Abstract

How do drug addictions form and how do they affect the dopaminergic pathways in the brain?

Dopamine gets a lot of attention from the public for being the pleasure neurotransmitter, but it does so much more, including regulating motivation, reward learning, cognition, memory, mood, and movement to name a few. In reward learning, if the activity is better than expected, then dopamine is released, but if the activity doesn't meet expectations, then less dopamine is released, helping us learn what actions to focus on. Although highly adaptive, or perhaps because it is, this complex reward system can be hijacked by drugs that mimic dopamine, giving users more-than-natural amounts of pleasure. As addictive stimulants, such as cocaine enter the body and brain, they give intense feelings of euphoria, much more than anticipated, and users become addicted. As their brains and dopamine pathways adapt to the dopamine fluctuations, they become more dependent on these drugs to live and experience joy. Eventually, the brain adapts and develops tolerance, decreasing the amount of dopamine released by doing the pleasurable action. This leads to less pleasure release in other actions and more cravings for this sole source of relief. In this research paper, we will discuss how drug addictions progress and become less controllable, and the neurological changes that ensue. It will detail how and why addictions develop. I will also look at how a goal can become a habit and then an addiction, through damage to the brain areas that control motivation and habit formation.

Introduction:

There is an opioid epidemic in the US, where 3 million individuals 1 are addicted to drugs, from simply getting prescribed pain meds at the doctor, or in order to escape from life circumstances. To put this into context, 46% of U.S. adults say they have a family member or close friend who is addicted to drugs or has been in the past 2. Addiction is formed in the brain, and there is so much that we don't understand about the brain. Still, these statistics demonstrate that the brain is negatively affected by drugs, which negatively impact the quality of life of many. These drugs are hijacking the reward system in the brain and causing compulsive dependency, and by understanding these processes, we can determine ways to subdue these drugs and reduce the number of victims in this epidemic. This paper will also provide information about dopamine and its reward pathways in the brain to give context to dopamine's roles in addiction.

In normal circumstances, the **reward system** pushes us to achieve our goals and experience the most pleasure in our lives. Whether the goals are getting that ice cream, or studying for that A+, dopaminergic activity in the brain tracks pleasure to reinforcing stimuli in order to maximize pleasure and prioritize what actions should be repeated. More specifically, this learning involves reinforcing, novel, unexpected, or aversive stimuli, which produce differing concentrations of extrasynaptic dopamine, energizing differing amounts of motivation or aversion. For example, a dip in dopamine when touching a hot stove can help you learn to not do that, while a spike when eating candy can reinforce that habit.

The forebrain dopamine systems are activated by the motivation to use addictive drugs. Excessive activation of this system reinforces the particular behaviors that existed before the activation, making the individual more receptive to the circumstances that trigger such habits.

However, when drugs are administered, they over-stimulate the system and neuroadaptations quickly give priority to drugs. Soon drug administration transforms from goal-oriented pleasure to a dependency in order for the people who take the drugs to feel normal. This comes from neuroadaptations that decrease dopamine transporters (DAT), which recycle dopamine, so more dopamine is present in the brain. However, this also means that other actions that are used to excite and motivate cause less of a reaction, devaluing other stimuli and making the reinforcer the only option for pleasure. It's important to understand these impairments and how they are created in the brain in order to create better treatments. In order to learn about these impairments we need to understand reward prediction errors (RPE), a reward system that will be discussed in this paper.

Although **dopamine** does several things in the body, such as increasing blood pressure and heart activity 3, here it will be discussed in regard to its purposes and effects in the brain. Additionally, there are also other neurotransmitters and systems that are involved with drug-seeking behaviors and are highly connected to dopamine's, such as systems involving serotonin, norepinephrine, and glutamate systems, but we will focus on the dopamine pathways.

Dopamine plays a huge part in our motive systems, demonstrated by different diseases in which there is an abnormal amount of dopamine in the brain. These diseases such as schizophrenia, Parkinson's disease, and ADHD can help us understand the crucial roles dopamine plays 4. Additionally, this information is corroborated by mouse studies, where the dopamine-producing part of the brain is lesioned. Even though they seem normal at birth, these lesioned mice merely employ their reflexes for basic needs such as eating food when it is placed in their mouths and escaping from unpleasant stimuli. They cannot, however, learn to seek out positive stimuli or stay away from negative ones 5**.**

Having too much dopmaminergic activity can cause problems, specifically in addiction to drugs. **The definition of addiction** is a chronic brain disease associated with disruption of reward and motivation, memory, conditioning, executive function, self-control, mood, and stress, due to environmental, genetic, and social variables 6. Some symptoms that are used to identify the severity of the addiction are loss of control, craving, and preoccupation with use, and use despite negative consequences. For instance, if severe, people who are addicted might feel the need to use the drug regularly, have intense urges for the drug that block out any other thoughts, and over time, need more of the drug to get the same effect 7**.**

In this paper, I will discuss the reward system (with a focus on dopamine), reward prediction error, and burst/pacemaker firings, as well as how drugs (with a focus on cocaine) hijack this system and create a deep dependence and compulsion.

