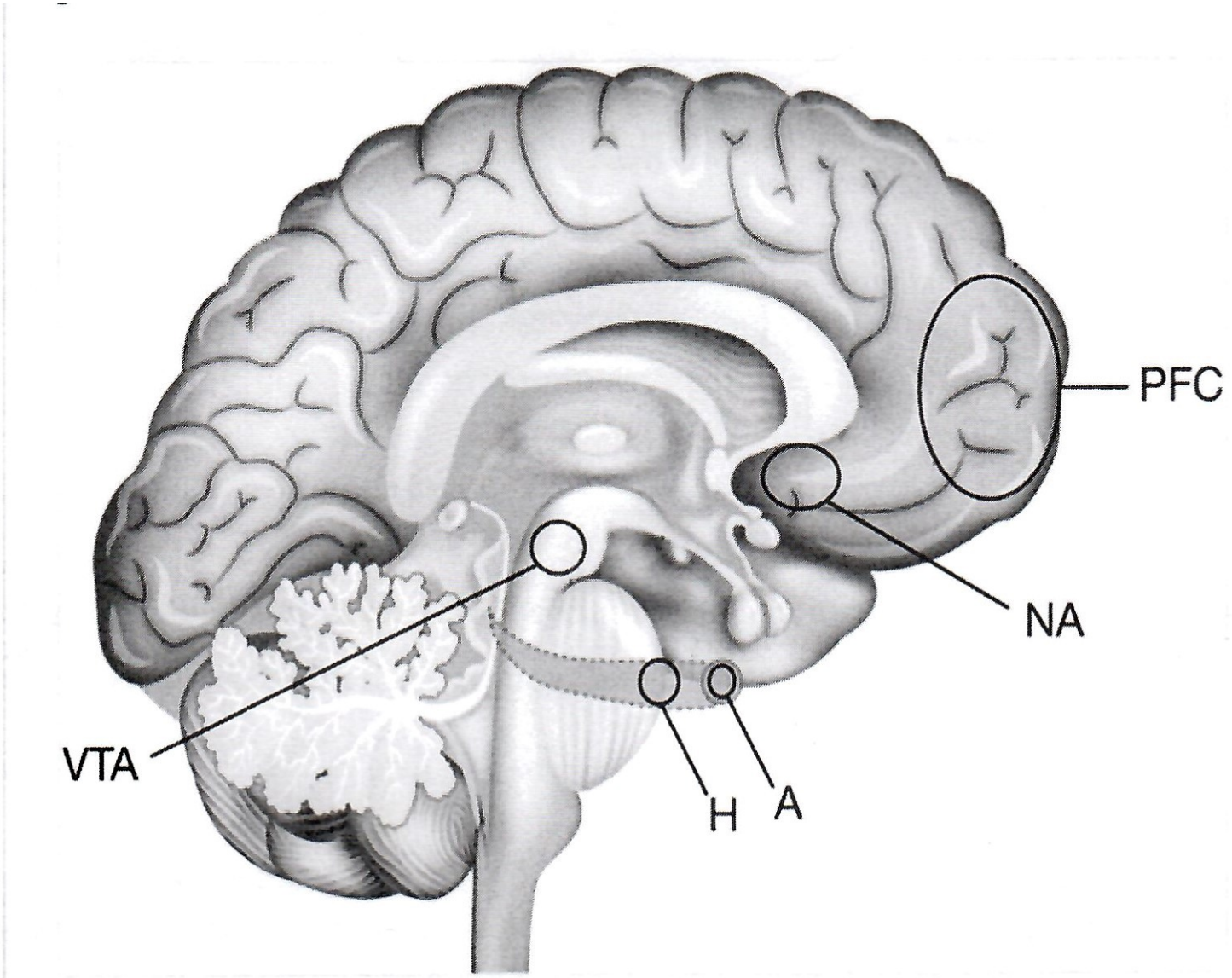
Neurobiology of Addiction



How we thought about addiction in the 1930's?

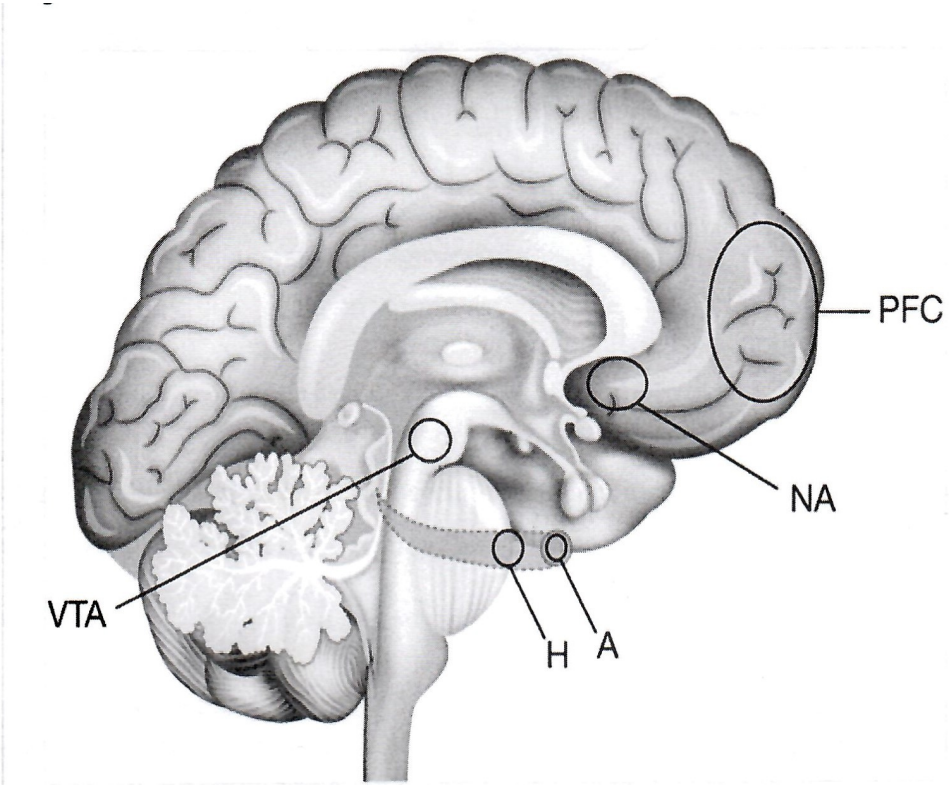
“When scientist started to study addictive behavior in the 1930s, people with an addiction were thought to be morally flawed and lacking in willpower”.

This shaped society's response, which led to an emphasis on punishment rather than prevention and treatment.

How we think about addiction today?

"Addiction is defined as a chronic relapsing disorder characterized by compulsive drug seeking and use despite adverse consequences.

It is considered a brain disorder, because it involves functional changes to brain circuits involved in reward, stress, and self-control. Those changes may last a long time after a person has stopped taking drugs."



Ventral tegmental area of midbrain is the origin of the reward system

Nucleus accubens second stop on reward pathway leading to the mesolimbic and mesocortico pathways

Amygdala assesses the pleasure of the drug and the hippocampus remembers the experience (temporal lobe hippocamus dependent memory).

Prefrontal cortex – planning, self-control, and drug taking behavior

How we think about addiction today?

Addiction is now classified as a “substance use disorder”.

Recreational substance use may become a substance use disorder. There are many variables which include the type of the substance but also the user's genetic, epigenetic, and environmental factors.

This lecture will review the historical record of addiction, how evolution's reward system contributes to addiction, the brain's neurobiology circuits of addiction, and concluding with a review of the different hypotheses addiction models.

Opposing-process Hypothesis of Addiction

Dopaminergic Hypothesis of Addiction

Incentive Sensitization Hypothesis of Addiction

Habit and Compulsion Hypothesis of Addiction

Allostasis Hypothesis of Addiction

Addiction in the Ancient World

Sumeria is an ancient civilization in the land of Mesopotamia, between the Tigris and Euphrates rivers in modern day southern Iraq. Over five thousand years ago Sumerians built the first city, called Ur, invented agriculture, the wheel, the first plow, and the first written language called cuneiform. In their written records they called the poppy plant, the source of opium, the joy plant. Five thousand years ago people in the ancient world were already addicted to opium.

Other addictive substances were used in the ancient world. Wine making was discovered in present day Georgia around 8,000 years ago. Beer likely brewed in China around 7,000 years ago. Tobacco was smoked by North American Indians dating back 12,500 years ago.

Opium, alcohol, and tobacco are all addictive substances still used today. Alcohol and tobacco is legal but regulated. Opium, the source of all natural opioids, are illegal but sanctioned for use only in medical procedures.

Chemical addictive substances share no common molecular structure. However, they all activate a common neurobiology circuit in the midbrain, the Ventral Tegmental Area. Behaviors like gambling, pornography, compulsive eating, excessive video game playing, and cell phone usage also activate the VTA. These behaviors are also classified as substance use disorders.

The VTA in the midbrain is the origin of the “reward pathway”. This is an ancient brain circuit that starts at the VTA and connects to the nucleus accubens. The Nac then leads to the mesocorticolimbic pathways.

All addictive drugs and behaviors operate along this pathway.

Opioid Addiction in the United States

Opioid addiction has had a long history in the United States.

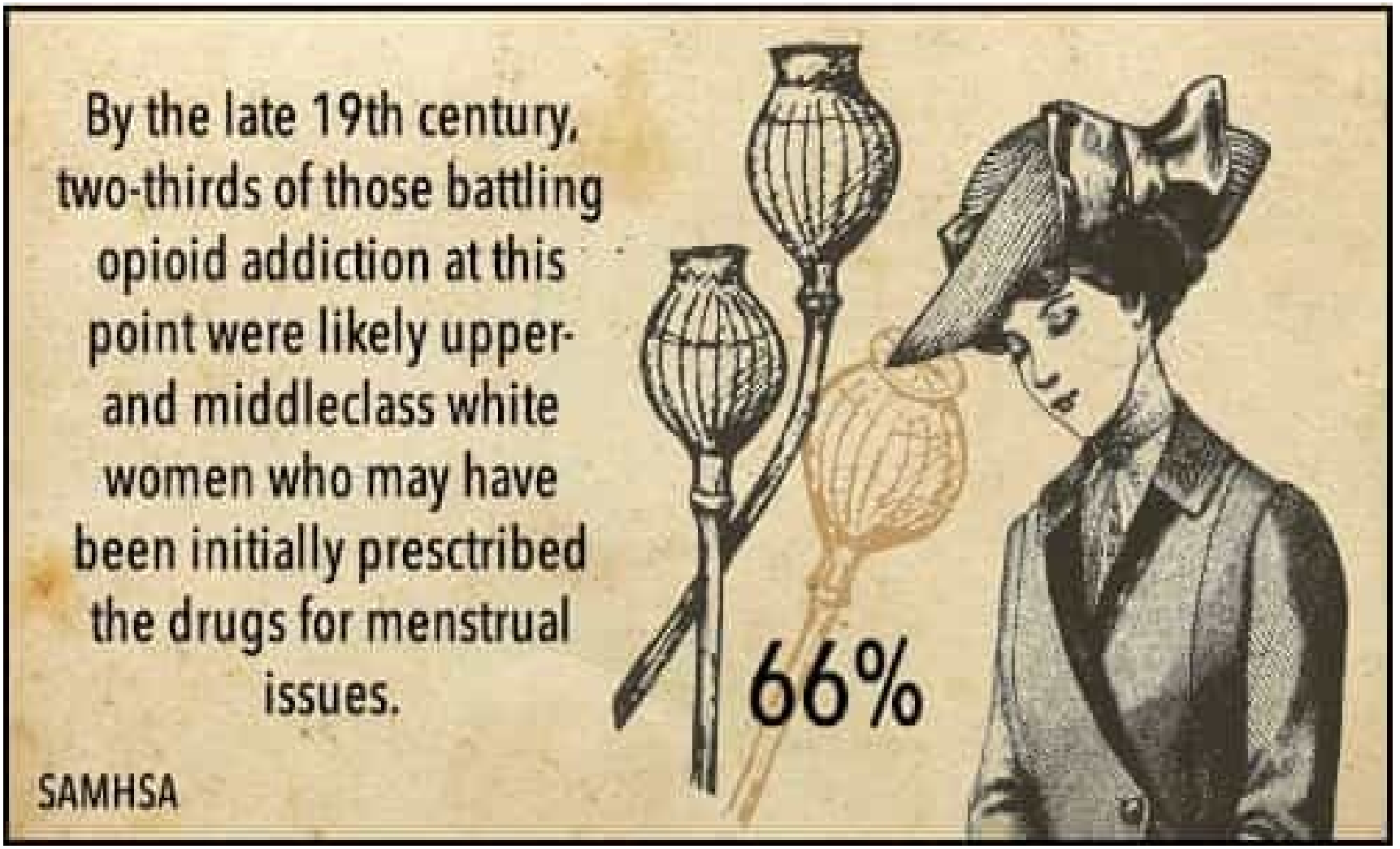
The two greatest motivators of behavior are pain and pleasure. Opioids is unique as an addictive drug because it provides both euphoria (pleasure) and blocks pain. Opioid's “mu receptors” on the respiratory center also block respiration. This is what causes opioid's overdose deaths.

