

Neurobiology Of Addiction

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Vulnerability to Addiction

The initial use of a substance or addictive behavior is more associated with environmental factors, whereas the movement to abuse and addiction are more associated with neurobiological factors.

Allostasis

is the process of achieving stability, or homeostasis, through physiological or behavioral change. This can be carried out by means of alteration in hormones or the Autonomic Nervous System.

Nervous System

Central Nervous System

Brain

Spinal Cord

Peripheral Nervous System

Autonomic

Somatic

Sympathetic

Parasympathetic

Central Nervous System

Consists of nerve cells (Neurons) in the brain and the spinal chord.

1. Brain
2. Spinal cord

Spinal Cord

Extends from the lower end of the medulla to the upper levels of the sacral vertebrae.

1. Carries sensory information from the skin, muscles, joints, and internal body organs to the brain.
2. Organizes and modulates the motor outflow to the muscles
3. Modulates sensory input
4. Provides autonomic (involuntary) control of vital body functions.

The Neuron

Dendrite

Soma

Nucleus

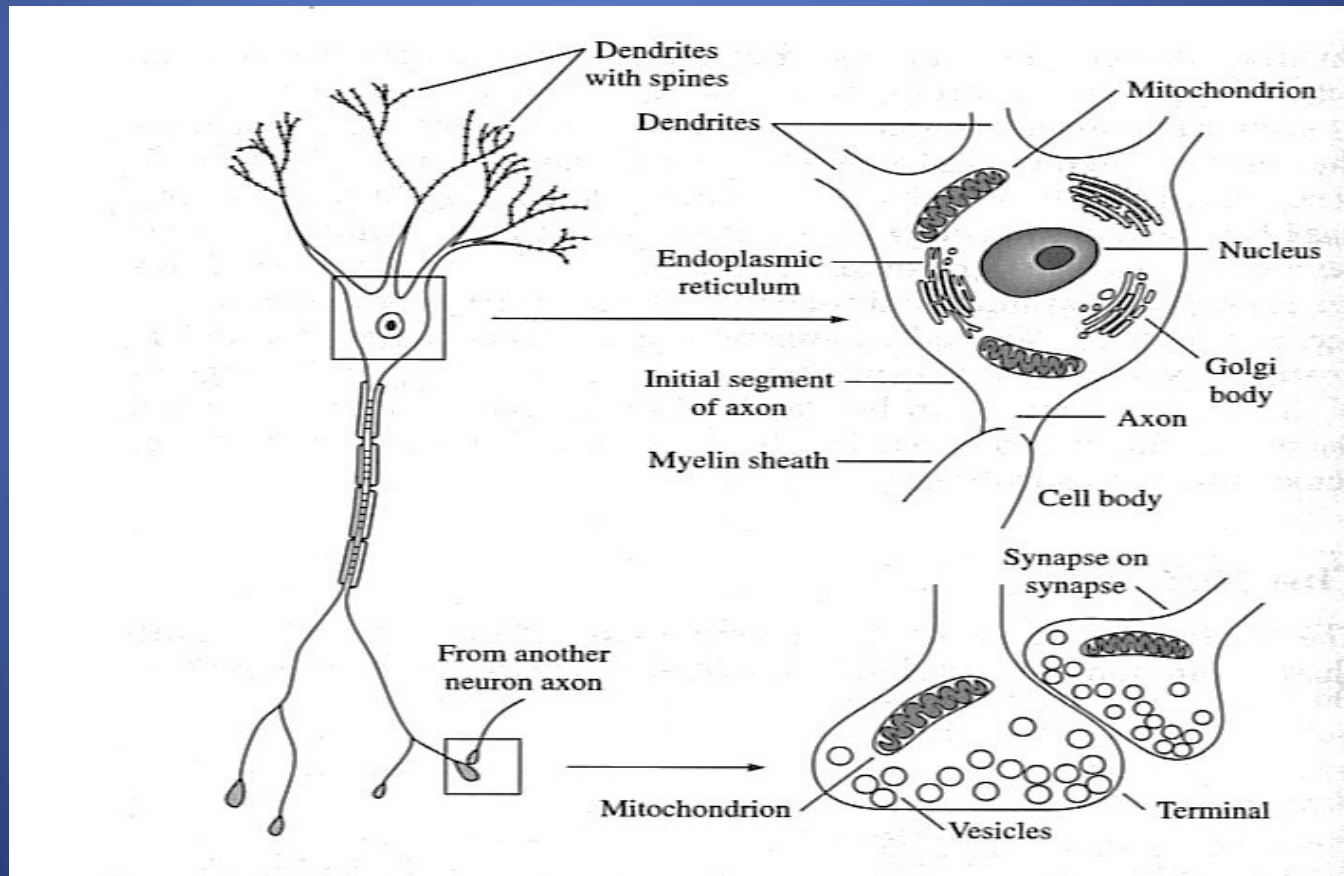
Axon

Terminal Buttons

Myelin Sheath

Neuron

Neuron



The Neuron

Neurotransmitters

Action Potential

Resting Potential

All or None Theory

Presynaptic Neuron

Postsynaptic Neuron

Brain

Frontal Lobe

Parietal Lobe

Occipital Lobe

Temporal Lobe

Olfactory Bulb

Wernicke's Area

Broca's Area

Hypothalamus

Thalamus

Brain

Basal ganglia:

The caudate nucleus, globus pallidus, putamen and amygdala. The first three are important parts of the motor system, located just rostral to the thalamus.

Association Cortex:

The regions of the cortex that receive information from the sensory area or that project to the primary motor cortex. Plays an important role in perception, learning, and planning.

Brain

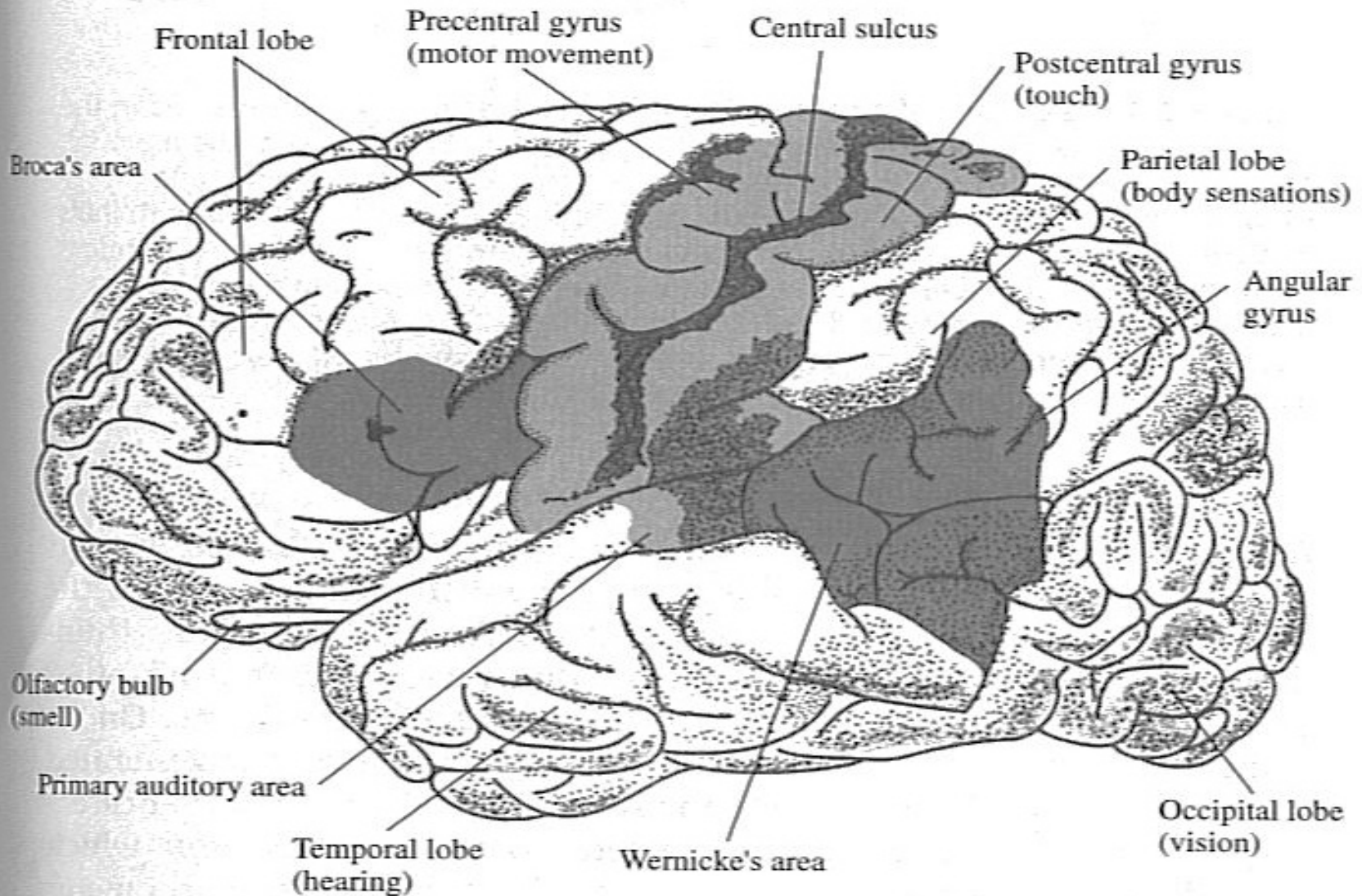
Nucleus accumbens:

A nucleus of the basal forebrain near the septum; receives dopamine-secreting terminal buttons from neurons of the ventral tegmental area; thought to be involved in reinforcement of attention.

Ventral Tegmental area:

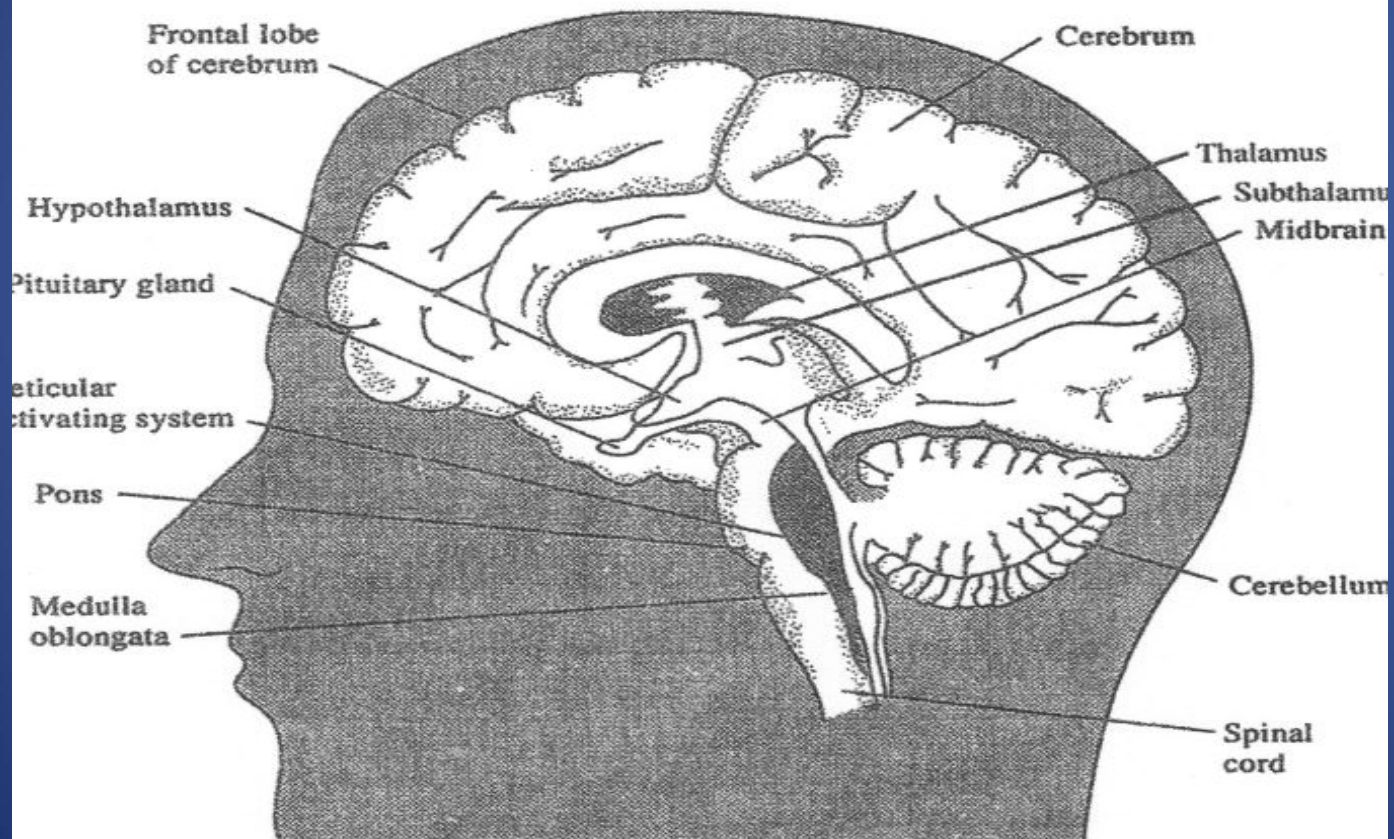
A nucleus in the ventral tementum that contains dopamine secreting neurons whose axons project to the forebrain, especially to the cortex and nucleus accumbens; thought to be important in arousal and reinforcement.