Dopamine

Although commonly known as the pleasure neurotransmitter, dopamine has many functions in the brain, such as movement, memory, pleasurable reward, behavior and cognition, attention, inhibition of prolactin production, sleep, mood, and learning 8. Motivational drive is dependent on the concentration of dopamine in specific brain areas such as the striatum.

We can learn more about the role of dopamine in the brain by studying dopamine-deficient mice. These mice were only born with only the knowledge learned in utero, and unless they are force-fed, cannot learn to find food on their own and starve to death. These mice only display innate, reflex-based responses since they haven't developed eating habits. In

addition, they fail to learn how to seek or avoid different rewards, displaying the importance of dopamine in learning and even living 9.

It is important to note that the amount of dopamine released frequently differs between individuals, with some responding more strongly to punishments than rewards. The striatum and prefrontal cortex, two regions known to affect motivation and reward, both display more dopamine signaling in "go-getters" who are more motivated to work hard, according to Vanderbilt University researchers 10.

Because of dopamine's role in the reward system, it also plays a role in addiction. More specifically, drugs that release unnaturally high amounts of dopamine often result in addiction, and the desensitization and relapse associated is one of the most devastating side effects. In desensitization, the release of dopamine and the amount of receptors decrease, and the amount of pleasure you experience in normal activities is diminished. The drug creates such strong memories and association in your brain that even after the withdrawal symptoms (such as irritability, anxiety, aches, and tiredness) have disappeared, relapse is extremely common.

Dopamine Pathways - main sources as 11, 12, 13

There are many dopamine pathways in the brain that contribute to different behaviors such as motivation, reward-seeking, and addiction.

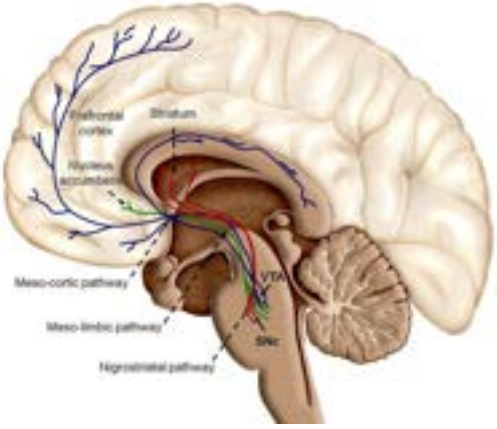
First is the Mesolimbic Pathway. The mesolimbic pathway is often referred to as the "reward pathway" and is involved in the experience of pleasure and reinforcement. It originates in the ventral tegmental area (VTA), a region in the midbrain, and projects to several areas in the limbic system, including the Median Forebrain Bundle (MFB), the nucleus accumbens (NAc), and the amygdala. Activation of this pathway is associated with the experience of pleasure and motivation, as well as the reinforcing effects of drugs of abuse. Drugs of abuse, such as cocaine, opioids, or alcohol, can directly or indirectly increase dopamine levels in this pathway. This leads to a surge of dopamine release in the nucleus accumbens, resulting in a sense of pleasure and reward. The NAc needs to be stimulated in order for us to continue with our daily activities. Overstimulating the NAc, however, may result in cravings for the substance that initially activated it. These drugs produce strong feelings of euphoria by directly increasing dopaminergic activity in the mesolimbic pathway 11. Over time, repeated drug use can cause neuroadaptations, altering the functioning of this pathway and leading to the development of addiction.

Next is the Mesocortical Pathway. The mesocortical pathway also originates from the VTA, but projects to the prefrontal cortex, which is involved in executive functions such as decision-making, working memory, and attentional control. This pathway plays a crucial role in cognitive processes, emotional regulation, and motivation. Disruptions in the mesocortical pathway have been implicated in psychiatric disorders such as schizophrenia and ADHD. Chronic drug use can dysregulate dopamine transmission in this pathway, impairing executive functions and decision-making abilities. These changes contribute to the loss of control and impaired judgment often seen in addiction.

There is also the Nigrostriatal Pathway. This pathway originates in the substantia nigra, a region located in the midbrain, and projects to the striatum, which is involved in motor control. This pathway plays a crucial role in coordinating movement and is particularly associated with the motor symptoms of Parkinson's disease. The degeneration of dopamine-producing neurons in the substantia nigra leads to a deficiency of dopamine in the striatum, resulting in the

characteristic motor impairments of Parkinson's disease, such as tremors, rigidity, and bradykinesia (slowness of movement) 11. It also has implications in addiction. Some drugs of abuse, such as amphetamines, can increase dopamine release in this pathway, leading to heightened motor activity. The reinforcing effects of drugs on the nigrostriatal pathway can contribute to the development of drug-seeking behaviors.

Finally, there's the Hypothalamic Pathway (HPA axis). This originates in the arcuate nucleus of the hypothalamus and projects to various regions within the hypothalamus itself. This pathway is involved in the regulation of feeding behavior and body weight. For the purposes of this paper in the reward system, this pathway regulates more primary rewards, rather than goal-oriented rewards like in the beginning stages of drug abuse. However, the HPA axis can also activate in times of stress, sending the need to have a reward such as a drug 13. Additionally, chronic cocaine use is known to lead to hypothalamic dysfunction and diminished response to natural rewards 14.