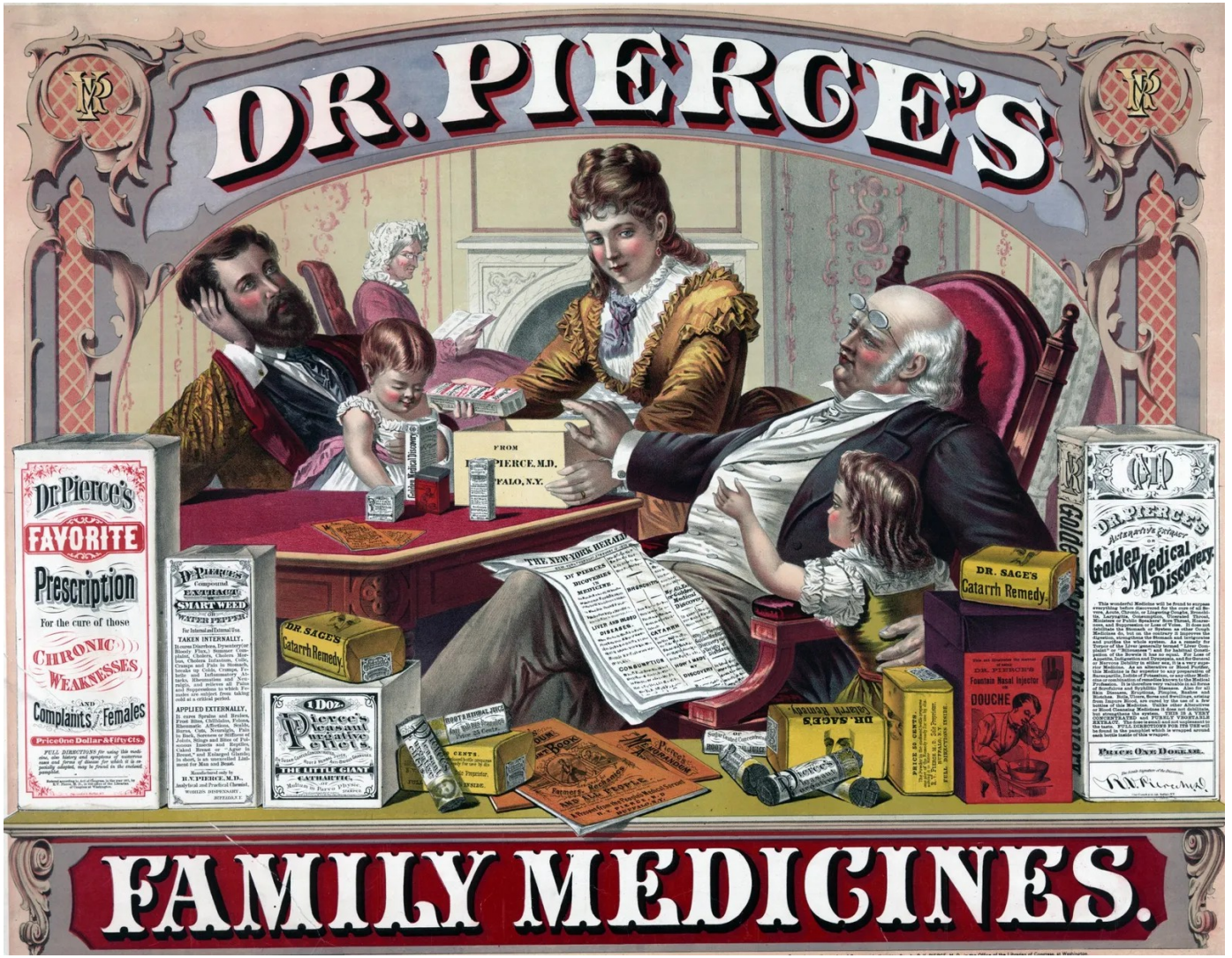
> 200 years ago chemist isolated the active molecule from opium, morphine.

> In the mid 1800s the first opioid epidemic was caused by over prescription of morphine to Civil War Soldiers. They were prescribed morphine to block pain from their battle wounds but then became addicted to morphine. This was called solder disease.

Opioid Addiction in the United States

> In the late 1800s house wives became the largest users of opioids.





In the early 1900s some doctors created business models for their medical practice by providing patients morphine shots. The same patients would come in multiple times throughout the day to get their morphine shot.

This business model was repeated by some doctors in the late 1990 by over prescribing opioid pills. This is the main cause of today's opioid epidemic.

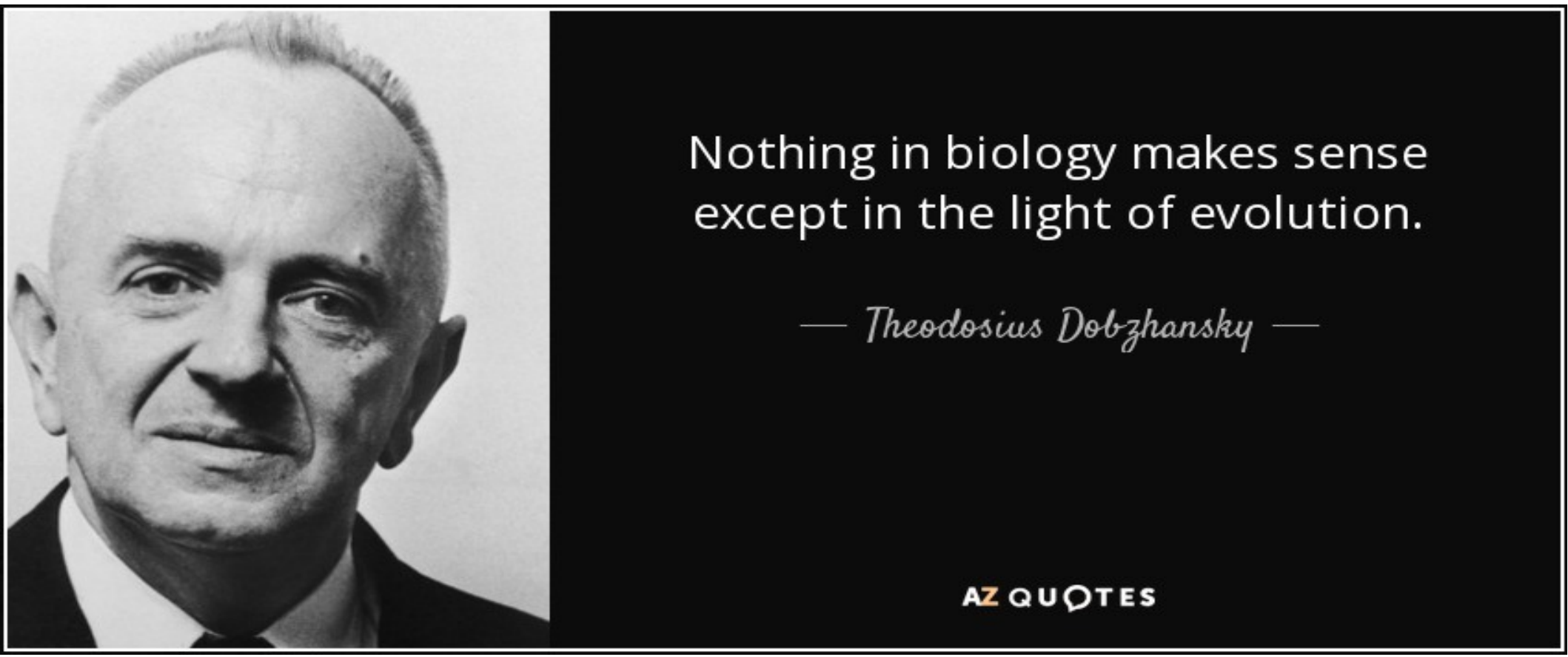
Addiction in the United States (continue)

> 1914 Federal Government pass laws to regulate sale of narcotics // decline

> 1945 – after World War Two next opioid epidemic targeting non-white Americans in the inner city. Black market illicit manufactured low grade heroine. This drug was cut so many times before it was sold on the street that users needed to inject the drug. This epidemic plagued the non-white American population in urban cities throughout the 1970s.

> 1996 started the next opioid epidemic that we are dealing with today. This is far worst than any previous opioid epidemic. Centers for Disease Control and Prevention has been very clear about the cause of this current epidemic and the cause in the surge in opioid deaths. It was caused by a rapid increase in doctor prescriptions for opioids driven by the by pharmeceutical companies aggressive marketing campaign promoting “compassionate medicine”.

> Oxycodone introduced in 1996 by Purdue Pharmeceutical. The company was sued and settled in court for 7.4 billion dollars for damages caused. (This pays less than $3,500.00 per survivor.) Deaths due to oxycodone since its introduction in some years exceeded 100,000. The Sackler family, owners of Purdue Phameceutical, were able to keep billions of dollars in profit made from the marketing and sale of opioids.



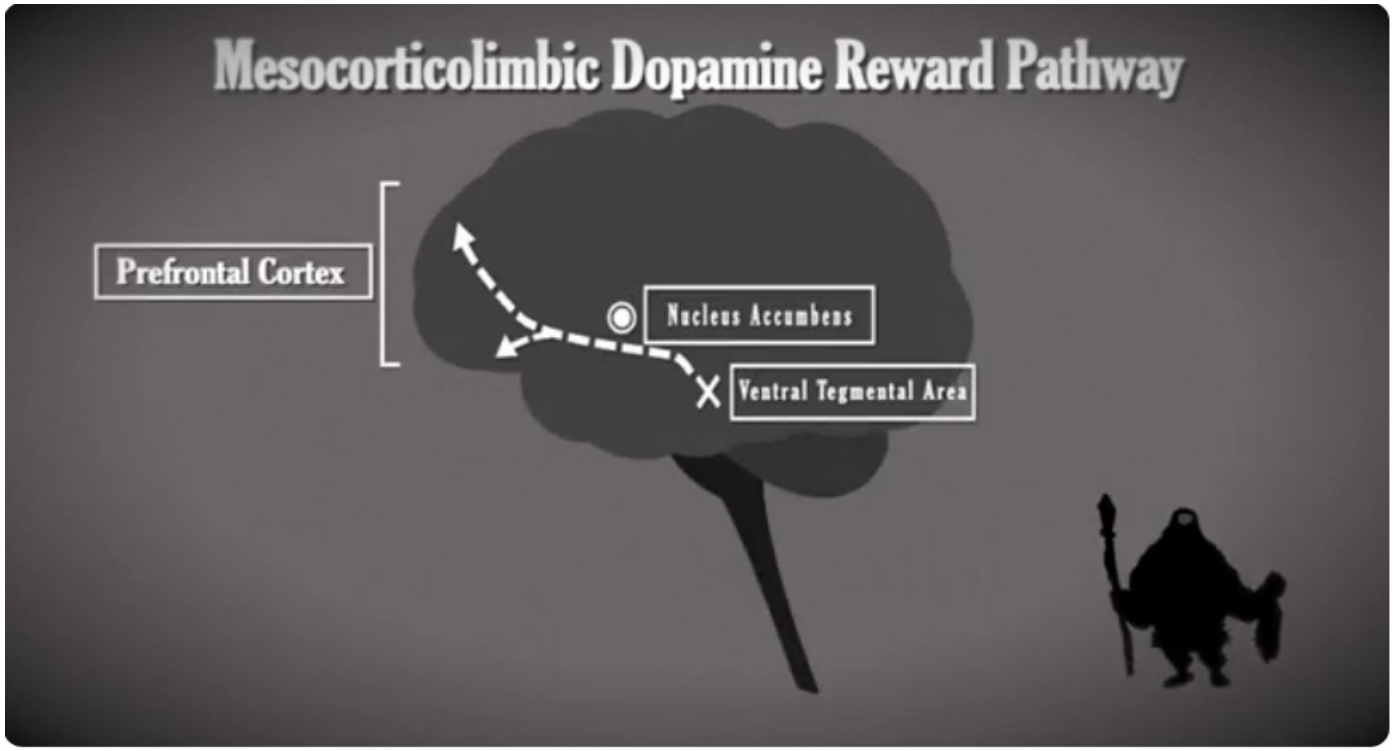
Addiction is a biological process so to understand addiction you need to understand addiction in the light of evolution.

