medicines that have been misused, withdrawal symptoms and early cessation are associated with reduced dopaminergic function. Reduced dopamine D2 receptor levels have been found in neuroimaging investigations during this time, which may last for months. The early phases of abstinence are marked by the increased risk of relapse, drug-seeking behaviour, and heightened desire levels, which are probably mediated by hypodopaminergic function. (Lingford-Hughes, A., & Nutt, D.,2003).

While modern psychotherapy therapies like harm reduction therapy, 12-step de-addiction and support groups like Alcoholics Anonymous are widely popular, Lingford-Hughens in their paper painstakingly explains the significance of medication as the baseline treatment for stabilization and further planning the addiction treatment plan. While pharmacological therapies have shown effective results for substance abuse, however, non-substance behavioural addiction (gambling addiction, sex addiction, internet addiction etc) requires intensive research for their treatment as traditional pharmacological treatment may not

be fully sufficient. Table 3 summarizes the drug and the substitution therapy and antagonist or blocker that can be utilised in clinical settings by the medical professional.

Table. 3 Pharmacological approaches to different drugs

Drug	Substitution Therapy	Antagonist /Blockers
Opiates	Methadone	Naltrexone
		Naloxone
		Nalmefene
Cocaine	Buprenorphine	GRI2909
Amphetamines	Bupropion	D_3 receptor drug
Nicotine	Nicotine Patches etc	Mecamylamine
Alcohol	BDZs	Acamprosate
		Naltrexone
BDZs	BDZs	Flumazenil
GHB	BDZs	None
Cannabis	None	SR141716A
Ecstasy	SSRIs	SSRIs
LSD	None	5HT antagonists

Note: **Table 3** in Lingford-Hughes, A., & Nutt, D. (2003). Neurobiology of addiction and implications for treatment. *The British Journal of Psychiatry*, *182*(2), 97-100.

Table 4 Study Information

S.No	Author and Year	Study	Relevant finding
1.	Antons, S., Brand, M., & Potenza, M. N. (2020).	The Person-Affect-Cognition-Execution (PACE) model for addictive behaviours is a detailed	The similarities between altered brain activation during cue-

		conceptual framework designed to understand and explore how addictive behaviours develop and persist.	reactivity in addiction and non-substance addictive behavior.
2.	Becker, J. B. (2016).	The neural mechanisms underlying addiction were investigated with a focus on gender differences using rodents.	In the rodent study, females exhibit higher levels of drug acquisition, a rapid increase in drug use, greater motivation for drugs of abuse, and relapse-like associated behaviors compared to males. In drug-naive rats, a distinction in biological sex is observed in the dopamine (DA) response within the nucleus accumbens (NAc), where ovariectomized (OVX) females show a smaller initial DA increase after cocaine treatment compared to castrated males. This biological sex difference in the neural network balance between the NAc and DLS is suggested as a mechanism underlying sex differences in addiction.

3.	Ceceli, A. O., Bradberry, C. W., & Goldstein, R. Z. (2022).	Impaired response inhibition and salience attribution (iRISA) framework and neuroimaging techniques to observe the involvement of the PFC in addiction in human and non-human Primates	Disturbances in the PFC related to the impaired response inhibition and salience attribution (iRISA) syndrome are fundamental to the clinical symptoms of drug addiction, such as relapse. Specifically, severe deficits and impairment in inhibitory control in homo sapiens (humans) with addiction specifically drugs and are linked to decreased activity in various PFC regions, including the dorsolateral prefrontal cortex (dlPFC), anterior cingulate cortex (ACC), inferior frontal gyrus (IFG), and orbitofrontal cortex (OFC). Similar patterns are observed in non-human primate models, which contribute to ongoing drug use and relapse.
4.	Chao, J., & Nestler, E. J. (2004).	The cycle of addiction is studies at the molecular level.	The aggregation of ΔFosB strengthen the drug sensitivity and escalates the incitement

			characteristics of cocaine, potentially acting as a "molecular switch." Its distinctive and idiosyncratic stable expression links the severe responses to drug vulnerability with long-term neural and behavioral adaptations associated with addiction.
5.	Darcq, E., & Kieffer, B. L. (2024).	The contemporary advances in neuroscience in addiction research.	The significance of medication in the treatment of Substance Use Disorder and the modern treatment technique of brain stimulation has a relevant impact on future treatment plans.
6.	Hyman, S. E. (2007).	Addiction is a voluntary controlled behavior or an act not fully controlled by the individual.	Perspectives rooted in cognitive neuroscience and research on addiction suggest that certain behaviors, initially perceived as voluntary, might not be as consciously planned and executed as commonly believed. However, these cognitive perspectives have not yet influenced popular