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Over time, repeated drug use and the associated neuroadaptations can lead to long-lasting changes in the brain, including downregulation of the inhibiting D2 dopamine receptors and blunted dopamine response to natural rewards. This contributes to the cycle of craving, withdrawal, and compulsive drug-seeking behavior that characterizes addiction. Furthermore, genetic, environmental, and individual factors contribute to the vulnerability to addiction and the specific neural adaptations that occur. 12

Reward learning - main sources as 16, 17, 18, 19, 20 - *See "Brain Areas in Reward Learning" below for more details*

Reward learning is a type of reinforcement learning in which positive outcomes are predicted, through behavior modification when a novel or better-than-expected reward occurs. There are many different models for reward learning and are much more complicated than what we currently understand. What we know about reward learning is that dopamine is highly involved, firing to predict pleasure, in order to maximize pleasure and continue to make the right choices in life.

The dopamine pathways previously explained are activated when someone predicts and anticipates receiving a reward, but not when they consume or take pleasure in receiving it. Therefore, it is known that these systems motivate people to pursue rewards 21. This is in sharp contrast to drugs, as dopamine (at least initially) continues to increase release during drug consumption 22. Interestingly, in this reward learning, the dopamine signaling decreases on

repeated pleasurable actions and starts to fire when exposed to stimuli that predict pleasure instead of the pleasurable outcome. For example, if a person eats candy for 5 minutes a day at the same table, their dopamine neurons will start to fire when they sit at the table because it is recognized as a predictor of pleasure.

One proposed process for reward learning is in reward prediction error (RPE). Generally, if the activity is better than expected, then dopamine is released, (positive prediction error), if the activity exactly meets expectations, then dopamine remains at baseline activity, and if the activity does not meet expectations, then the system depresses activity (negative prediction error) 10, 16. However, because the effects of drugs of abuse are unnatural and consequently so much larger than anticipated, drugs of addiction produce excessive dopamine, which changes neural connections in the brain 23. One of the experiments that supports this theory was done on monkeys who were taught to grab a treat from a little box with a door. The researchers previously thought that the dopamine neurons would fire as the monkeys moved to grab the treat. However, the neurons actually lit up as the monkeys snapped the door open. Furthermore, as the monkey got used to the task, receiving the same snack each time, the dopaminergic signals from the neurons went silent because the reward did not exceed or fall below their expectations 16. This can be explained with RPE, as the monkeys used dopaminergic signals to align the expectation of their treat with the reality of what they received.

It has been proposed that dopaminergic neurons in the VTA encode reward prediction error because they respond to unexpected rewards, as well as how dopamine edits information processing in the various target areas 18. Dopamine influences different learning behaviors such as goal-directed and habitual behavior. In the goal-directed system, dopaminergic neurons encode distinctions between rewards and expectancies, and in the habit system, distinctions between the selected and habitual acts. Goal-directed behavior uses cognition to determine whether you want to continue an action depending on the outcome. For example, going to the local farmer's market to get flowers is goal-directed, because you believe you are going to find flowers. 24. However, in habitual behavior, you might continue to do something even if the action has no effect, or even an adverse one. For example, putting on a seatbelt is so ingrained into you that you do it without thinking about why you're doing it, the outcome not directly affecting the behavior. It has been suggested that habit and goal-directed learning systems use different prediction errors and that these prediction errors are represented by various populations of dopaminergic neurons **18**. For instance, some prediction errors are based off of the outcome of a situation while others are mediated by your own actions.

According to active inference, prediction errors can be minimized through learning. This happens when expectations are adjusted to reflect inputs, and through action, where the actions are modified to reflect the expectations. The prediction errors minimized by actions are done so because we have certain expectations that are necessary for survival and can't be overwritten by learning, (ex. an expectation that food reserves should be at a certain level). When these predictions are not fulfilled, the brain makes preparations to lessen the associated prediction mistakes, such as by locating food. The predicted pleasure in eating a bite of the treat is compared to what it tastes like, thus changing future actions of getting that same treat or not. The brain releases dopamine to create a more effective action plan if the two are different, such as when no movement has been planned yet. (**18**)

The Mechanisms of Reward Learning - main sources as 16, 17, 18, 19, 20

These mechanisms of reward learning involve pacemaker (tonic) firings and burst (phasic) firings, which are encoded into and continually updated to the Orbital frontal cortex.

To understand phasic firing, it is important to understand the role of tonic firing, which establish the dopaminergic background for behavior. Tonic firing tends to be slower and more gradual and set the background **19**, only being about half the frequency of burst-firing 25. More specifically, tonic firing releases dopamine to sensitive (high-affinity) D2 receptors, which helps determine motivational arousal, or sensitivity/readiness to respond to external stimuli **19**.

Sudden and not long-lasting, phasic firing is triggered by exposure to more important/noticeable (reinforcing, novel, unexpected, or aversive) stimuli. Thus, phasic firing is used in all of RPE, and all of reward learning, even in addiction. Phasic firing is also involved in long-term potentiation (LTP) 9, or the synaptic strengthening that leads to more long-lasting signal transmissions 26. This is because these firings communicate information about any sudden changes in the intensity and rate of stimuli, meaning adaptations to the stimulus. More specifically, because phasic firing is able to activate the D1 receptors, they consolidate recent memory engrams (conditioning to positive and negative reinforcers) **19**. This helps you remember more about the entire experience the stronger the connection, including more stimuli preceding the event. Additionally, the bursts in phasic firing patterns also on average increase the amount of D1 receptors, whereas the pauses lower the amount of the D1 and D2 receptors. Thus, the balance of tonic and phasic firing affects, the amount of dopamine receptors and the strength of the connections in pathways.