The Brain

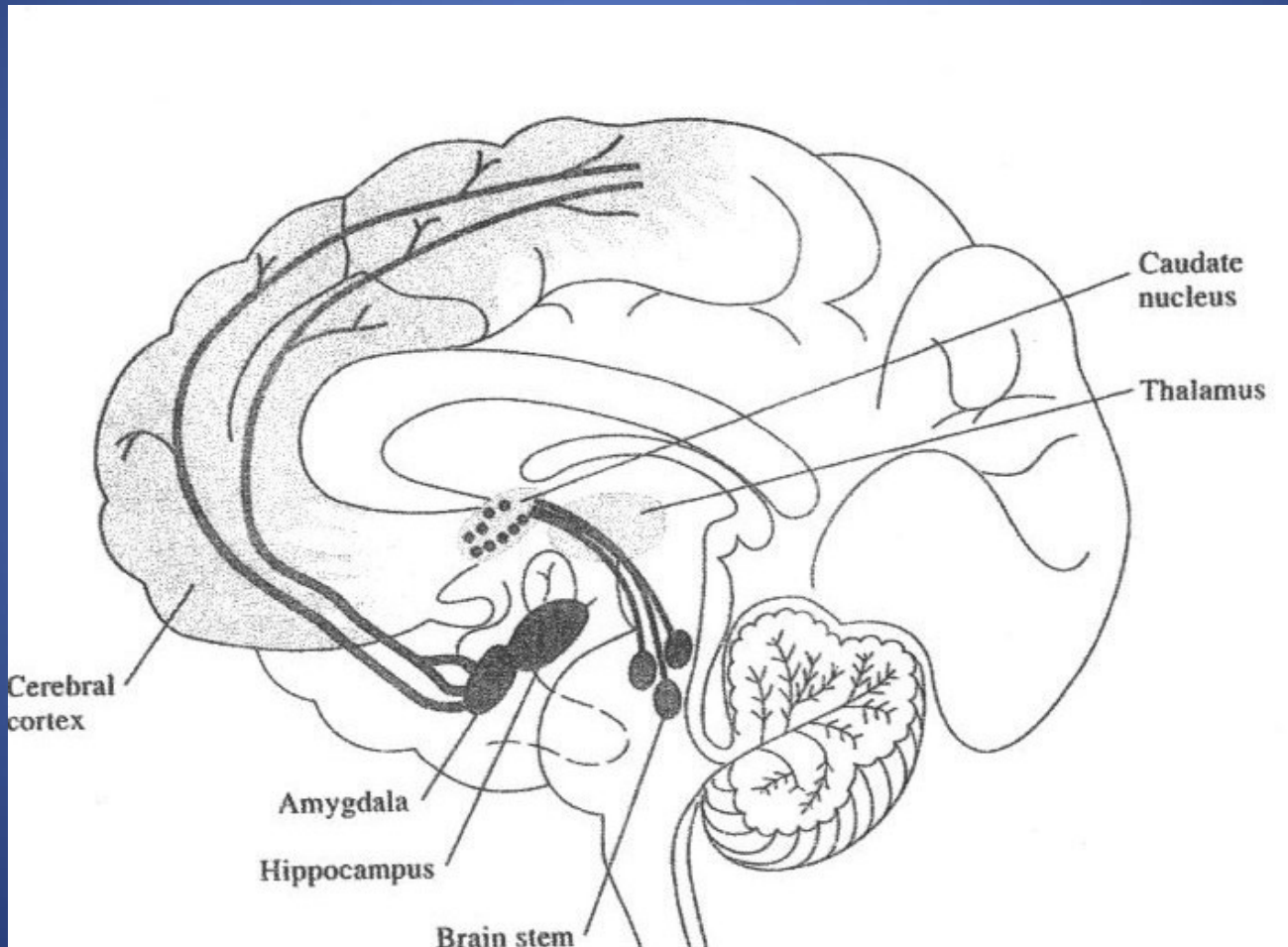


Brain

SPINAL CORD 445



Brain



Limbic System

The seat of all emotions

Amygdala

Hippocampus

Mammillary Bodies

Neuroadaptational Views Of Addiction

Incentive Salience:

The motivations or drug wanting. It is the psychological process that is responsible for instrumental drug-seeking and drug-taking behavior.

a-process:

This is the affective process one experiences when taking a drug.

b-process:

This is the biological process. This process has a slower decay.

Neuroadapational Views Of Addiction

The first few self-administration of a drug produce a pattern of motivational changes where the onset of the drug effects produces a euphoria that is the *a-process*. This eventually is followed by a decline in intensity.

The *b-process* emerges with cravings from the neurophysiological change. This then creates a craving state. This b-process gets larger and larger over time. This then results in a tolerance to the initial euphoric state of the drug and a-process.

Neuroadaptational Views Of Addiction

If the development of the b-process is blocked, no tolerance appears. (drugs that inhibit craving thus are effective)

Allostasis & Neuroadaptation

The allostatic view indicates that not only does the b-process get larger with repeated drug taking, but the reward set point from which the a-process and b-process are anchored gradually shifts downward creating an allostatic state.

The allostatic state is fueled by dysregulation of neurochemical elements of reward circuits but also by the activation of brain and hormonal stress responses.

Allostasis & Neuroadaptation

- This dysregulation is associated with specific neurotransmitter function in the extended amygdala (this includes the central nucleus of the amygdala, bed nucleus of the stria terminalis and the shell of the nucleus accumbens).
- Decreases in the functioning of GABA, dopamine, serotonin, and opioid peptides, as well as dysregulation of the brain stress systems contribute to the shift in the reward set point.

Allostasis & Neuroadaptation

- A combination of the above neurobiological changes are the key elements in the development of addiction and the **chronic** elevation in the reward thresholds.

Neurocircuitry Hypotheses Of Addiction

Mesolimbic Dopamine Reward Hypothesis of Addiction (Wise 1980)

The actions of drugs of abuse affect the reward system of the brain by changing the dopaminergic synapse where all reward sites are located.

Two components of the brain reward system are affected:

1. Myelinated fibers of the medial forebrain bundle.
2. Ventral tagmental dopamine system that synapse directly on the dopamine link.

Later the mesolimbic dopamine system was added.