In our evolutionary journey, our distant cousin was the chimpanzee. We shared a common ancestor. The chimp became a knuckle walker and lived in the trees and we became an “upright two legged walker” called a hominid. We also developed a larger brain. And this organ had one simple function, keep us alive.

A million years ago we did not have big sharp teeth or long sharp claws. We were not the strongest or fastest of animals in our neighborhood. We were not the apex predictor. We were the the prey hiding in caves to stay alive. So our brain evolved a circuit to reward us for two behaviors we needed to survive.

We needed to find food.

We needed to find a mate to reproduce, sex.



We needed a reward system to motivate us to leave the safe cave so we could find food and a mate. This reward pathway is called the mesocorticolimbic dopamine. It starts in the midbrain at the ventral tegmental area and connects to the nucleus accumbens. The next stop is to the limbic system and prefrontal cortex.

Behavior is dictated by the type and concentration of the neurotransmitter in the synaptic cleft. The neurotransmitter for the reward pathway is dopamine. It provides motivation and focus.

Today, dopamine is what motivates you to get out of bed in the morning, go to work so you have money to buy food, have a place to live, and to attract a mate.

A substance abuse disorder hijacks the reward system. Now what becomes important is compulsive seeking and using the substance that will release dopamine from the VTA.

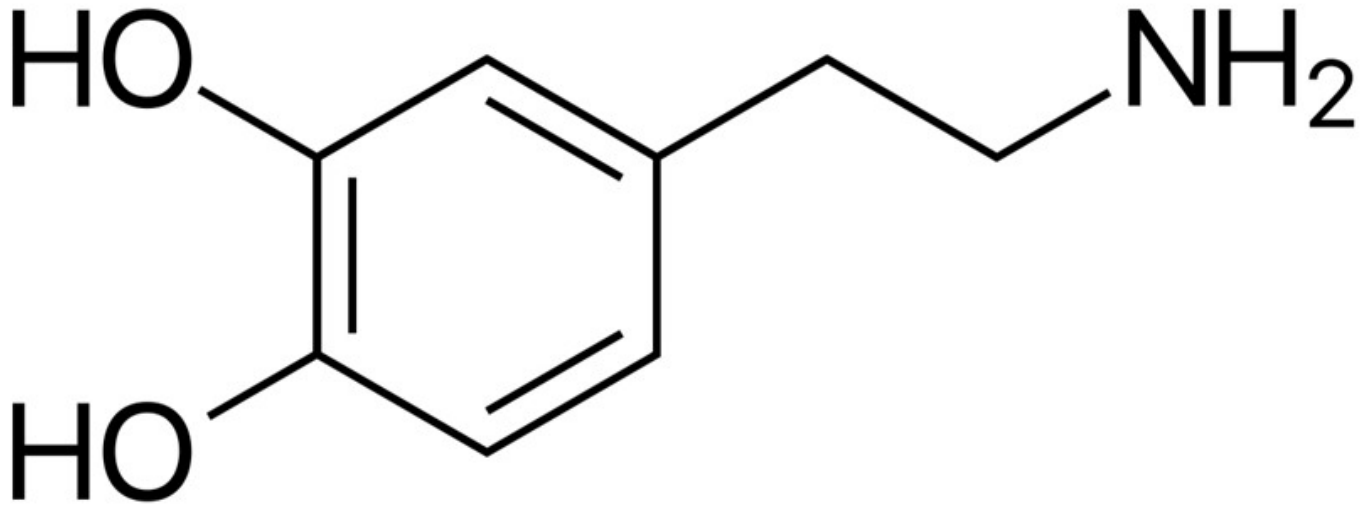
drugs associated with physical addiction

- tobacco
- alcohol
- cocaine
- opiates

We are exposed to thousands of different molecules every day. However, only a few molecules dock on the VTA toinitiate the reward pathway.

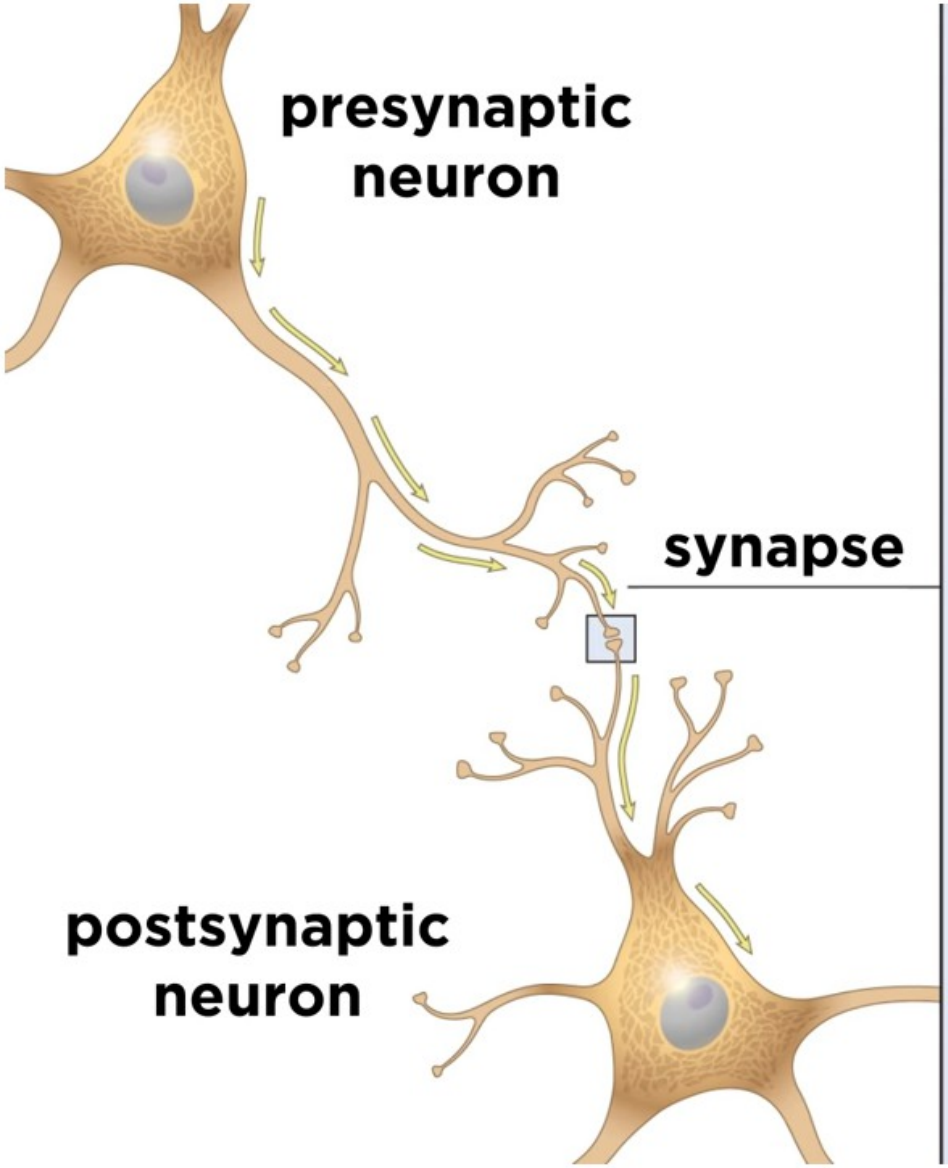
The NcA will release two neurotransmitters, enkephalin and dopamine. The enkephalin Provides a feeling of euphoria (pleasure) and the dopamine may have different outcomes depending on the drug.

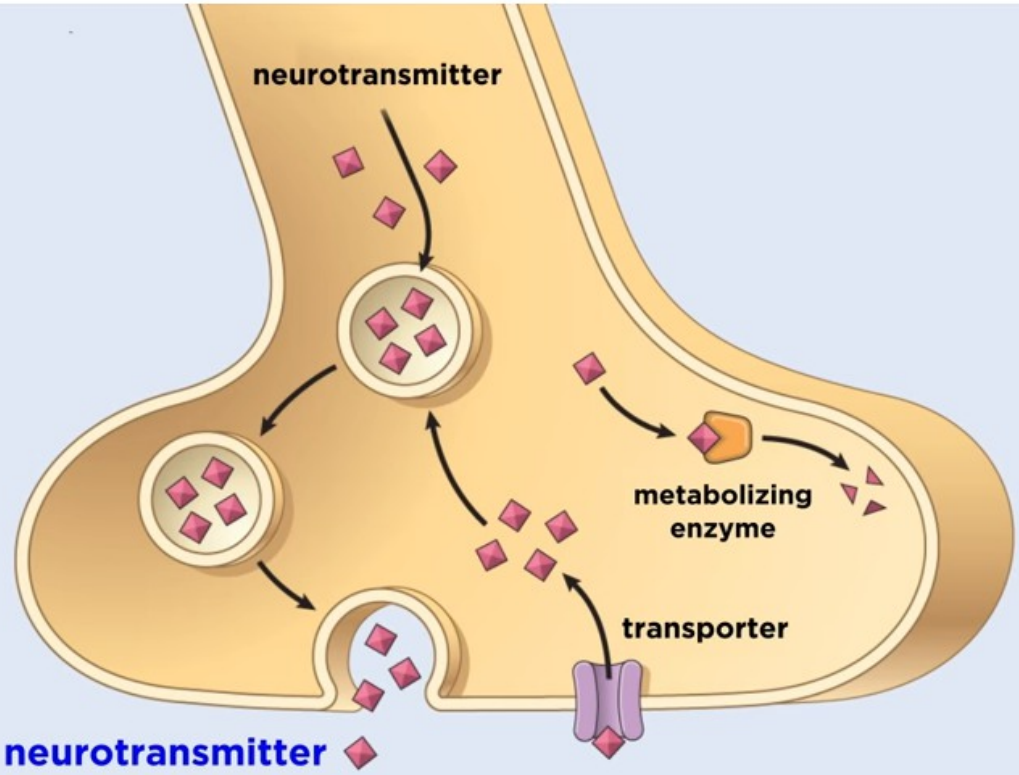
dopamine



crucial component of addiction

Dopamne is the first molecule of addiction. It is released from the VTA, travels to the NcA, and then to the mesocorticolimbic areas. Glutamate is the second molecule of addiction. Glutamate is the CNS stimulatory neurotransmitter. Glutamate plays a role in forming the memory linking the release of dopamine to the drug of choice.