In relation to addiction, tonic and phasic dopamine neuronal firing changes are likely triggered by repeated drug administration, and reflect neuroplastic changes in these regions and on their inputs. 27.

To understand the reward system, knowing the functions of dopamine receptors is crucial. In essence, there are MSNs (Medium Spiny Neurons) that express the D1R and the D2R. When dopamine binds to D1, the “go” or excitatory pathway is initiated, while when dopamine binds to D2 receptors, the indirect, or inhibitory pathway is initiated. But it is more complex than just this because dopamine has five receptor subtypes 28, D1 through D5, which have high densities in the striatum, nucleus accumbens, olfactory bulb, and substantia nigra. These receptors are grouped into the D1-like receptors (D1 and D5) which help regulate the development of neurons when the dopamine hormone binds, and the D2-like receptors (D2, D3, and D4) which help regulate the activity of dopamine neurons and control the synthesis, release and uptake of dopamine 29. There are also different receptor isoforms within the subtypes, meaning the two groups of receptors may promote opposite effects. Dopamine receptors can be located postsynaptically or presynaptically 30. Phasic dopamine firing patterns also modify the strength of glutamatergic synapses, thus altering signaling in D1R and D2R GABAergic MSNs 26

It’s important to note that the receptors can combine, or heteromerize, which often enhances their signaling and is known to contribute to substance abuse 31. For example, the enhanced signaling in the D1-D2 heteromer is correlated with addiction has more affinity when amphetamine is administered 32. In fact, it has been shown that heteromeric complexes are essential for the development and upkeep of cocaine-induced conditioning of place preference. In a mice study, after a period of abstinence from cocaine, the heteromerization of receptors that formed because of cocaine persisted, and it was linked to the drug's behavioral sensitization. Here, the heteromeric complexes were demonstrated as necessary for conditioned place preference to develop and persist. 33

Lastly, how do the receptors connect with their function in the dopamine pathways? The ventral and dorsal striatum inputs are 95% Medium Spiny Neurons (MSNs), which control motor function, habit formation, and motivated behaviors. D1R MSNs signal through the direct striatal cortical pathway and are stimulated by DA, reinforcing certain connections and consolidating memories, whereas D2R MSNs signal through the indirect striatal cortical pathway and are predominantly inhibited by dopamine.

Different kinds of addictive drugs - main source as 20

More recent research has discovered links between the reward system and feelings of prosocial conduct such as generosity, kindness, and gratitide. By making it more difficult to feel positive emotions, damage to these structures may actually make people resent things that at first made them feel good. Alternatively, it could encourage people to look for riskier pleasures like drugs, making them more likely to become addicted 15.

Although I will primarily focus on cocaine and its relation to addiction later in this paper, there are many other drugs of abuse that are important to learn about, as they all work in different ways. However, despite the many differences, all addictive drugs enhance (directly or indirectly) dopaminergic reward in the nucleus accumbens 34. Drugs of abuse also utilize the same chemical mechanisms that underpin learning and memory, long-term potentiation (LTP), and long-term depression (LTD). 35

Amphetamine and cocaine are strongly established as addictive drugs. They both elevate dopamine levels over fourfold. The use of dopamine antagonists, or negative reinforcers, at high doses blocks drug self-administration, and dopamine-selective lesions cause loss of control in self-administration. Cocaine and amphetamine also both cause long-term changes in the glutamate–GABA synapses of the striatum. Through several synaptic pathways, the stimulants cocaine and amphetamine directly enhance the mesolimbic dopaminergic signal at the postsynaptic dopamine receptor. By inhibiting the presynaptic dopamine transporter (DAT), cocaine raises synaptic dopaminergic concentrations. When cocaine occupies the DAT, synaptic dopamine cannot be reabsorbed into the presynaptic neuron for which it was originally intended, and thus levels of cocaine in the synaptic cleft keep building. In the meantime, amphetamines largely enhance dopamine release from synaptic vesicles, which increases synaptic dopamine 36. Finally, motivation is lost when dopamine levels double or triple, as they do when amphetamine, cocaine, or opiates are self-administered. **20**

Opiates are also established as addictive drugs through dopaminergic activity. Opiates more than triple dopamine levels, and animals are known to continually self-administer heroin once levels are two times their normal. As in the previous section, dopamine antagonists block opiate self-administration, and place-preference experiments further confirm them as habit-forming. **20**

Nicotine is also shown to be dopamine-dependent and addictive, as self-administration causes burst firing of dopaminergic neurons, raising dopamine levels to 150 to 200% of normal levels. Self-administration is also disrupted by dopamine antagonists and narrow chemical lesions. Further, deleting the nicotinic subunit beta2 lowers self-administration, Nicotine infused directly into the nucleus accumbens enhances local dopamine release, and nicotine has place preference confirmations. **20**

