

# Ethology of Addiction and Dopamine

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## SUBSTANCE ADDICTION

Substance abuse is manifested by the desire to take the substance periodically to affect the nervous system and to enjoy the drug or to avoid the negative mood resulting from its absence. It differs from substance use disorder defined by the diagnostic and statistical manual of mental disorders (DSM–5) as repeated use of substance that results in clinically and functionally significant deterioration. Such deterioration may adversely affect one's health, social networks and ability to perform the functions necessary for maintaining of his or her life. When substance abuse is exacerbated, it becomes synonymous with the term of addiction.<sup>[1]</sup>

It is known that genetic factors besides environmental, developmental and social factors play an important role in substance abuse and addiction.<sup>[2]</sup> The role of the environment in the interaction of genetic factors history<sup>[3]</sup> is indicated by the interaction of both hereditary aspects and child rearing practices in individuals with a history of addiction in their family. It is also known that some mental disorders such as attention deficit-hyperactivity disorder, psychoses and anxiety disorders are accompanied by substance use.<sup>[4]</sup>

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## ABSTRACT

Addiction is based on common cellular, molecular and neurochemical mechanisms involving multiple neural circuits. The origin of addiction is the activation of the mesolimbic and mesocortical reward system, which is stimulated by natural motivational systems. Dopamine is the most studied neurotransmitter due to its strong reactive system in the brain and its strong association with many addictive substances. The addictive effect of substances develops in the brain with increased dopamine secreted by dopaminergic neurons from the ventral tegmental area to the nucleus accumbens. Addictive substances provide more stimulation compared to natural rewards, enhancing the stimulus-drug relationship abnormally, and excessive motivational power allows learning to be attributed to stimuli from the substance. There are some associated systems that provide dependence on the reward pathway in which dopaminergic neurons play a role; prefrontal cortex, amygdala and hippocampus are among the affected structures at the beginning of the dependency cycle.

**Keywords:** Addiction, dopamine, mesocortical, mesolimbic, nucleus accumbens, reward.

The psychological factor in substance use is shaped by the belief that the substance used reduces stress and increases aggression. Accessibility to substance (exposure to high- risk environments), socio-cultural factors, cultural and political environment about the substance also play a role in explaining addiction.

### *Etiology of addiction*

Addiction is a complex behavioral model and a brain disorder, but has some typical features:

a) Strong desire for the use of the substance and uncontrolled use of the substance

b) Negative affect in the event of deprivation (anxiety, dysphoria, aggression, etc.).<sup>[5]</sup>

In explaining these typical behaviors, the brain's important structures in terms of personality and

behavior can be explained around the biological axis by using the interaction of neuroanatomical and neurochemical structure of the brain.<sup>[6]</sup>

Neurotransmitters that play an important role in the physiology of addiction are dopamine, glutamate, endogenous opioids, serotonin, gamma aminobutyric acid (GABA), noradrenaline and nitric oxide.<sup>[4]</sup> Addictive substances usually act by mimicking these neurotransmitters (Table 1).

## DOPAMINERGIC REWARD PATHWAY

Naturally (eating-drinking, sexual activity, etc.), the reward system in the stimulated brain plays an effective role in the selection and maintenance of behaviors. The reward system of the brain may also be characterized by chronic and compulsive behavior by stimulating with some psychotropic substances.<sup>[7]</sup>

The dopaminergic system is characterized by its functions in the motor, cognitive and endocrine systems, and its function in the brain reward system.<sup>[8]</sup> The mesocorticolimbic dopaminergic system in the brain is due to firing of dopaminergic cells starting from the ventral tegmental area (VTA) and extending from the nucleus accumbens (NAc) to the prefrontal cortex.<sup>[9]</sup>

Ventral tegmental area, NAc and amygdala are the structures of the limbic system and they are centers of impulse, emotion, motivation and memory. This system is linked to reinforcement, control of emotion and purposeful behaviors. The euphoric effect of increased dopamine release is the main cause of addiction. Clinical studies have shown that drug consumption in addicts triggers much smaller increases in dopamine levels than in

non-addicts, ie contrary to popular belief, addicts are not more sensitive to the rewarding effects of the substance. Decreased dopamine release reduces the sensitivity of the brain to rewards, which means a decrease in euphoria.<sup>[10]</sup>

There are other brain structures that are affected by substance abuse and addiction. Secreted dopamine with substance use triggers neuroplasticity. These changes in communication are fundamental to learning and memory.<sup>[11]</sup> The prefrontal cortex in the frontal subcortical loop through the mesolimbic reward system is also damaged. The working memory of the prefrontal cortex, responsible for our metacognitive functions, the dorsolateral prefrontal cortex (DLPFC) responsible for executive functions and attention, and the axis orbitofrontal cortex (OFC) responsible for social behavior, motivation and obsessive-compulsive movements are among the affected regions. Deficiencies occur in functions such as self-regulation, flexible thinking capacity, selection and initiation of behavior, and recognition of error.<sup>[12]</sup>