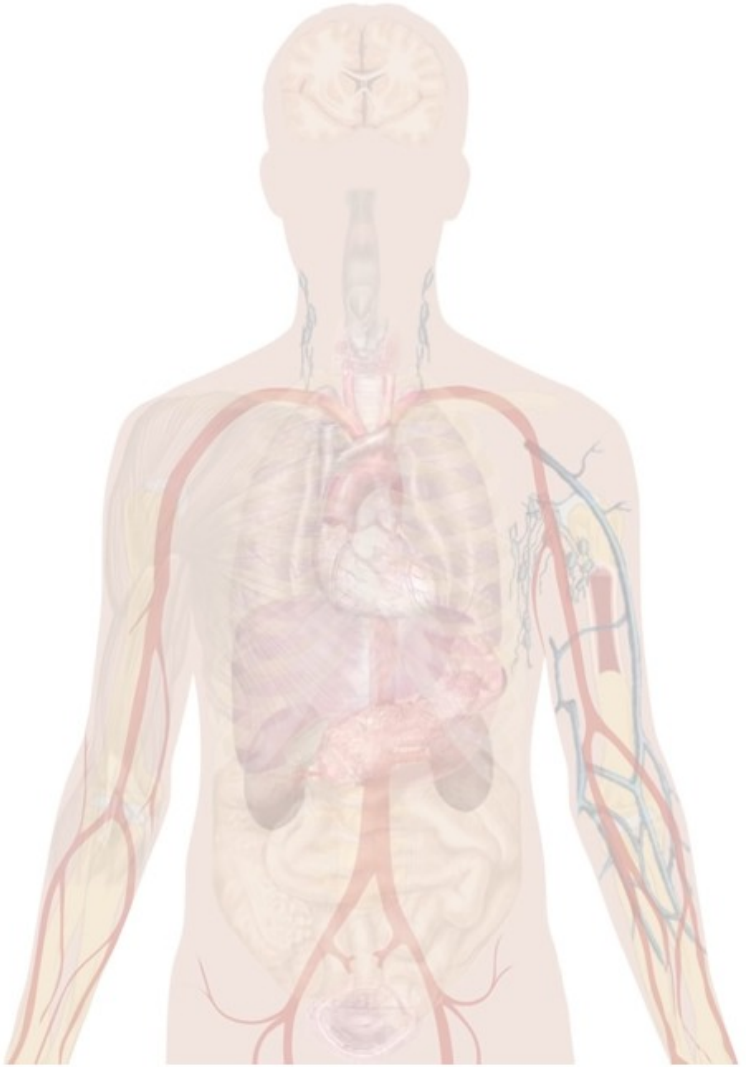
some drugs influence:

- **synthesis** of neurotransmitters
- **transport** of neurotransmitters
- **release** of neurotransmitters
- **deactivation** of neurotransmitters

the body will eventually develop tolerance to a drug

metabolic tolerance

less and less of the drug makes it to its destination



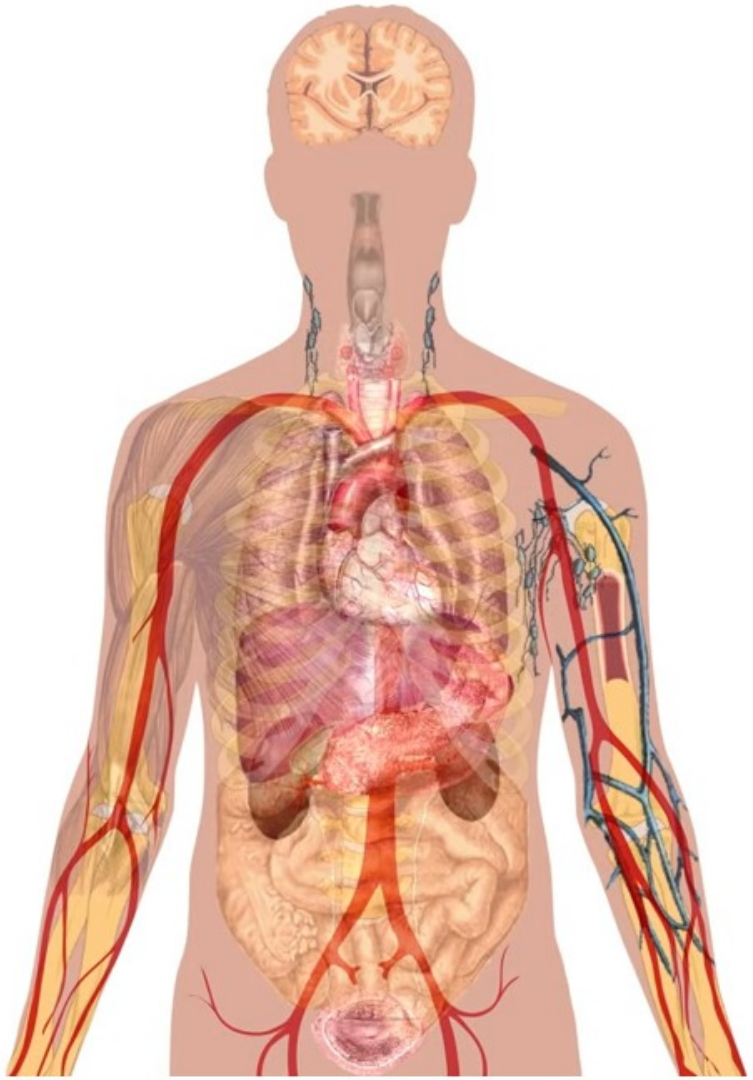
functional tolerance

the drug reaches its destination but has reduced efficacy

receptors for the drug may undergo endocytosis

Tolerance occurs when you need to take more of the drug to get the same effect.

sudden elimination of the drug can trigger withdrawal

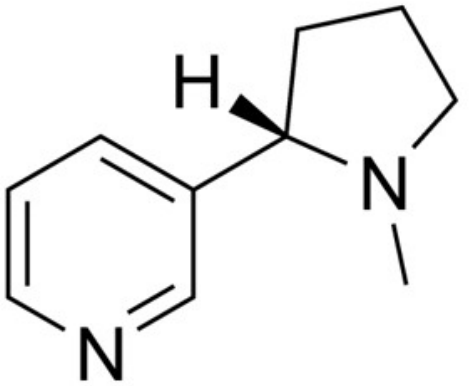


physical dependency has developed

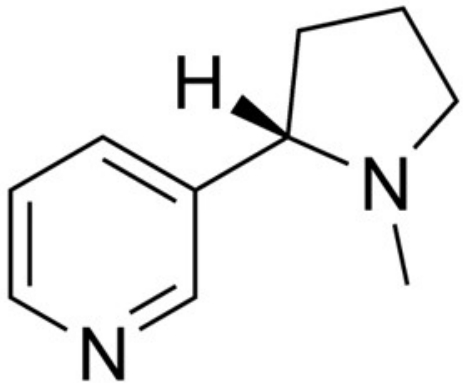
sudden elimination of the drug can trigger withdrawal

opposite effects of the drug itself

the component of tobacco that causes addiction is nicotine

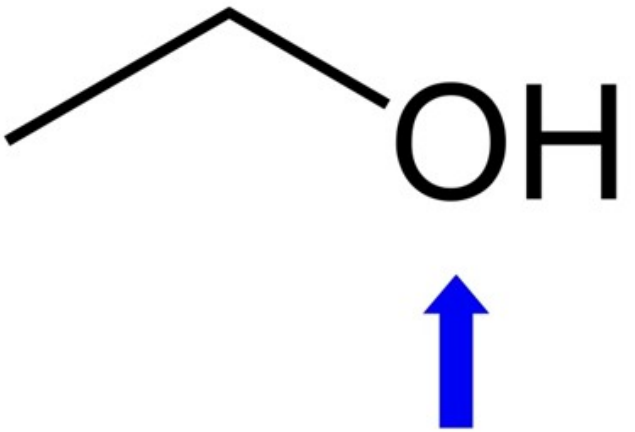


nicotine addiction



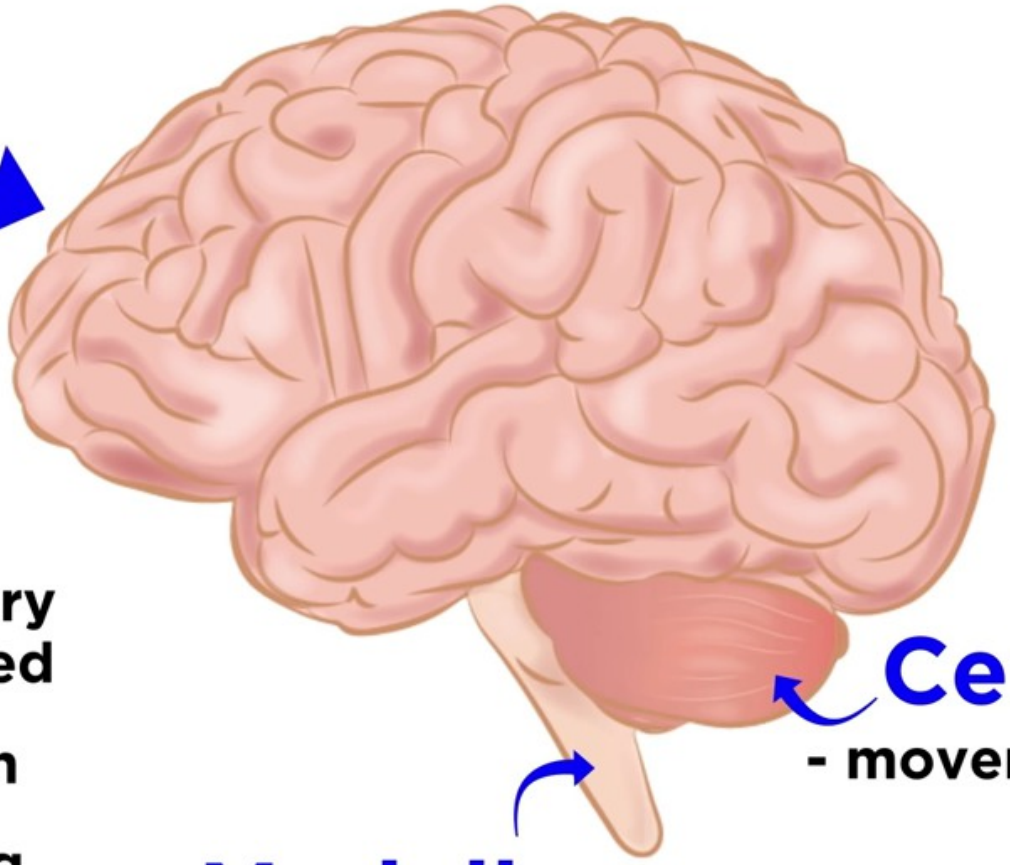
can arise after just a few weeks

alcohol



the active agent is ethanol

Effects of Alcohol



Cerebral Cortex

- behavioral inhibitory centers are depressed
- lowered inhibition
- slowed processing