The evidence is weaker than that supporting dopamine involvement in **alcohol** reward. Part of the problem is that we still have no animal model of self-administration, as voluntary

self-administration that maintains dependence is not seen. in a conditioned place preference study, alcohol is reported to be dopamine-dependent in alcohol-naive animals but not in withdrawn, experienced, animals. One possible reason for this is that a dopamine-independent pathway is also involved in ethanol reinforcement]. Despite this issue, ethanol (and ethanol withdrawal) increases burst-firing and pacemaker-like firing in the VTA. Ethanol can increase dopamine levels to 150–200% of baseline, and ethanol enhances synaptic plasticity in the striatum. note, however, that a subset of VTA dopamine neurons are instead inhibited by ethanol. **20**

***Cannabis**, or* THC self-administration is even more difficult to sustain self-administration. Newer rodent models of edible or vaporized THC self-administration hold promise, but differences between species in cannabinoid receptor distribution and expression, particularly in the VTA, may underlie differences in the rewarding effects of THC between species. Cannabis sees its reinforcing effects through endogenous analogues, or neurotransmitters that are expressed by dopaminergic neurons, already native to the body. Two of its endogenous analogues are expressed by dopaminergic (and other) neurons and are released when dopaminergic neurons fire **20**

Hijacked - Addiction in the brain

What is addiction?

From what we know so far, "Hedonic dysregulation" within these circuits leads to addiction, meaning the motivation to obtain natural rewards is reorganized around seeking drug-associated rewards and the desire to alleviate aversive states (ex: stress and pain) 37. Addiction appears to correlate with a hypo-dopaminergic dysfunctional state within the reward circuitry of the brain. In other words, the overactivation of the dopamine system in addiction downregulates the dopamine receptors, leaving the subject less interested in other activities.6 Addiction can also cause problems with decision-making, judgment, and learning, not to mention withdrawal, lack of control, negative emotional states, and tolerance to the drug 38.

But how do we know dopamine is so important in addiction? First, the one pharmacological characteristic that all addictive medications have in common is dopamine agonism. Additionally, self-administrations in dopaminergic regions are produced by intracerebral microinjections of dopamine agonists. Last but not least, synaptic neurochemistry in the nucleus accumbens of test animals that self-administered addictive drugs via intravenous injection demonstrates that dopamine overflow in the nucleus accumbens tonically increases by 200% 37. Thus, dopamine contributes to addiction through its roles in reinforcement, regulation, and responses. 39

To better understand how addiction causes these issues, it is necessary to study how addiction gets to this point, and how it becomes less controllable. How does a drug of abuse guide goals into habits and then addictions?

Addiction seems to emerge gradually, although the rate of this transition can vary as a function of several factors (including the type of drug, the amount of exposure, and age) 40. In a study of rats' brains as they pressed a lever and got rewarded with cocaine, the pressing of the lever started as goal-directed and depended upon an amygdala-ventral striatal (nucleus accumbens) system. But, after a few weeks of seeking drugs in this way, control over the behavior shifted from the ventral to the dorsal striatum. After this shift, the action was no longer goal-directed, but instead, the rats' lever presses were started and maintained automatically by

drug cues in the environment. The objects in their environment became associated with the drug, and those objects gained control over their behavior. Additionally in these early stages of addiction, the dysregulation of important projections from the prefrontal cortex and insula to the basal ganglia and extended amygdala contributes to desire and executive function deficiencies. 41, **17**.

There is also another factor in becoming addicted, which is what makes the drug-seeking behavior so compulsive. An impairment in 'top-down' cognitive control over habits, as a result of the overactivation of systems because of the stimuli abuse, is what takes an action from a strong habit to an addiction. This could also be explained by disrupted connectivity between prefrontal and striatal regions **19**. The loss of top-down control essentially takes the breaks off of potentially harmful compulsive behavior. In the rat experiment mentioned previously, researchers added a 'seeking lever' which gave an electric foot shock after they pressed the level to get a reward. After a short exposure to the drugs, 20% of the rats had become compulsive to the action of pressing the lever, even if they received a foot shock. The other rats were able to break the habit and didn't push the lever after receiving foot shocks. In this 20% of compulsive rats, a shift in the neural circuitries was involved, as functional activity of areas of the prefrontal cortex that underlie top-down control over behavior decreased **17**. In other words, this means addiction comes from a lack of control over the goal-directed system, too much habit-forming, or a combination of both with prefrontal hypoactivity. 42

In relation to the tonic and phasic firings, there is first tonic activation, where preference for the reinforcer and predictive stimuli are recorded. Next, phasic firings strengthen those connections, and lastly, repeated phasic firings downregulate dopamine receptors.

Now, repeated drug use has eroded the function of brain networks necessary for self-regulation, thereby facilitating impulsive, inflexible, and compulsive actions. Basically, the executive brain system focuses on the short-term reinforcer cues and immediate gratification rather than the long-term - because the brain records the short-term dopamine fluctuations and reacts to this information 6. As a result, the addicted brain is now primed to return to drug use when triggered by just a single use of the drug, contextual drug cues, craving, or stress, with each process defined by a relatively distinct brain region or neural pathway **19**.