Damaged dopamine and glutamate cells in the prefrontal regions weaken the will to resist progressive compulsive behavior,<sup>[13]</sup> explaining that addicts fail to act despite impulsive behavior. The secretion of glutamate neurotransmitter that provides stimulating power and activity of high permeability AMPA receptors for calcium increases sensitivity to glutamate released by cortical and limbic systems when exposed to drug cues.<sup>[14]</sup>

These substance-induced changes also occur in the NAc, dorsal striatum, amygdala, and hippocampus. These regions participate in various stages of addiction, including conditioning and

**Table 1. Neurobiological mechanisms of addictive substances<sup>[7]</sup>**

Substance used	Neurotransmitter	Area of influence
Cocaine and amphetamines	Dopamine	Nucleus accumbens
	Gamma aminobutyric acid	Amygdala
Opiates	Opioid peptides	Nucleus accumbens
	Dopamine	Ventral tegmental area
	Endo-cannabinoids	
Nicotine	Nicotinic-acetyl choline	Nucleus accumbens
	Dopamine	Ventral tegmental area
	Gamma aminobutyric acid	Amygdala
	Opioid peptides	
Alcohol	Dopamine	Nucleus accumbens
	Opioid peptides	Ventral tegmental area
	Gamma aminobutyric acid	Amygdala
	Endo-cannabinoids	

craving. These regions in the brain also regulate the firing and dopamine release of dopamine cells.<sup>[15]</sup> A study by Volkow et al.<sup>[16]</sup> presents a quadruple dependency ring covering these different regions in the brain: Reward (NAc), motivation (OFC), memory (amygdala and hippocampus) and control. The structures that make up the ring work in unity and form the experience - they change it. These four stages receive innervation from dopaminergic (DA) neurons and are also linked together by glutamatergic projections. During addiction, the effect of the drug in reward, motivation and memory rings predominates in control in the prefrontal cortex. In the dependent individual, the connection between the control carried out by the prefrontal cortex and the other rings weakened compared to the non-dependent individual; enlarged motivation and memory activation serve as positive reinforcers for substance use. Thus, the instantaneous response of a DA neuron to a stimulus is influenced by the memory processed by the amygdala and hippocampus, depending on whether the individual has previously been exposed to that stimulus. The positive or negative experience associated with the stimulus is stored as a moment and facilitated access by DA activation.<sup>[17]</sup>

The intensity of the stimulus is graded relative to other possible stimuli and varies as a function of individual internal needs processed in the OFC.<sup>[18]</sup>

## DEPRIVATION PERIOD

The substances used, with their different pharmacological effects, increase DA secretion in the shell lower region of NAc,<sup>[17]</sup> mimicking phasic DA neuronal firing, which leads to very rapid DA increases.<sup>[19]</sup>

This causes three to five times higher stimulation than the naturally occurring DA increase.<sup>[20]</sup> Acute use of the drug allows to increase DA neurotransmission; however, a significant decrease in DA activity is observed in chronic use.<sup>[16]</sup> Repeated exposure to these effects of the reward results in an increased reaction to stress in the amygdala circuit, resulting in reduced reactivity of dopamine cells in the brain.<sup>[21]</sup>

With the withdrawal of the substance, dopamine release in NAc decreases and acetylcholine release increases during the withdrawal period.<sup>[22]</sup> It leads to stress resulting in dysphoria and anxiety, with dopamine reduction in the ventral tegmental area. It provides amygdala motivation in stressful

situations such as anxiety and nervousness parallel to withdrawal after the drug effect has passed due to the decrease in sensitivity to learning and natural stimuli (Drugs, Brains and Behavior: The Science of Addiction). Activation of the reward regions of the brain during substance use increases and activation of limbic system structures during withdrawal results in increased mood and stress sensitivity. Reduction of prefrontal cortex activity makes it difficult to put it back into the substance and the dependence cycle is restarted.<sup>[1]</sup>

The difference between normal rewards for the brain and the prize provided by the drug; it is like the difference between whispering in someone's ear and yelling from the microphone. Thus the person needs a higher amount of substance to obtain the same level of euphoria as the initial condition with the effect of developed tolerance.<sup>[9]</sup>

We see the interconnectedness of many factors in the formation of dependence. I looked at the neurobiological factor from these factors in terms of reward pathway systems. We can roughly explain the reward system in the brain through Pavlovian learning (which serves as a reinforcing pleasure in substance use). Increased artificial dopamine release affects other systems in the brain, causing physiological dependence.

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