Stimulants excited the action, Depressants diminished the dopamine reward link.

Neurocircuitry Hypotheses Of Addiction

Mesolimbic Dopamine Reward Hypothesis of Addiction Updates (Wise 2002)

There is also an operant condition that takes effect. The memories of early drug experiences are “stamped in” by the same reinforcement process that stamps in ordinary habits.

There are also neuroadaptations within the mesolimbic dopamine system . The mesolimbic dopamine system via its cortical inputs and nucleus accumbens output comprise a major portion of the endogenous circuitry through which pleasures of the flesh come to shape the habits of an individual.

Neurocircuitry Hypotheses Of Addiction

Wise has moved the role of dopamine more from a primary reward function to the preoccupation/anticipation or craving stage.

Neurocircuitry Hypotheses Of Addiction

Motive Circuits: Prefrontal Cortex/Ventral Striatal Hypotheses of Addiction (Jentsch & Taylor 1999)

Regions of the frontal cortex are involved in inhibitory response control that are directly affected by long-term exposure to drugs of abuse.

Drug seeking behavior is due to two related phenomena:

1. Increased incentive motivational qualities of the drug and drug associated stimuli due to limbic/amygdalar dysfunction.
2. Impaired inhibitory control due to frontal cortical dysfunction.

Neurocircuitry Hypotheses Of Addiction

- Drugs and drug associated stimuli rely on dopaminergic function in the nucleus accumbens. This modulates behavioral output.
- The amygdala and prefrontal cortex contribute to learning about the associations between drugs and external and internal cues and also may contribute to impulsivity.
- As lesions occur in the amygdala, they may block the conditioned reward creating a suppression in behavior produced by a fear stimuli and also prevent the development of autonomic responses to primary or secondary conditioned stimuli. This may result in needing more of a drug to get where a person wants to be.

Neurocircuitry Hypotheses Of Addiction

- Lesions of the frontal cortex can lead to larked cognitive impairments including disinhibition.

Neurocircuitry Hypotheses Of Addiction

Frontal Cortex Dysfunction, Cognitive Performance, and Executive Function: Disruption of Frontocerebellar Circuitry and Function in Alcoholism (1997 & 2003)

- Classical neuropsychological behaviors that are typical of frontal lobe dysfunction characterize alcoholics and include impaired judgment, blunted affect, poor insight, social withdrawal, reduced motivation, and attention deficits.
- Evidence for alcohol induced abnormalities in frontal lobes and cerebellum that are of particular relevance to these alcohol-related impairments in cognitive function.
- Alcoholics may require more extensive activation of frontal lobe function to maintain normal performance in cognitive tasks.

Neurocircuitry Hypotheses Of Addiction

Brain Circuitry for Addiction From Brain Imaging Studies (Volkow, Fowler and Wang 2003)

Four circuits that are disrupted in drug addiction:

1. Reward, localized to the nucleus accumbens and ventral pallidum.
2. Motivation/drive, localized to the orbitofrontal cortex and the subcallosal cortex.
3. Memory and learning, localized to the amygdala and hippocampus.
4. Control, localized to the prefrontal cortex and anterior cingulate gyrus.

Neurocircuitry Hypotheses Of Addiction

- Individuals who became drug abusers or addicted showed long lasting decreases in the number of dopamine receptors in the striatum.
- Cocaine abusers have reduced dopamine release.
- Therefore, decreased dopamine receptors and decreases in dopamine system activity results in decreased sensitivity of reward circuits to stimulation of natural reinforcers. This would put individuals at greater risk for seeking drug stimulation to temporarily activate these reward circuits.

Neurocircuitry Hypotheses Of Addiction

- There were also disruption of the motivation/drive circuit in addicts. The orbitofrontal cortex is hyperactive in active cocaine abusers during intoxication, during presentation of cocaine associated cues and during presentation of cigarette associated cues. But, hypoactive during withdrawal . Because increased orbitofrontal activation is seen in OCD, activation of this structure may contribute to the compulsive nature of drug taking.