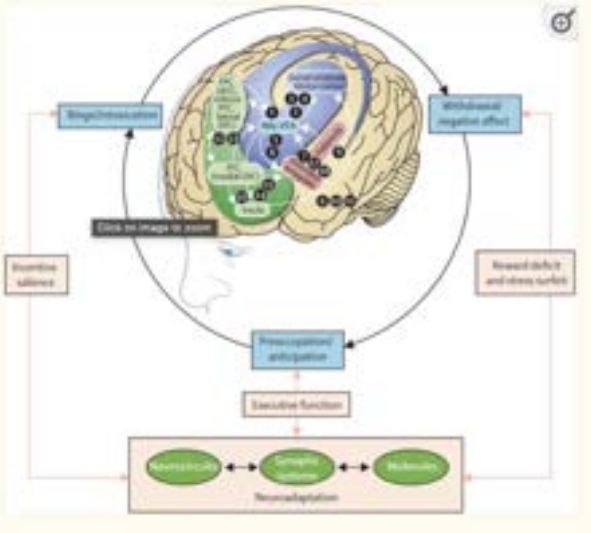
There's also tolerance and desensitization that occur in the later stages of addiction, which can even persist for some time after total rehabilitation and detoxification. It is characterized as the "reduced sensitivity of the DA motive system to the consumption of the reinforcer in addiction to continue consumption of the drug in order to achieve the expected outcome" 36. As an alternative, compulsive drug use in addiction and obesity may be a reflection of perseverative behaviors, possibly as a result of the downregulation of the D2R striatocortical pathway and sensitization to downstream reinforcer responses. As a result, the motive system's sensitivity to other stimuli, or to stimuli other than drugs in addiction, is consequently reduced 36.

Another serious side effect of drugs is the symptoms of withdrawal, which often deters addicts from stopping use. With this, users and addicts transition from seeking the drug for its positive reinforcement towards seeking it to avoid negative reinforcement. The symptoms of specifically cocaine withdrawal range from moderate to severe: dysphoria, depression, anxiety, decreased libido, psychological and physical weakness, pain, and compulsive cravings. Withdrawal can also change brain structure and function, as circuits that play a part in stress signals become more sensitive, so, when cocaine is not being used it increases an individual's displeasure, negative moods, and stress response. This occurs by decreasing the function of

the dopamine component of the reward system and recruitment of brain stress neurotransmitters in the extended amygdala. 43. Lastly, acute withdrawal was associated with the lack of D2R inhibition in the indirect pathway (which generates an aversive response) and the changes in the stress responses, contributing to the aversive state of withdrawal and perhaps the dysphoria in addiction as well 26.

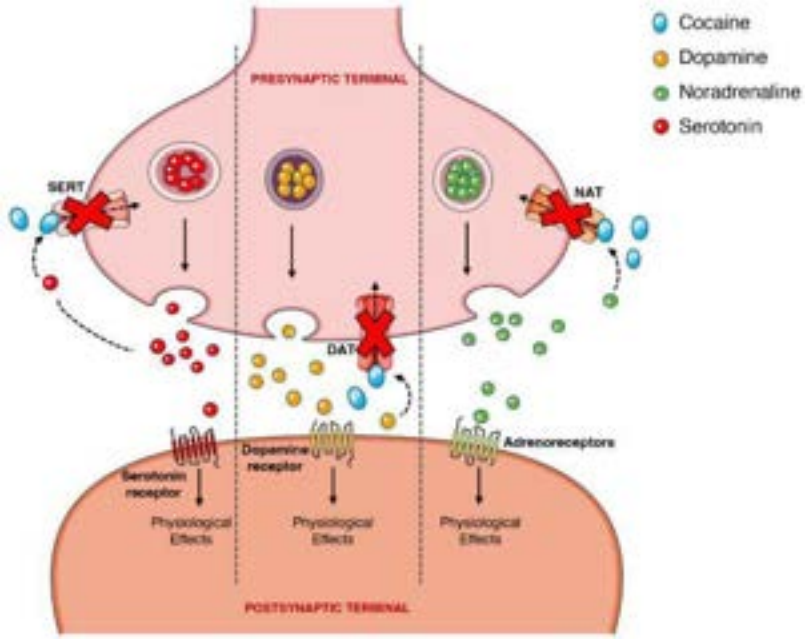
To conclude, the neuroadaptations from abusing drugs can lead to biological cravings, withdrawal symptoms, tolerance, and negative emotional states, as observed through a decrease in top-down control and deficiencies of dopamine. **44**

Adapting to cocaine in the brain - main sources as 44, 45, 19



The highlighted areas in the brain correspond to the main systems in drug addiction: binge/intoxication (reward and incentive salience: basal ganglia [blue]), withdrawal/negative affect (negative emotional states and stress: extended amygdala and habenula [red]), and preoccupation/anticipation (craving, impulsivity, and executive function: PFC, insula, and allocortex [green]) 46

To begin, it's important to note the prevalence of cocaine abuse, and according to the EMCDDA Drug Report, it remains the second most abused substance in the European Union, second only to cannabis. In the US, 1.7% (or about 4.8 million people) reported using cocaine in the past 12 months 36.



How does cocaine work? -

47.