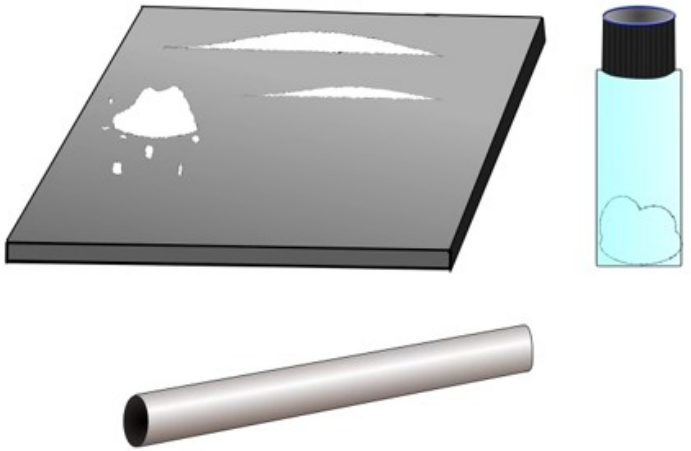
Cerebellum

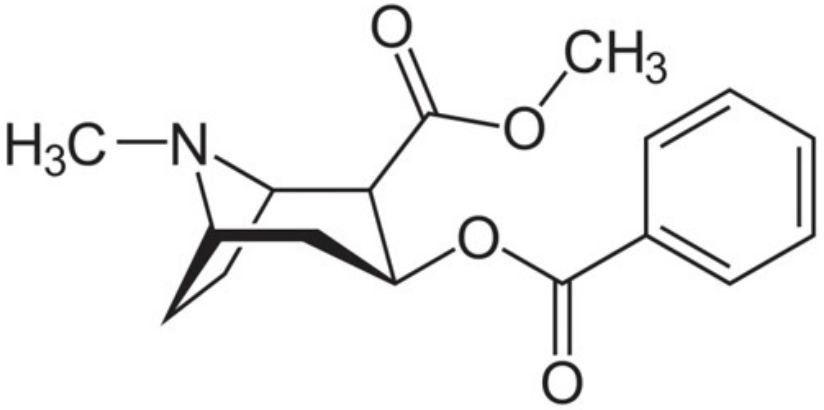
- movement and balance

Medulla

- breathing and consciousness

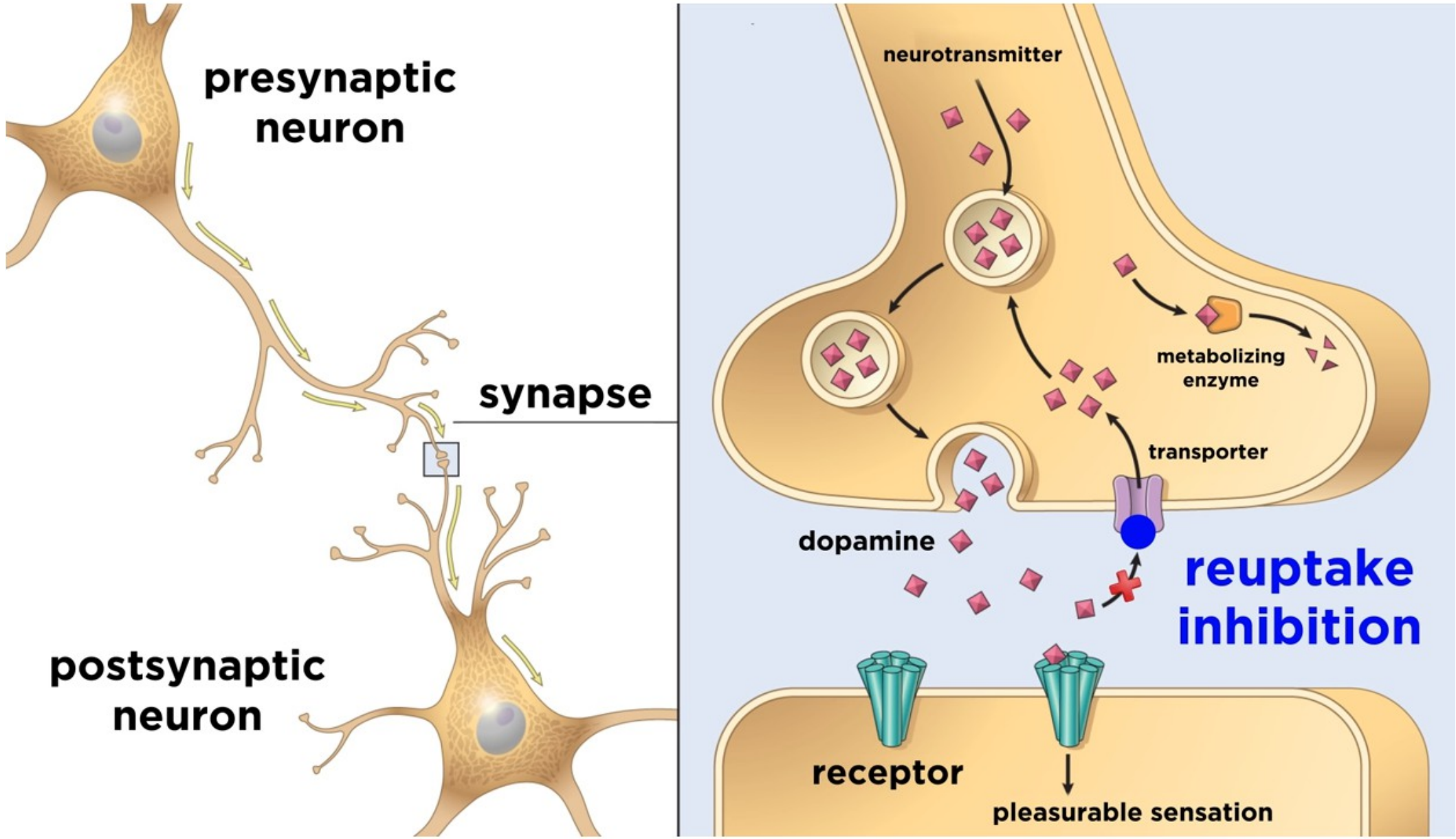
cocaine



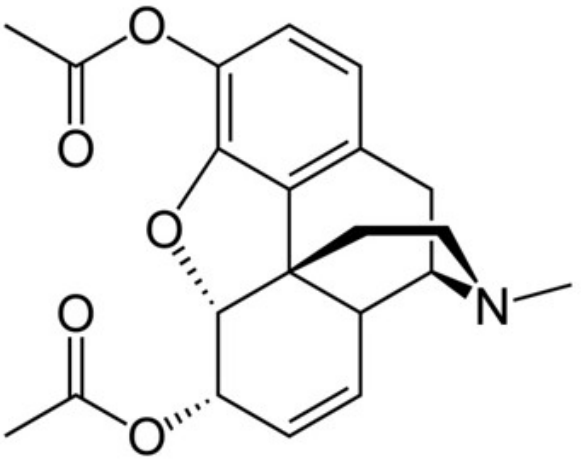


acts as a stimulant

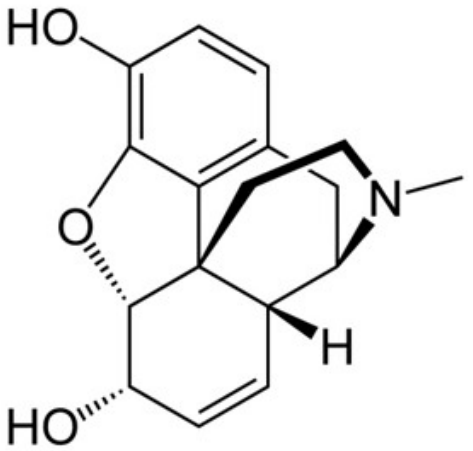
(increases neural activity)


presynaptic neuron
synapse
postsynaptic neuron
neurotransmitter
metabolizing enzyme
transporter
dopamine
reuptake inhibition
receptor
pleasurable sensation

opiates



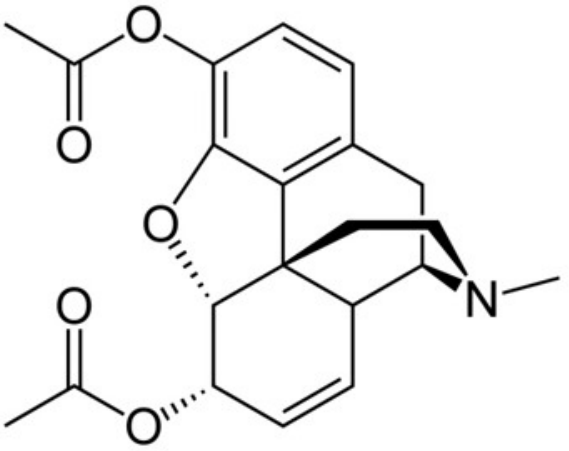
heroin



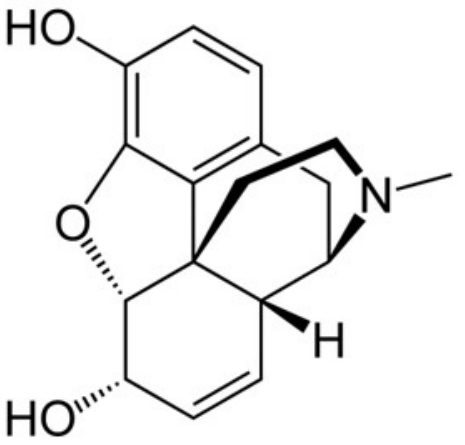
morphine

- bind to opioid receptors meant for endorphins
- mimic mechanisms of pain reduction and euphoria