Neurocircuitry Hypotheses Of Addiction

- Amygdala/prefrontal systems may be involved in conditioning how neutral stimuli paired with drug taking acquire reinforcing properties and motivation.
- The amygdala and anterior cingulate have been shown to be activated during intoxication and during craving induced by drug exposure.

Neurocircuitry Hypotheses Of Addiction

- Disruption of the prefrontal cortex would impair the inhibitory control and decision making that leads drug addicts to choose immediate rewards over delayed reward and could contribute to the loss of control over intake.

Neurocircuitry Hypotheses Of Addiction

Impaired Response Inhibition and Salience Attribution Syndrome of Addiction (Goldstein & Volkow 2002, Volkow, Fowler, Wang 2003)

- The activity in the prefrontal circuits and the subcortical reward pathways are differentially represented at various stages of the use/relapse cycle (drug reinforcement, craving, bingeing and withdrawal).
- During the drug intoxication stage, strong positive and negative reinforcement effects are strengthened through repeated administration of the drug. The prefrontal and orbitofrontal cortex are activated.
- During the relapse and bingeing stage, high levels of brain activation have been observed in the prefrontal cortex and orbitofrontal cortex. There is an increase in glucose metabolism and cerebral blood flow in the frontolimbic area.
- During the drug withdrawal, brain metabolism is lower in the orbitofrontal cortex, frontal cortex and the anterior cingulate.

Neurocircuitry Hypotheses Of Addiction

Brain Circuitry of Reinstatement of Drug Seeking (Kalivas & Mcfarland 2003, Shaham, Shalev, Lu, Dewitt, and Stewart 2003)

- Reinstatement of drug-seeking behavior by the drug itself (drug priming), drug cues, or stressors converge on the medial prefrontal cortex and output through the core of the nucleus accumbens.
- Changes from the above result in changes in the glutamate system neurotransmission creating a vulnerability to relapse.
- Three stimuli that may result in the above happening include:
 - Exposure to pharmacological stimuli that are similar to the drug of choice
 - Exposure to an environmental stimuli
 - Exposure to stress

Neurocircuitry Hypotheses Of Addiction

- The dorsal prefrontal cortex, core of the nucleus accumbens, and the ventral pallidum, but not the amygdala, appear to play a role in relapse.
- However; the medial prefrontal cortex and amygdala appear to be particularly involved in cue induced relapse.
- Stress induce relapse may be associated with a link between the extended amygdala and the prefrontal cortex and the nucleus acumbens.

Neurocircuitry Hypotheses Of Addiction

Drug Addiction & Relapse: Amygdala and Corticostriatopallidal Circuits (Everitt & Wolf 2002; Fuchs, Ledford & McLaughlin 2003)

- Cocaine related cue activate the amygdala
- Cue induced relapse depends on a circuit the involves the amygdala, prefrontal cortex and the core of the nucleus accumbens.
- Also included in the activation of the amygdala & the nucleus accumbens is the Pavlovian instrumental transfer (learned response)
- There may also be activation of the corticostriatal loops (cortisol).

Neurocircuitry Hypotheses Of Addiction

Drugs of Abuse: Anatomy, Pharmacology and Function of Reward Pathways (Koob 1992)

- The interaction of drugs of abuse engage rewards pathways consisting of a midbrain-forebrain-extrapyrmidial circuit with focus on the nucleolus accumbens.
- Three neurochemical systems were involved in the initial reinforcing (rewarding) actions of drugs of abuse. These included dopamine, opiod and GABBA.
- Koob also proposed a neurobiological circuit for drug reward. The starting point for the reward circuit was the medial forebrain bundle which is composed of myelinated fibers connecting the olfactory bulbs and the nucleus accumbens with the hypothalamus and the ventral tegmental area.