Being a dopamine transporter blocker, cocaine increases synaptic dopaminergic concentrations by blocking the presynaptic dopamine transporter (DAT). DAT is responsible for reabsorbing synaptic dopamine back into the presynaptic neuron, and occupancy of the DAT by cocaine prevents dopamine reuptake 48. This means that cocaine effectively stops dopamine uptake to increase the presence of dopamine, which then mediates the pleasurable effects reported by users and contributes to the addictive potential and toxic effects of the drug. Additionally, cocaine can exert local anesthetic action by inhibiting voltage-gated sodium channels, thus halting electrical impulse propagation. 45

The effects of cocaine are quick to begin, significant, and short-lived. It involves depression and cravings more prominently in withdrawal, making the drug more addictive and harder to stop using without professional help 49. While D1R are excitatory and thus used in reward learning, the binding to D2R will be longer-lasting and persist even after peak levels have subsided. This is important because fast-acting drugs achieve fast peak concentrations, stimulating D1 *and* D2R. This explains why fast-acting drugs are more addictive. 50

As with all other addictions, the nucleus accumbens (and dorsal striatum) is where cocaine abuse is modulated. We know this because in dependent individuals the exposure to cocaine cues (a video of subjects consuming ‘crack’) reduced the binding to the D2 receptor in the dorsal striatum, which corresponded with craving.

Further, the drug is proven to affect working memory. But this is not where its **neurotoxicity** ends 45.

Specifically in cocaine abuse, and especially over time, reduced sensitivity is seen in cocaine’s capacity to inhibit dopamine uptake. Because of this, people who use cocaine can feel compelled to administer more while plasma concentrations are still high, raising the risk of severe, potentially deadly poisoning. In addition to this, it has also been shown to decrease prefrontal cortex activity and dopamine.

The "dopamine depletion hypothesis" or the "general anhedonia model" are two different names for drug-induced DA depletion, which, when combined with top-down control, may make

it easier for impulsive and compulsive reactions to drug cues to emerge 26. The need for substance-induced increases in dopaminergic activity was thought to be increased by the diminished D2 striatal concentrations because they reduced the prominence of natural rewards that reinforce behavior. For instance, in rats, increased D2 receptor levels reduce alcohol self-administration, whereas lower D2 receptor levels in primates are associated with greater cocaine self-administration. Furthermore, it has been shown that extracellular dopamine concentrations in the NAc are negatively correlated with the rate at which rats self-administer cocaine, with low DA concentrations producing moderate to high self-administration rates and high DA concentrations producing moderate to low self-administration rates. In other words, decreased dopamine levels may be the reason why cocaine's "high" gets weaker with each administration yet the desire to keep using it remains strong. 26

Lastly, increased cellular stress is another mechanism contributing to cocaine's neurotoxic effects. One study investigating cocaine's effects in rat cerebellum proved that, after 18 days of a 15 mg/Kg administration, the drug increases oxidative stress 26.

Discussion

Other factors play a part in addiction, not just dopamine neurotransmitters. We can now improve our understanding of reward circuits in addiction and make significant strides in treating addiction thanks to recent advances in technology like optogenetic methods, or modulation of neuronic firings and functions by light, and DREADDs, along with genetic modification of certain neuronal cells or circuits. A gene transcription factor – overexpression in the D1-type medium spiny neurons has been shown to influence addiction 51. The gene "FosB" also encourages the self-administration, reward sensitization, and reward cross-sensitization effects of particular addictive substances and behaviors. It is also known that specific epigenetic changes to the histone protein tails play a significant part in the biological foundation of addictions 52. Lastly, factors can also include Stress, Diet, exercise, sleep, gut bacteria, and the microbiome as a whole **19**.

On a positive note, there are many possible solutions that could help control drug addictions. It may be possible to limit how addictive the drugs are, but pharmaceutical researchers haven't made significant progress with this. There are also substitute substances to common drugs of abuse, such as methylphenidate, but have not been systematically examened yet. Alternatively, it is possible that presenting drug cues or drug-taking videos in humans could make drug memories unstable in the brain, therefore limiting the addiction. Also, making someone forget one administration can help that memory not reform later. Lastly, increasing prefrontal cortex activity could potentially improve control of stopping. This could involve transcranial magnetic stimulation (TMS). This is not a comprehensive list and there are many other treatment possibilities, including medicinal supplements.

Tonic/phasic firings are a simplified model because the dopamine neurons in the midbrain have many alternative firing rates that also control the reward system. Not only do phasic firings participate in the reward system, but they also contribute to alertness and motivation. The brain is extremely complex, and because of the amount of overlap and intricate firings, it is extremely difficult to have a simplified model for any system, including the reward and motive systems.

Also regarding the reward system, it is not only dopamine pathways that play a role in reward-related systems, but it is also mediated by serotonergic, opioid, endocannabinoid,

GABAergic, and glutamatergic. Dopamine is however still the main contributor towards goal-related actions and rewards. It is the key to 'getting through' the dorsal striatum and having the output of signals from there to real-world behavioral motivations [19].