opiates



heroin

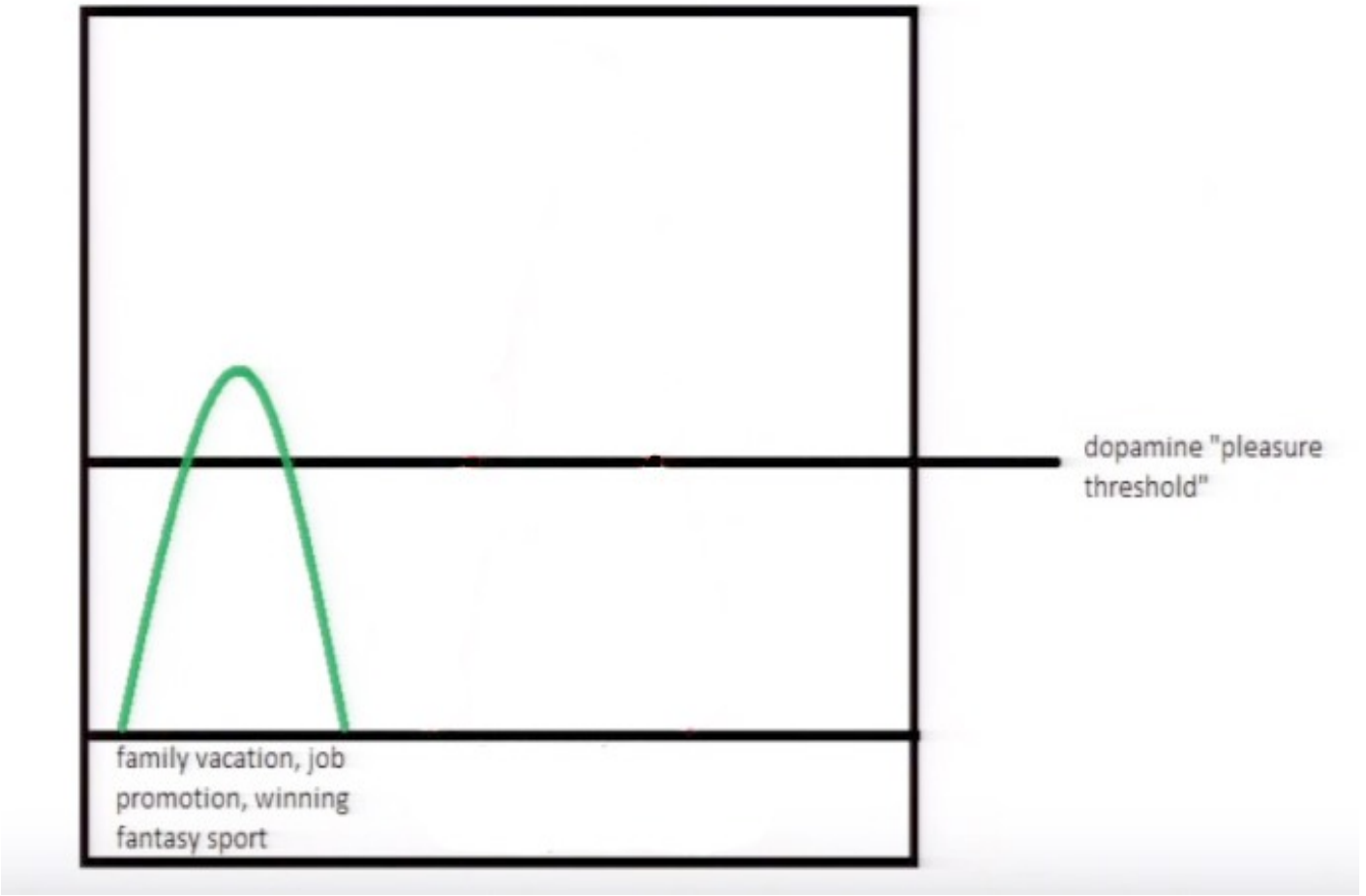


morphine

the most addictive substance known

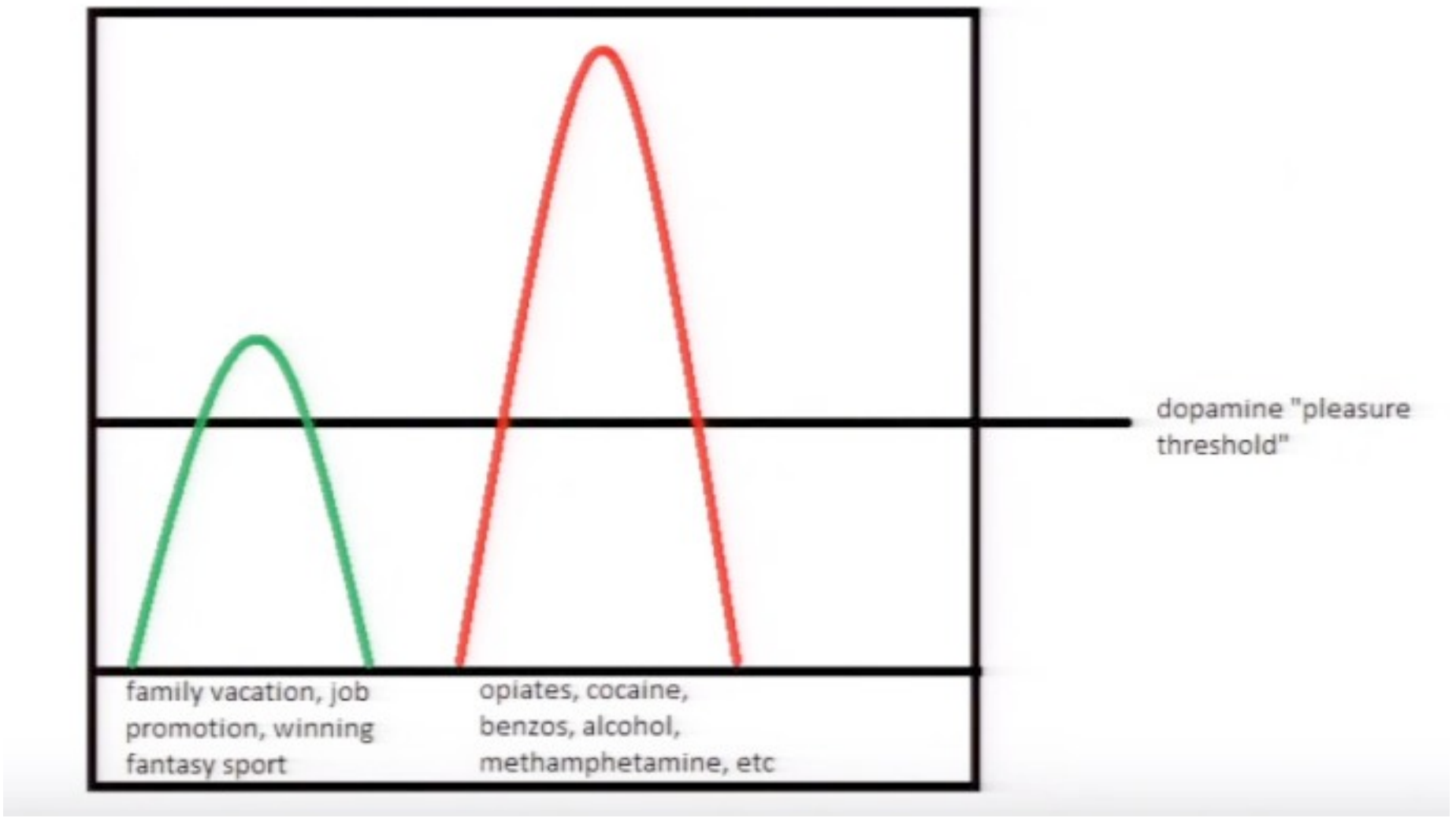
gambling addiction does not depend on any substance

Gambling and some other behaviors cause dopamine to be release from the VTA. These behaviors become addictive. There is only one reward pathway.



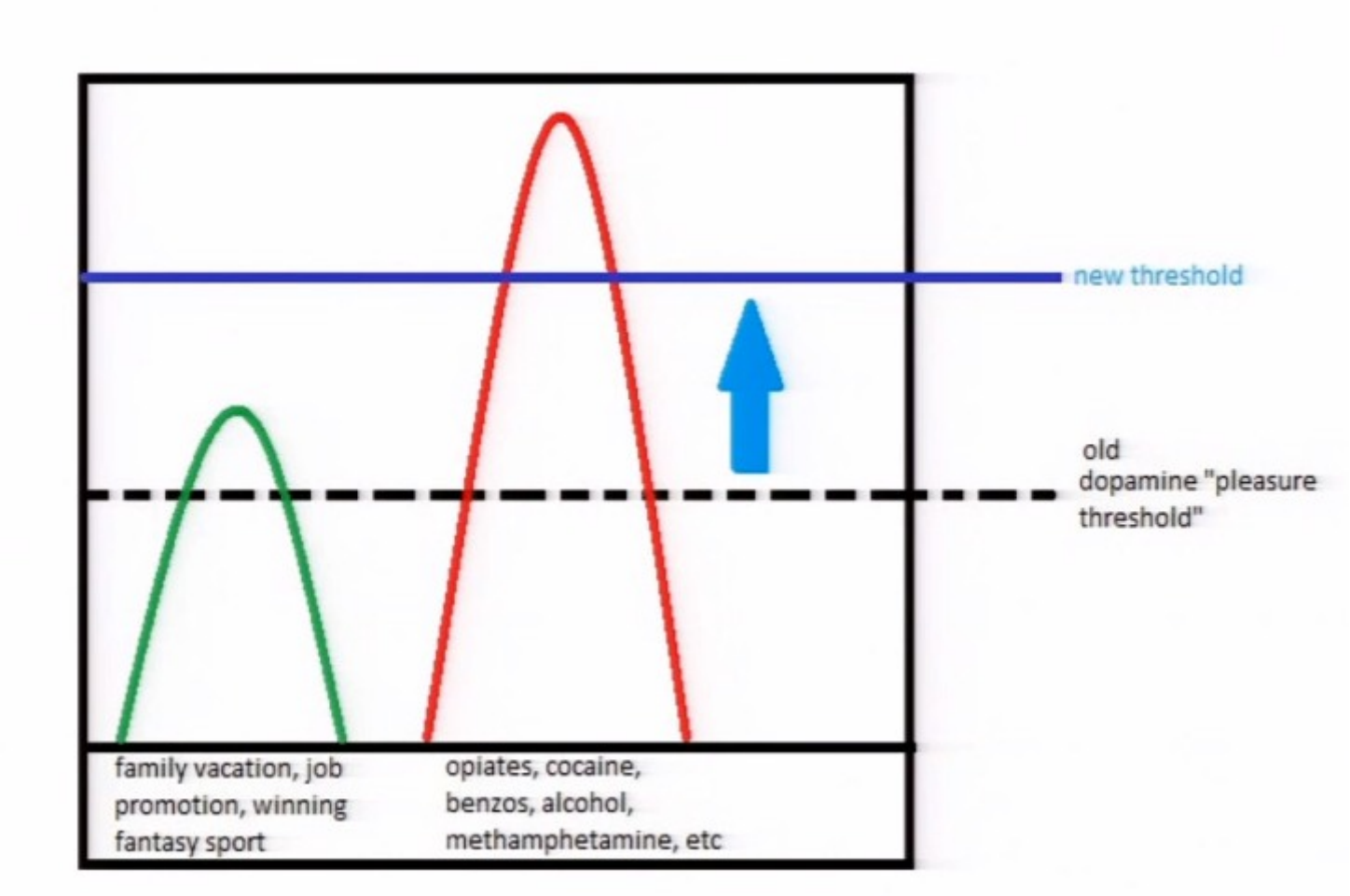
Dopamine is responsible for your “motivation and focus”. Dopamine concentrations create a hedonistic set point level. This is the minimum level needed to provide pleasure and to motivate you to start an activity. The pleasure is the reward. Below this level you are not motivated. Below this pleasure threshold you will not want to get out of bed in the morning to face the world!

You need 50 ng/dl in order to get out of bed in the morning. All normal activities you do that give you pleasure will release more than the 50 ng/dl.



When someone tries an addictive drug for the first time, the amount of dopamine released maybe 100 times greater than normal. This is not a normal reward level.

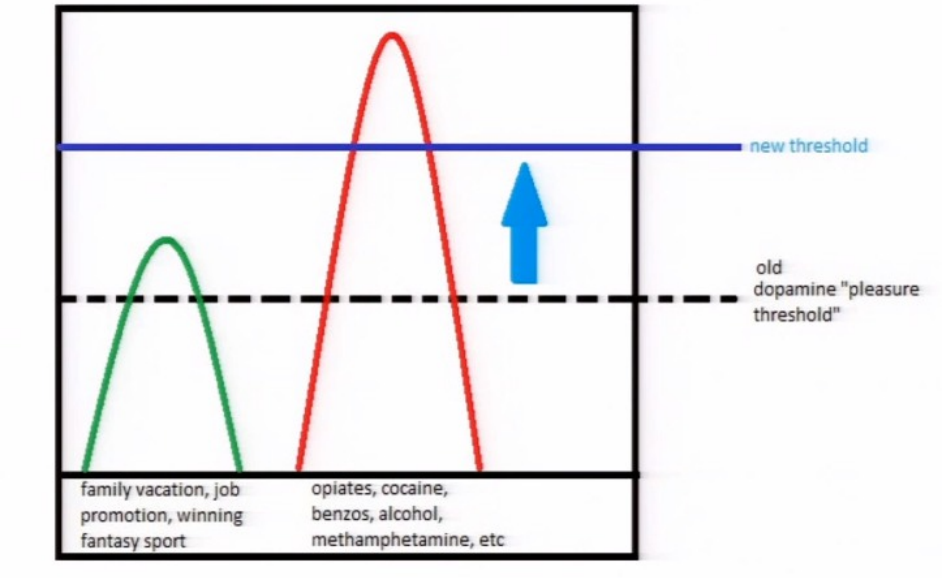
The drug now establishes a binge or intoxication phase. This is the liking phase. The person will take the drug again to experience the excessive release of dopamine.



The substance abuse disorder now establishes a new pleasure threshold. This threshold is only achievable by the dopamine level released by the drug.

Other activities like family functions, vacations, sports, movies, and the other activities you use to enjoy no longer reach the new pleasure threshold.

Normal activities simply do not release enough dopamine. Now you have no motivation or focus except to take the drug to reach the new threshold.



Our brain is designed to operate with dopamine levels between 40 and 100 ng/dl

> Normal day – get out of bed = 50 ng/dl

> Worst day – call in sick and don't go to work = 40 ng/dl

> Best day – win lotto and living on the beach = 100 ng/dl

> Favorite food = 94 ng/dl

> Sex = 92 ng/dl

> Methamphetamine and other addictive drugs = 1,100 ng/dl

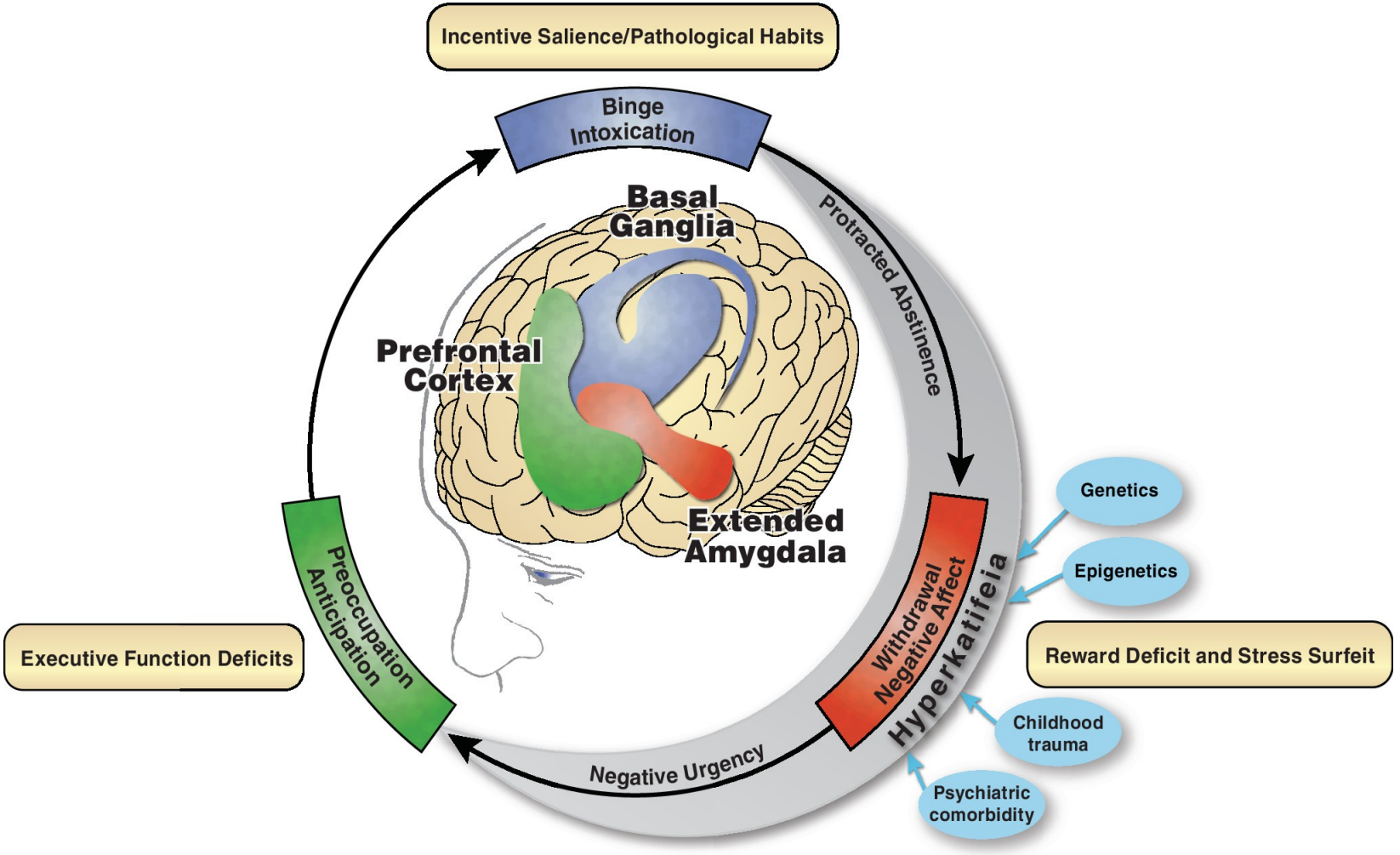
> Addict in withdrawal have dopamine levels as low as 20 mg/dl

