The Relationship Between the Reward and Stress Systems and How They are Perturbed in Addiction

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Koob, G. F. and Volkow. N. D. Neurocircuitry of Addiction, Neuropsychopharmacology Reviews 35 (2010) 217-238

Koob GF. Theoretical frameworks and mechanistic aspects of alcohol addiction: alcohol addiction as a reward deficit disorder. In: Spanagel R, Sommer W (eds) Behavioral Neurobiology of Alcohol Addiction (series title: Current Topics in Behavioral Neuroscience, 2013 Vol. 13), Springer, New York, pp. 3-30

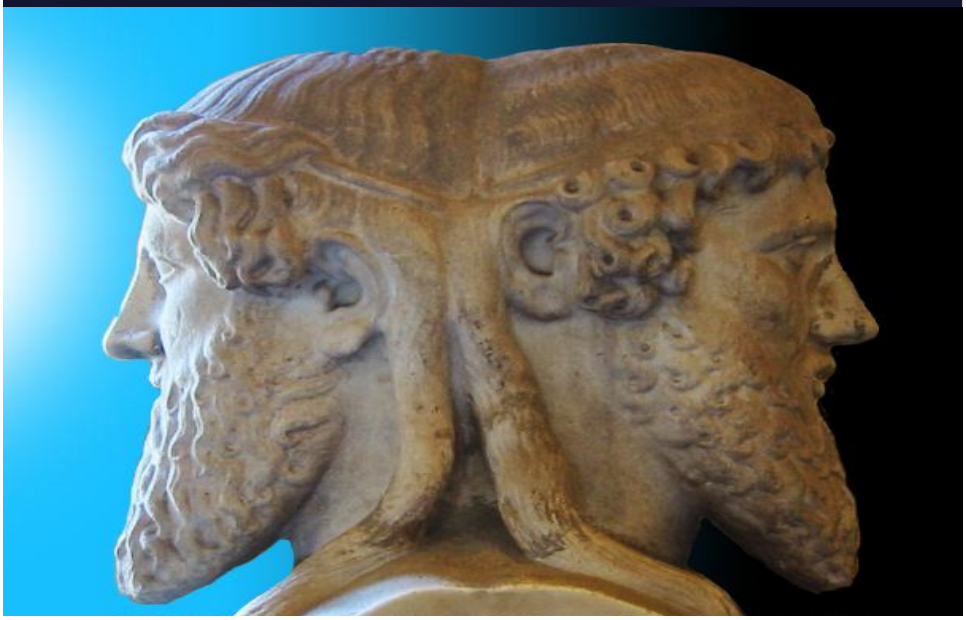
Learning Objectives

1. Understand a conceptual framework of addiction that goes beyond the acute rewarding effects of drugs

2. Understand the neuroplasticity in the brain reward, stress systems and executive function systems associated with the transition to addiction

3. Understand how such knowledge may predict vulnerability and novel treatments for addiction

Stress and Reward: The Two Faces of Janus



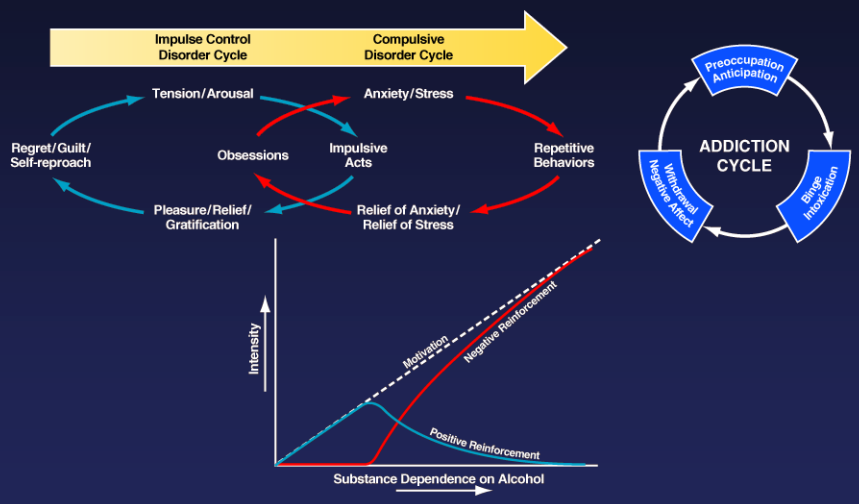
Bottom lines

1. Addiction is an incentive salience disorder
2. Addiction is a reward deficit disorder
3. Addiction is a stress surfeit disorder
4. Addiction is a self-regulation disorder