Neurocircuitry Hypotheses Of Addiction

- Drug reward was dependent on dopamine release in the nucleus accumbens for cocaine and amphetamine, opioid receptor activation in the ventral tegmental area and nucleus accumbens for alcohol

Neurocircuitry Hypotheses Of Addiction

Neural Substates of Alcohol self-administration: Neurobiology of High Alcohol Drinking Behavior (McBride and Li 1998)

- A neurocircuit with focal points in the ventral tegmental area, nucleus accumbens and the extended amygdala mediates the acute reinforcing effects of alcohol.
- There is neurochemical changes in four key neurochemical systems – dopamine, serotonin, GABA and opioid peptide resulting in acute reinforcing action of alcohol.
- Changes in these systems at specific points in the neurocircuit may convey vulnerability to the excessive alcohol consumption of alcoholism.

Neurocircuitry Hypotheses Of Addiction

Stress, Dysregulation of Drug Reward Pathways and Drug Addiction (Aston-Jones and Harris 2004)

- Drugs of abuse acutely activate the hypothalamic-pituitary-adrenal response to stress, and as dependence develops ultimately engage brain stress systems.
- The brain and brain pituitary stress systems have a role in the initial vulnerability to drugs of abuse.
- High initial corticosterone responses creates increased activity and blockage of the secretion of cortisone decreases psychomotor responses to cocaine.
- The brain stress systems involving NE may be activated during the development of dependence and contribute to the motivation for excessive drug-seeking associated behavior.

Neurocircuitry Hypotheses Of Addiction

- The hypothalamic-pituitary-adrenal hormonal stress system and the brain stress systems are engaged by drugs of abuse and may contribute to not only the initial vulnerability to take drugs but also the development of dependence and vulnerability to relapse.
- The hypothalamic-pituitary-adrenal hormonal stress system appears to have an important role in the initiation of drug seeking and in the maintenance of drug taking behavior.
- The brain's extrahypothalamic stress systems appear to have a more important role in the motivational effects of both acute withdrawal and protracted abstinence and stress induced reinstatement.

COCAINE

- PET showed increased glucose metabolism in cortical and limbic regions implicated in several forms of memory in long-term cocaine abusers exposed to cocaine related cues and drug paraphernalia.
- Cravings resulted in metabolic increases in the prefrontal cortex, temporal lobe (amygdala) and the cerebellum.
- Cocaine cues resulted in left hemisphere activation of the lateral amygdala, lateral orbitofrontal cortex, rhinal cortex and the right hemispheric activation of the dorsolateral prefrontal cortex and cerebellum.
- A decrease in grey matter is also identified and minimal white matter decrease is noted.

Alcohol

- Decreased blood flow mainly in the frontal and temporal cortical regions.
- The limbic-basal ganglia and thalamus networks were involved in the loss of control in alcohol intake associated with alcoholism.
- Acute and chronic withdrawal have shown decreases in brain metabolism that resolve over time, with more recovery the longer the detoxification.
- Deficit in brain metabolism began to disappear after the second week of abstinence and returned to normal after two months.

Alcohol

- Abstinent alcohol abusers showed that deficits in the brain metabolism, blood flow and cognitive performance improved with the passage of time.
- Alcoholics drinking for more than 15 years show a reduced brain wt.
- Lesions and atrophy were present in majority of chronic alcoholics and it is only partially reversible during abstinence.
- 20% reduction of neuronal loss in specific regions including the frontal association area, hypothalamus, thalamus and cerebellum.
- Female alcoholic showed greater loss of grey matter than males

Opioids

- Decreased cerebral glucose metabolism in the whole brain.
- When opioid addicts received heroin or placebo or are presented videos showing heroin injection scenes, PET scans showed that the effects of heroin and the drug video were centered on the amygdala and limbic cortices.
- In withdrawal, CBF is decreased as indicated by a SPECT mainly in frontal, temporal and parietal lobes at one week, but less at three weeks after last use.

Marijuana

- Increased brain metabolic activity in the orbitofrontal cortex, prefrontal cortex and basal ganglia.
- Increased CBF in frontal, temporal, parietal, thalamus and cerebellum.
- Evidence of tolerance effects in the frontal cortex in chronic users.
- Chronic users show decreased brain metabolism in frontal lobe and cerebellum.
- Heavy long term use is associated with structural changes in the hippocampus.