Craving occurs after the addict becomes drug dependent and then stops taking the drug. This is withdrawal. Now craving occurs. Craving is different than wanting something. Craving is when you feel like you will die if you can not get it. Imagine you are trapped under water and can not breath. This is the feeling an addict has if they can not get the dopamine (dopamine is the drug).

Craving puts the addict in a survival mode (limbic system function). Without the dopamine you will die. You will do whatever you need to do to get the dopamine.

It is the craving that causes the addict's chronic relapse, and the compulsive drug seeking and use despite adverse consequences.

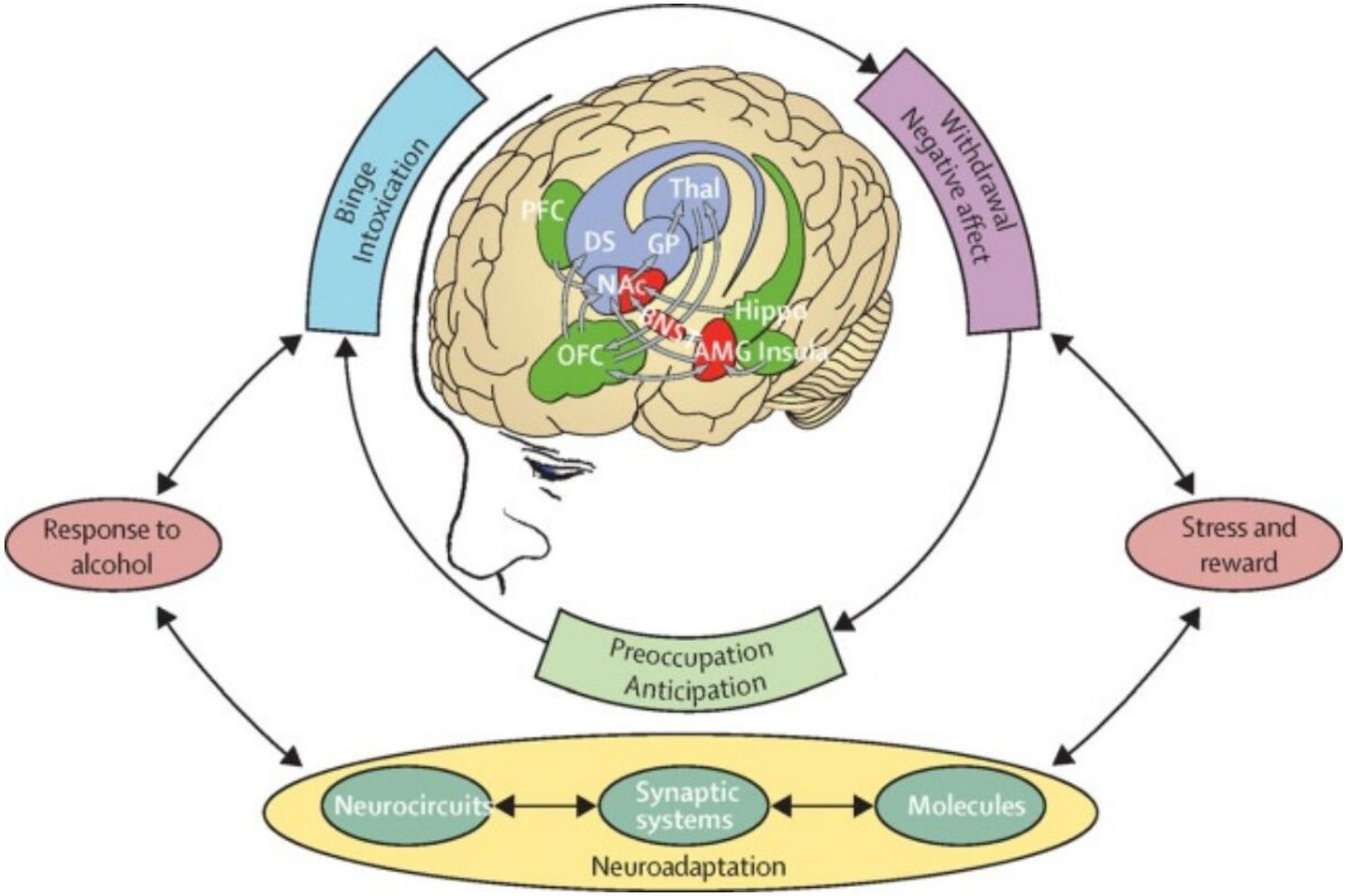
The Framework for the Addiction Cycle



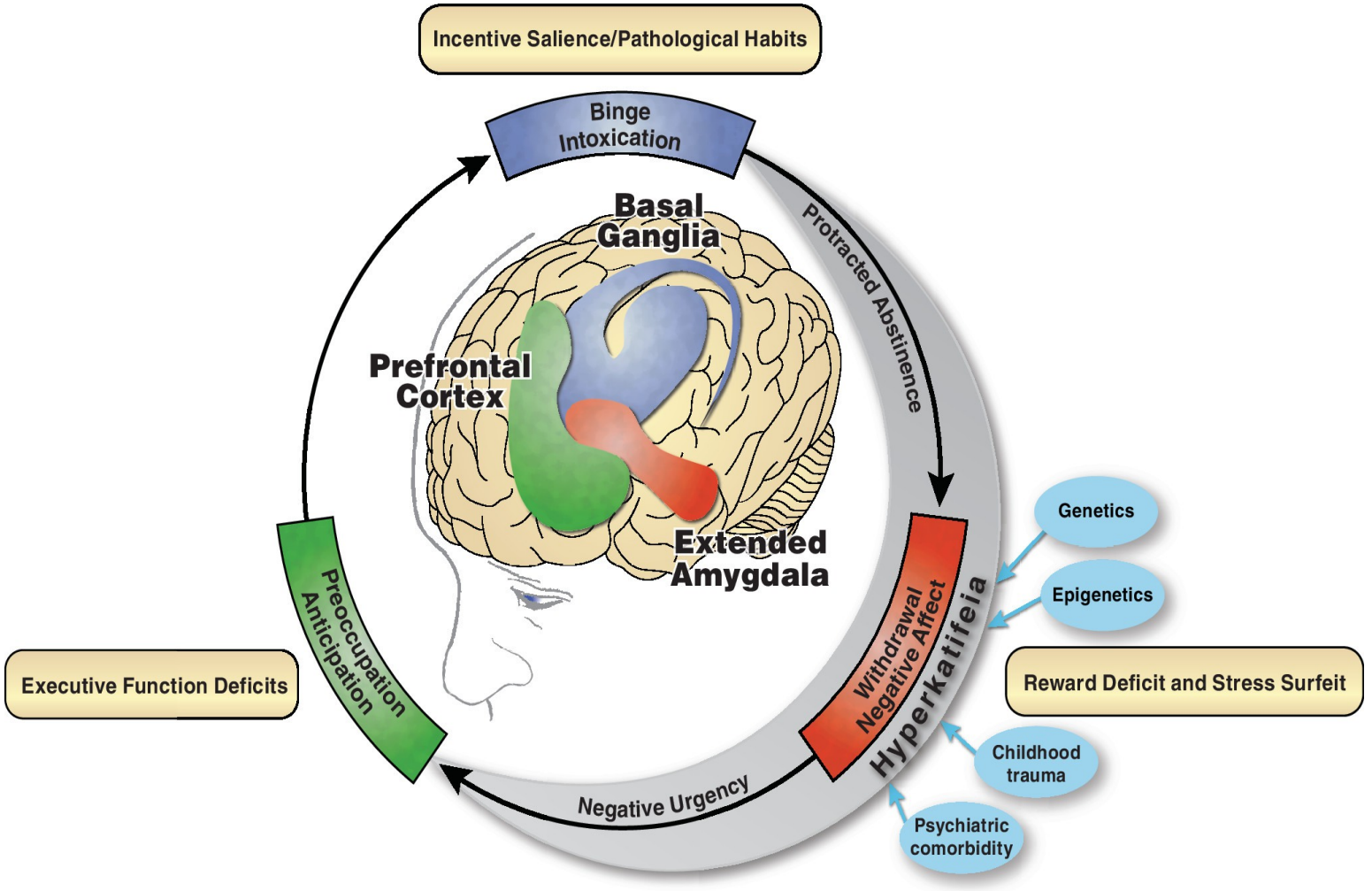
Addiction causes functional changes to brain circuits involved in reward, stress, and self-control.

The binge and intoxication phase is the liking phase. This is positive reinforcement.