Addiction

Addiction — **can be defined as a chronically relapsing disorder that is characterized by a compulsion to seek and take drug or stimulus, loss of control in limiting intake, and emergence of a negative emotional state (e.g. dysphoria, anxiety, irritability) when access to the drug or stimulus is prevented (here, defined as the "dark side" of addiction)**

Theoretical Framework Relating Addiction Cycle to Motivation for Drug Seeking



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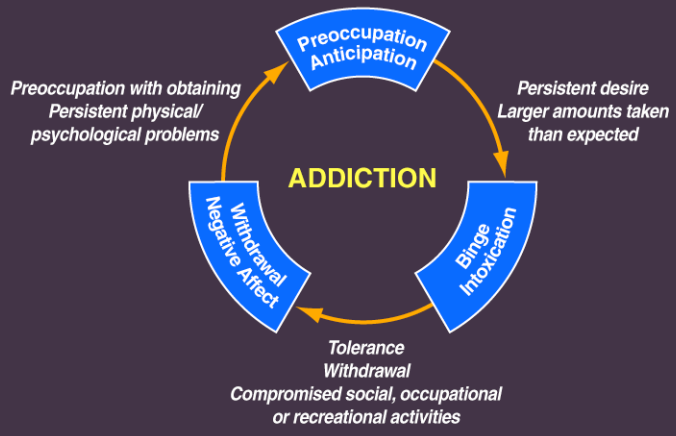
Positive and Negative Reinforcement- Definitions

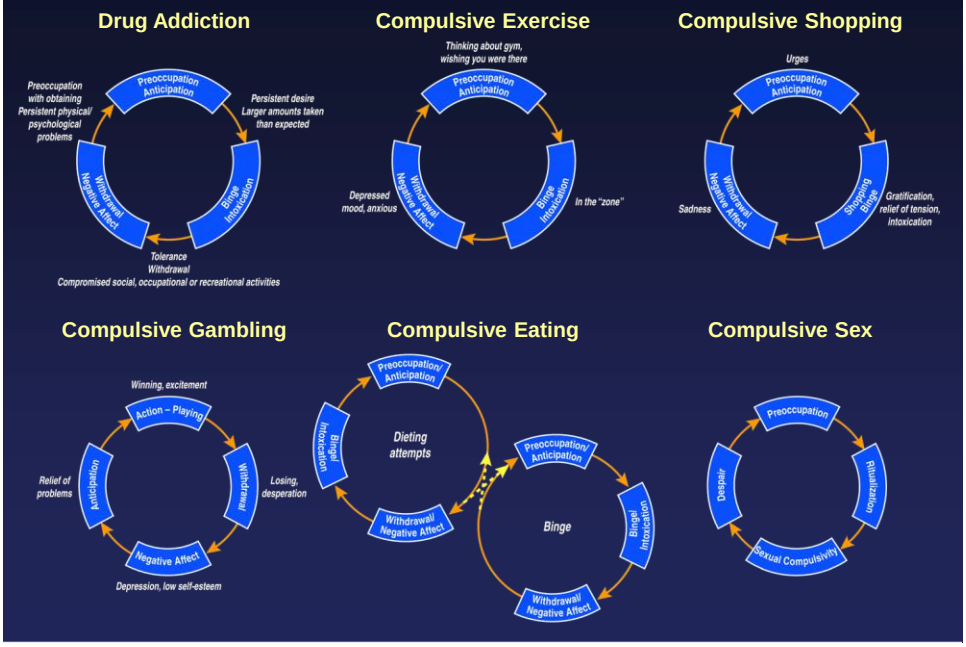
Positive Reinforcement — defined as the process by which presentation of a stimulus (drug) increases the probability of a response (non dependent drug taking paradigms).