Summary

The brain's reward system is amazingly complex, and researchers are learning more and more every day. Positive and negative reward prediction errors are important in reward learning, which is modulated by tonic and phasic dopamine signals. But what happens when man-made drugs hijack these systems? What are the stages and symptoms of addiction? As modulated by the nucleus accumbens, the more gradual process of drug dependency results in dysregulated and hypoactive dopamine pathways, and less active dopaminergic activity that is inhibitory. This means that the addiction will become less and less controllable. Since dopamine release during consumption is so high, the brain focuses on drugs more, meaning other dopamine sources become less enjoyable. In specifically cocaine abuse, neurotoxicity creates real consequences, sometimes resulting in decreased cognitive abilities and susceptibility to compulsivity.

Brain Areas Involved in Reward Learning

The **Ventral Tegmental Area** (VTA) plays a crucial role in responding to signals that indicate the presence of rewards. When we encounter rewarding experiences or addictive substances, they affect this brain region by triggering the release of dopamine signals into the nucleus accumbens, either directly or indirectly. The VTA comprises two significant pathways: the mesolimbic pathway, which connects to emotional and motivational regions and influences behaviors driven by motivation, and the mesocortical pathway, which connects to the prefrontal cortex and is responsible for cognitive functions such as learning from external cues.

The **Striatum (Nucleus Accumbens)** is broadly involved in acquiring and expressing learned behaviors triggered by rewarding cues. The VTA connects to the striatum and activates Medium Spiny Neurons via D1 and D2 receptors, both in the ventral (Nucleus Accumbens) and dorsal striatum. The Nucleus Accumbens (ventral striaum) plays a key role in acquiring behaviors when stimulated by the VTA and expressing behaviors when stimulated by the prefrontal cortex. Its shell projects to the VTA, regulating emotional and autonomic functions, thus modulating the reinforcing properties of stimuli and short-term aspects of reward. The Nucleus Accumbens Core projects to the substantia nigra and is involved in the development and expression of reward-seeking behaviors, spatial learning, conditional responses, and impulsive decision-making, representing the long-term components of reward.

The **Dorsal Striatum** is responsible for learning, the Dorsal Medial Striatum is involved in goal-directed learning, and the Dorsal Lateral Striatum is associated with stimulus-response learning. With repeated activation by stimuli, the Nucleus Accumbens can activate the Dorsal Striatum through an intrastriatal loop. This transition of signals allows cues associated with rewards to activate the Dorsal Striatum even when the reward itself is absent, leading to cravings and reward-seeking behaviors. This mechanism is responsible for triggering relapses during abstinence in addiction.

Dopaminergic neurons in the VTA project to the **Prefrontal Cortex** (PFC), activating glutaminergic neurons that project to various brain regions, including the Dorsal Striatum and Nucleus Accumbens. This connectivity enables the PFC to mediate the significance of stimuli and conditional behaviors in response to them. Importantly, abstinence from addictive

substances activates the PFC, along with glutamatergic projections to the Nucleus Accumbens, resulting in strong cravings and influencing the reinstatement of addictive behaviors following abstinence. The PFC also interacts with the VTA through the mesocortical pathway, helping to associate environmental cues with rewards.

The **Hippocampus** serves multiple functions, including the creation and storage of memories. In the context of the reward circuit, it plays a role in contextualizing memories and associated cues. It ultimately underlies the reinstatement of reward-seeking behaviors triggered by cues and contextual reminders.

The **Amygdala** receives input from the VTA and sends output to the Nucleus Accumbens. It is essential for forming powerful emotional memories and likely contributes to the formation of strong cue-associated memories. Additionally, the amygdala mediates the anxiety effects of withdrawal and the increased intake of addictive substances in cases of addiction.

Definitions

Active inference: In short, it assumes that action fulfills expectations based on perceptual inference or state estimation.

LTP: Long-term potentiation: persistent strengthening of synapses that leads to a long-lasting increase in signal transmission between neurons. 53

Top-down cognition: The prefrontal cortex is the first to process the executive funtions, then sending signals to different, lower parts of the brain such as your senses.

Place-preference studies: Frequently, these procedures are used to measure the rewarding effects of a stimulus. It does this by measuring the amount of time a subject spends in a certain location where they are receiving the rewarding stimuli. 54

NMDA and AMPA (α-amino3hydroxy5methyl4isoxazole propionic acid) Receptors and cholinergic stimulation of muscarinic and nicotinic receptors

Heteromers: A macromolecular complex composed of at least two (functional) receptor units with biochemical properties that are different from those of its individual components. 55

Nicotinic subunit beta2: A component of the nicotinic acetylcholine receptor. Nicotinic acetylcholine receptors are a type of ion channel that is activated by the neurotransmitter acetylcholine. While involved in many other processes, this one has been a focus of research in the context of nicotine addiction and the development of therapeutic interventions for nicotine dependence.

Incentive salience: The desire to do something - the attention-grabbing and motivational features of rewards and their learned cues 56.

DAT: The dopamine transporter (DAT) is a protein that is responsible for the reuptake of dopamine (DA) from the synaptic cleft and for the stopping of dopaminergic transmission. 57

Hedonic: In short, it is reward-based regulation. It can override the homeostatic pathway during periods of relative energy abundance by increasing the desire to seek rewards that are highly palatable. 58

Cellular stress: The many molecular changes that cells undergo in response to environmental stressors

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