			understanding, and it is premature for them to be widely accepted.
7.	Koob, G. F. (2000).	The understanding of the neurochemical systems implicated in the shift from drug use to compulsive addiction will offer a logical foundation for the creation of pharmacological treatments for drug addiction.	Animal models of craving encompass not just conditioning paradigms but also models simulating excessive drug intake during extended periods of abstinence, known as post-acute withdrawal. These models may mirror ongoing dysregulation of drug reinforcement, potentially increasing the risk of relapse.
8.	Koob, G. F. (2006).	A heuristic framework detailing neurological adaptation and alterations among crucial brain circuits throughout various cycles of addiction is presented. This framework is connected to human research, offering valuable insights for future diagnostic applications.	Animal research has linked the PFC and basolateral amygdala to relapse triggered by drugs and cues, respectively, while brain stress systems are associated with stress-induced relapse. Genetic research suggests that genes associated with reward and stress systems contribute to the risk of addiction. Molecular studies have

			pinpointed elements involved in the disruption of reward mechanisms due to dependence. Additionally, human imaging studies reveal that similar neural circuits are engaged in acute intoxication, long-term drug dependence, and the propensity for relapse.
9.	Koob, G. F. (2011)	The neurobiology of the negative affect stage, preoccupation and anticipation stage and molecular targets within the brain during addiction.	The phenomenon of drug abstinence is marked by the involvement of two systems, the first network or brain system is stress which involves the corticotropin-releasing factor (CRF) and nor-epinephrine, on the other hand, the second system which is the anti-stress system involving neuropeptide Y is disrupted leading to the negative motivational state experienced during drug abstinence. Animal genetic studies, involving the removal of specific genes, indicate that genes related to the

			neurochemical components of both the brain's reward pathway mechanism (dopamine, opioid peptide) and stress (neuropeptide Y) network of the brain play significant roles in susceptibility to addiction.
10.	Koob, G. F., & Volkow, N. D. (2016).	The effect of addiction on brain neural Circuitry and its implication on an individual's executive and other cognitive functions.	The binge/intoxication stage is characterised by alteration observed in dopamine and opioid peptides levels located in the basal ganglia which is even considered as the rewarding effect. Negative emotional states are seen with a drop in dopamine level in the withdrawal/ negative affect stage with the involvement of neurotransmitters associated with stress like corticotropin-releasing factor and dynorphin due to its extension to the amygdala. The third stage is called the preoccupation/anticipation stage,

			which is characterised by deficits in executive function and cravings which are regarded due to dysregulated projections emerging from the prefrontal cortex and insula to the basal ganglia and further extending to the amygdala.
11	Lingford-Hughes, A., & Nutt, D. (2003).	The overview about different neural pathways, engagement of disparate neurochemicals in addiction and discrete and variant pharmacological treatment associated with the same.	Pharmacological treatment for drug substitution for Opiates involves the utilisation of Methadone and Buprenorphine, while for cocaine Bupropion can be used as the drug substitution, for the Amphetamines Bupropion is effective for, and SSRIs
12.	Suckling, J., & Nestor, L. J. (2017).	A hermeneutic approach that conceptualizes the neurobiology of addiction and summarizes the results and effects of addiction on the brain through neuroimaging techniques.	The brain structure like the frontostriatal circuitry disturbances and changes in anterior white matter involved in the prediction of addiction

			resulting in relapses and treatment response.
13	Wise, R. A. (1996).	The conceptualization of the habit formation phenomenon due to addiction in different brain structures.	The reward mechanism and the habit formation drug action on the brain structures involving the medial frontal cortex, hippocampus, pedunculopontine tegmental nucleus, nucleus accumbens and ventral tegmental areas.

PACE indicates Person-Affect-Cognition-Execution, DA, dopamine, NAc, nucleus accumbens; OVX ovariectomized, iRISA Impaired response Inhibition and Salience attribution, PFC- Prefrontal cortex, (dlPFC), Dorsolateral prefrontal cortex, ACC, anterior cingulate cortex, IFG inferior frontal gyrus, OFC orbitofrontal cortex, CRF, corticotropin-releasing factor, SSRI, selective serotonin reuptake inhibitors,

Conclusion

Modern research techniques and approaches have widened the horizon for comprehending addiction-related processes and future treatment plans. The advancement in molecular science, imaging techniques and laboratory-based studies have provided significant pathways for future application and more detailed oriented approaches. While these pathways have widened the baseline for research, culture-based research and non-substance behavioural addiction are still essential to be explored. The cultural and community stigma associated with addiction and how addicts are considered someone with low will to someone who has psychological and is bound and chained to brain chemistry should also be explored.

Conflict of Interest Disclosures

No conflict of interest has to be disclosed regarding the review paper. The research review did not receive any specific entitled grants from any funding agencies or organizations in the public, commercial, or not-for-profit sectors.

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