Negative Reinforcement —defined as a process by which removal of an aversive stimulus (negative emotional state of drug withdrawal) increases the probability of a response (dependence-induced drug taking)

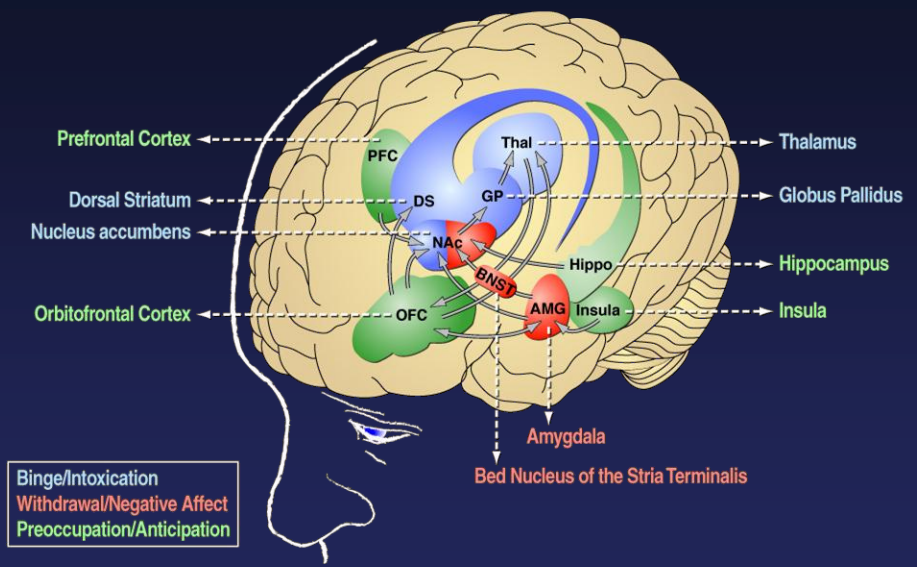
Stages of the Addiction Cycle



Non Drug "Process" Addiction Cycles

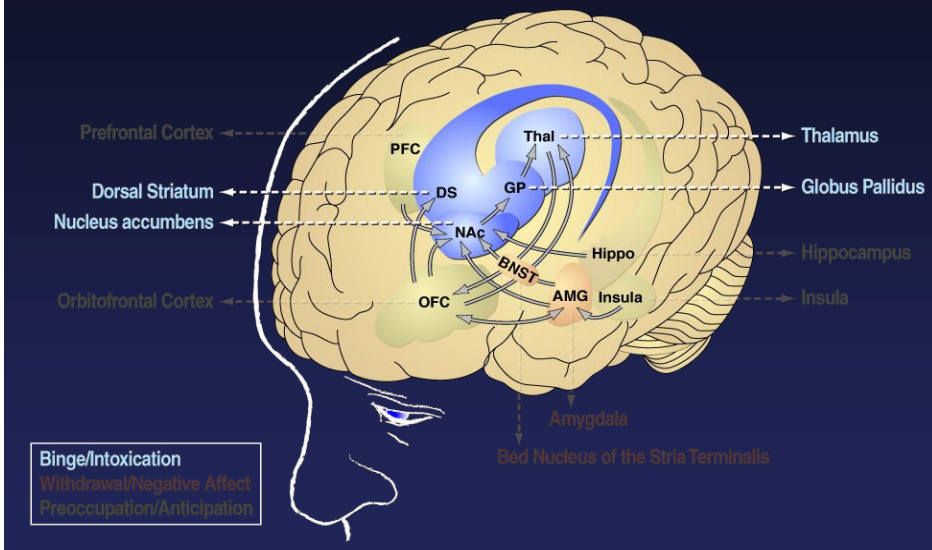


Neurobiology of Addiction



From: Koob, G. F. and Volkow. N. D. Neurocircuitry of Addiction, Neuropsychopharmacology reviews 35 (2010) 217-238