The Framework for the Addiction Cycle

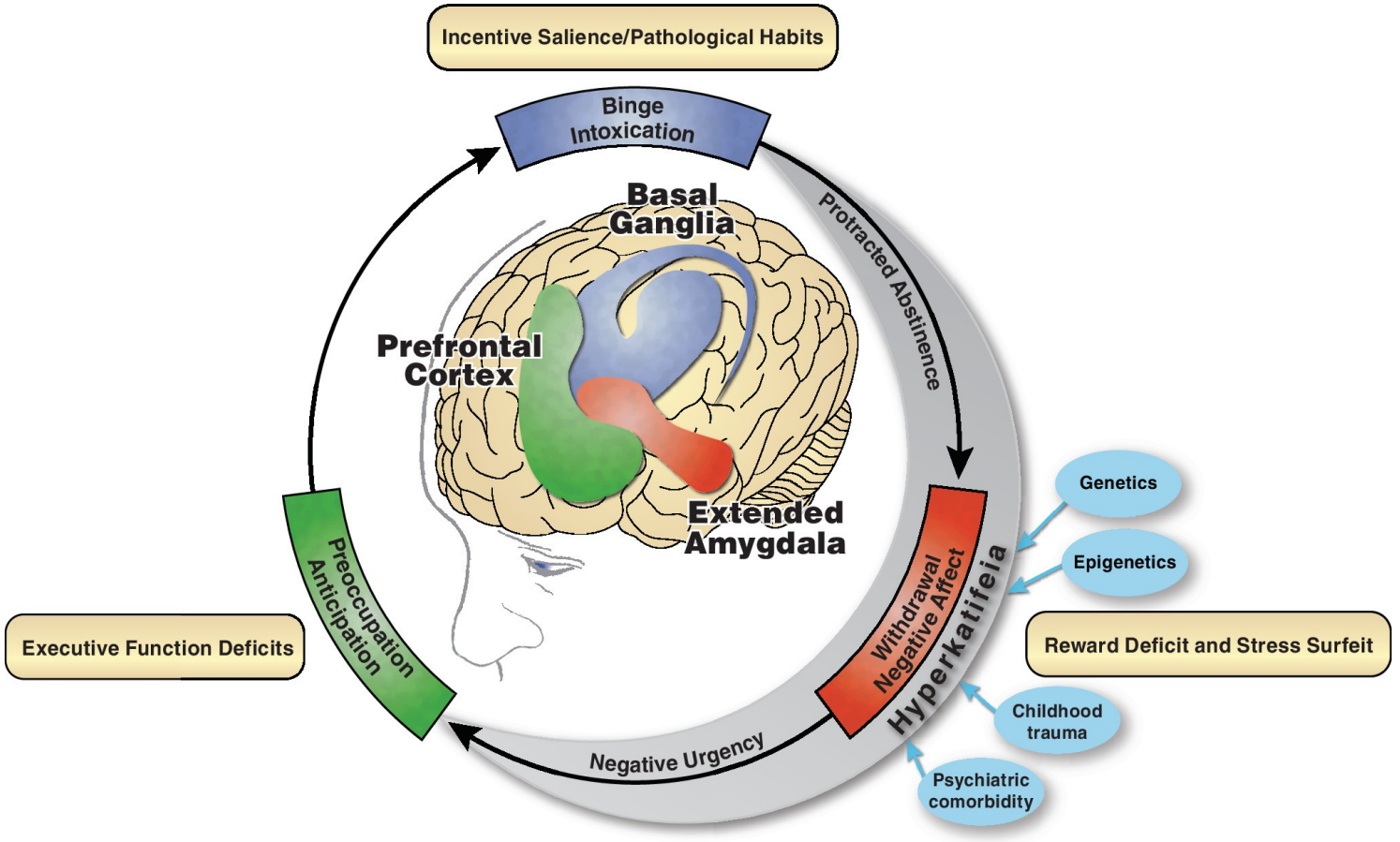


Tolerance and dependency develops during the binge and intoxication phase. Tolerance requires the user to increase consumption to experience the same euphoria and drug affect.



After dependence is established, the addict now needs to take the drug not to get high but to feel normal and avoid stress. This is the “extended amygdala trap”. The extended amydala releases cortio releasing factor within the brain which causes a stress response.

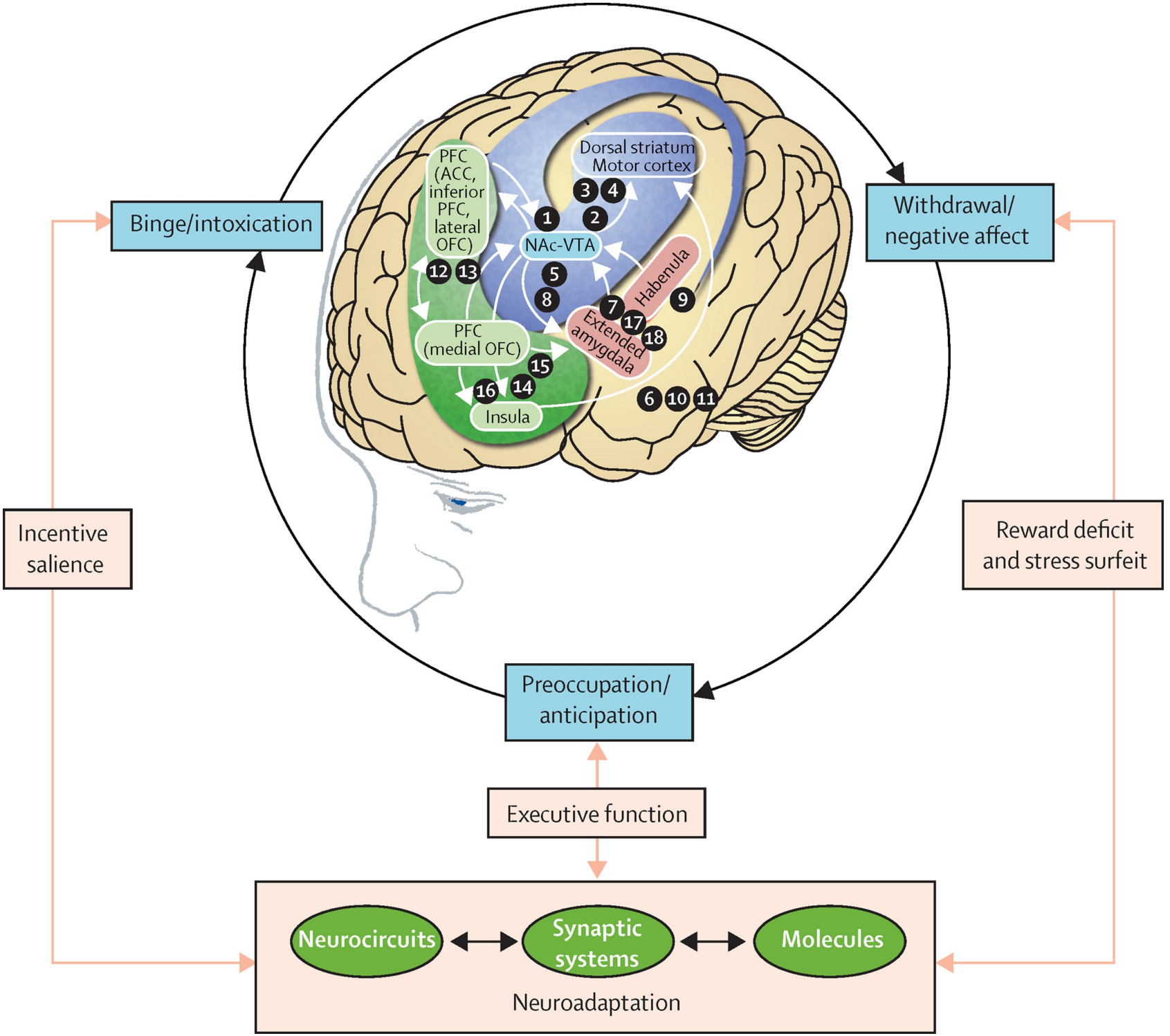
To escape from the stress, the addict must continue to take the drug. This is the negative reinforcement.



The extended amygdala creates a negative reinforcement to motivate the addict to continue compulsive drug seeking and use.

The addict continues to take the drug not to get the high but to avoid a stress response and to feel more normal (not stressed). Now the addict is trapped.

These changes to the brain's circuits may last a long time after a person stops taking the drug. Drug cues (people, places, or things) may cause a relapse years later initiated by stress.


Binge/intoxication
Withdrawal/
negative affect
Incentive
salience
Reward deficit
and stress surfeit
Preoccupation/
anticipation
Executive function
Neurocircuits
Synaptic
systems
Molecules
Neuroadaptation
PFC
(ACC,
inferior
PFC,
lateral
OFC)
Dorsal striatum
Motor cortex
NAc-VTA
Habenula
Extended
amygdala
PFC
(medial OFC)
Insula
1
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Hypotheses Addiction Models

Opposing-Process Hypothesis of Addiction

Dopaminergic Hypothesis of Addiction

Incentive Sensitization Hypothesis of Addiction

Habit and Compulsion Hypothesis of Addiction

Allostasis Hypothesis of Addiction

The Opposing-Process Hypothesis of Addiction

Key Concept:

> Primary Process (a-process) The initial, direct response to a stimulus (e.g. the initial feeling of pleasure when using a drug.

> Opponent Process (b-process) The secondary, opposing reaction that is triggered after the primary proess has subsided (e.g. the later feeling of sadness or withdrawal symptoms after the drug wears off)

> Homeostasis: The body strives for a stable emotional state. The a-process and b-process work together to bring the individual back to a neutral or baseline state.

> Drug Addiction: The initial euphoria of drug use is the a-process. The subsequent withdrawal symptoms and negative emotional states are the b-process. Over time, the initial high may diminish, while the withdrawal symptoms become moe intense, driving the individual to seek the drug again.

The Dopaminergic Hypothesis of Addiction

Key Concepts:

> Drugs act through a common mechanism of increasing dopamine in the brain's reward system, promoting positive reinforcement, and motivating drug consumption and addiction.

> Clinical studies sported that low dopamine release was a predictor of vulnerability to addiction, while an adequate dopaminergic tone played a role in the resilience of individuals who would not escalate in drug consumption.

> This hypothesis lacks explanatory value for various phenomena in the addictive process, such as withdrawal syndrome or craving.

> Others suggest the role of dopamine was not solely to mediate the experience of euphoria and reward but also to promote the formation of motivational salience, the establishment of habits, and reward expectation associated with cues. (The high before the high.)

Incentive Sensitization Hypothesis of Addiction

Key Concepts:

> Drugs of abuse induce a highly intense and prolonged activation of the reward system.

>Repeated consumption leads to alterations in the functioning of the reward system.

> Dopamine does more than encode for reward. Dopamine also participates in memory consolidation, habit formation, motivational salience associated with the drug.

> This neuroadaptation makes the individual hypersensitive to environmental cuse associated with the drug reward.

> Incentive salience is understood as an attention bias toward stimuli associated with drug consumption.

> After repeated use, the motivation shifts from an initial state of preasure-driven consumption (liking) to pathological craving (needing), reflecting a process of sensitization and conditioning of the reward system

> This hypothesis explains craving, drug seeking, and drug consumption when the addict Is exposed to environments and cues associated with drug use.

Habit and Compulsion Hypothesis of Addiction

Key Concepts:

> Central idea is the addictive process occurs voluntarily, driven by its recreational effect (positive reinforcement). Repeated consumption causes individual to lose control over consumption behavior, which turns into a compulsive behavior difficult to extinguish.

> In the transition from voluntary and occasional consumption to compulsive consumption, a progressive shift in the locus of control of drug-associated behaviors occurs. It moves from top-down control (prefrontal cortex-voluntary) to a regulation of the behavior controlled by the basal ganglia (involuntary-subconscious).

> Now behavior would cease to be controlled by ventral striatal regions, extensively connected with the prefrontal cortex and amygdala, to be controlled by dorsal striatal regions, specialized in the maintenance of motor sequences
(basal ganglia globus pallidus).

> Prefrontal cortex would increasingly have less inhibitory control over drug associated motor behaviors, which would become more compulsive and disinhibited

> Activation thresholds necessary to initiate drug motor habit seeking would be progressively reduced making environmental cues enough to trigger drug seeking and consumption behaviors.

Allostasis Hypothesis of Addiction

Key Concept:

> Allostasis theory shares with previous theories the idea that in the initial phases of the addictive process, consumption is motivated by the expectation of positive reinforcement.

> After chronic consumption, behavior maintenance should be attributed to a process of negative reinforcement, as only the drug can stop the activation and discomfort that occurs during periods of abstinence.

> Allostasis hypothesis of addiction integrates the opponent-process theory and the concept of homeostasis. Drug consumption leads to activation of the reward system above Its natural levels. This becomes a threat to homeostasis. This triggers two corrective mechanisms to counteract the drug. 1) loss of function in the reward system with increase in activation threshold (tolerance), and 2) hyper activation of stress which is an anti-reward system.

> Corrective process produce overcompensation beyond initial homeostatic level. A new set point or allostasis is established, as an attempt of anticipatory compensation for future drug consumption.

> This has a negative impact on individual motivation. Now person in chronic state of reward system hypo-function and a state of stress hyperactivity. Now natural rewards (food and sex) insufficient to retrun sysem to its natural level. Only drugs abuse will offset the negative consequences of this allostatic state, now consumption not for reinforcing Effects but for ability to alleviate dysphoric state during abstinence.

Addiction Is a Disease

There is no simple test for addition. Addiction is often simply diagnosed as being bad behavior.

When you have heart disease, it maybe diagnosed by measuring blood pressure or by an irregular EKG. If you come into an emergency room with a heart attack, you are admitted to the hospital and the disease is treated and managed.

If you come into an emergency room with an overdose, you are recovered and then released. Addiction is a disease but it is not treated or managed. Relapse will occur when there is no treatment or not enough treatment and because better disease managed program was needed.

Eighty percent of the current opioid addicts in the United States started taking opioids with a medical prescription There are tens of thousands of people unable to find effective treatment programs. More must be done.