Binge-Intoxication Stage



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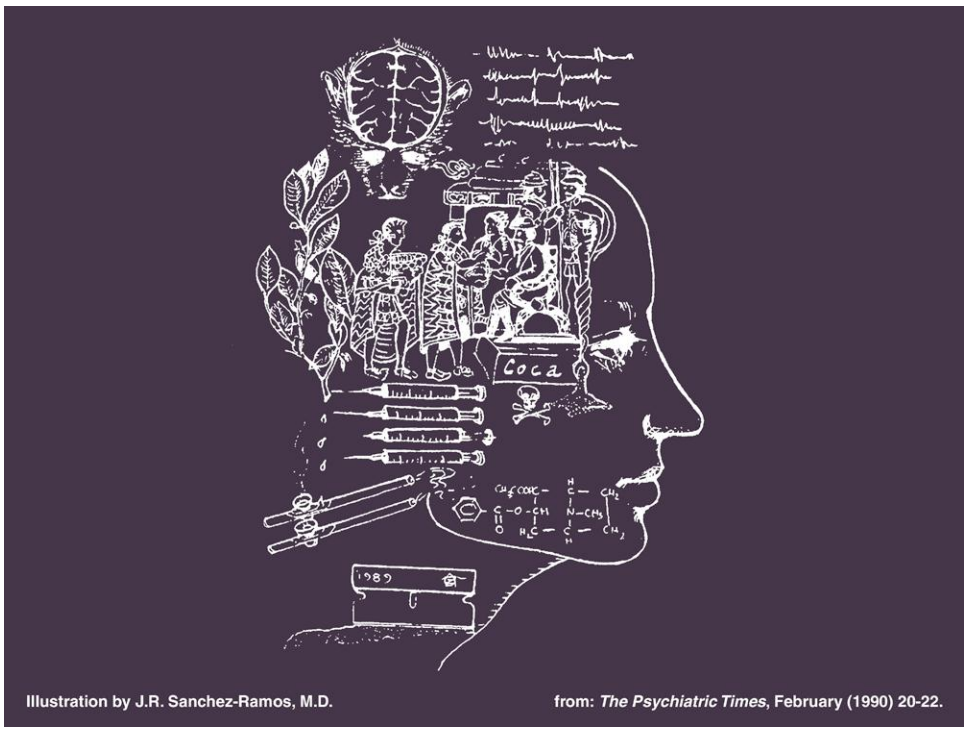
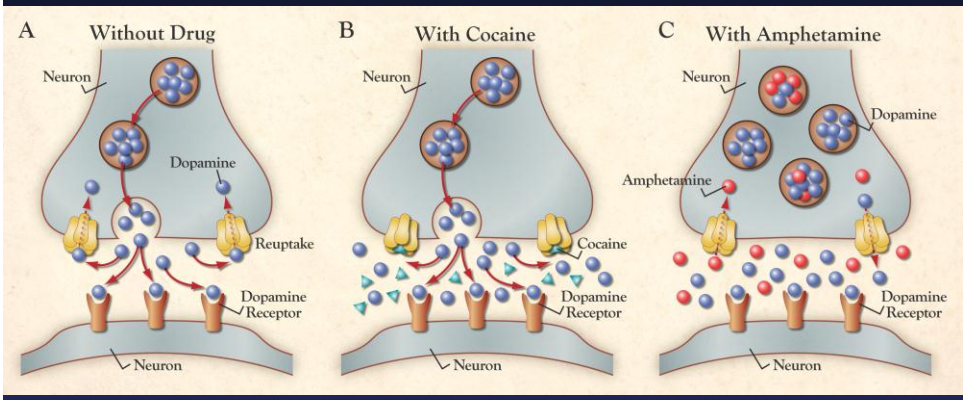


Illustration by J.R. Sanchez-Ramos, M.D.

from: *The Psychiatric Times*, February (1990) 20-22.

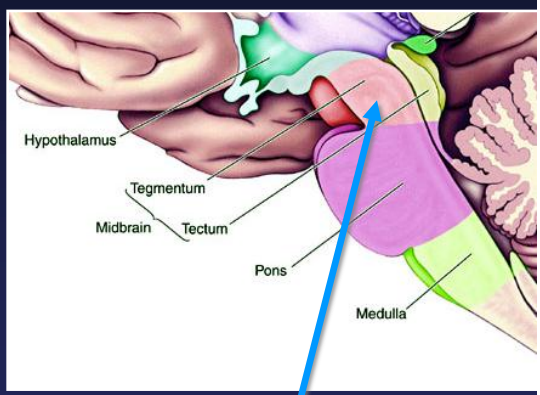
Effects of Cocaine and Amphetamine on Dopamine Synaptic Function

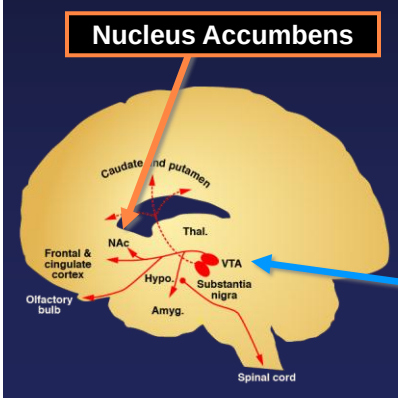


Mesolimbic Dopamine System

Mesolimbic dopamine system

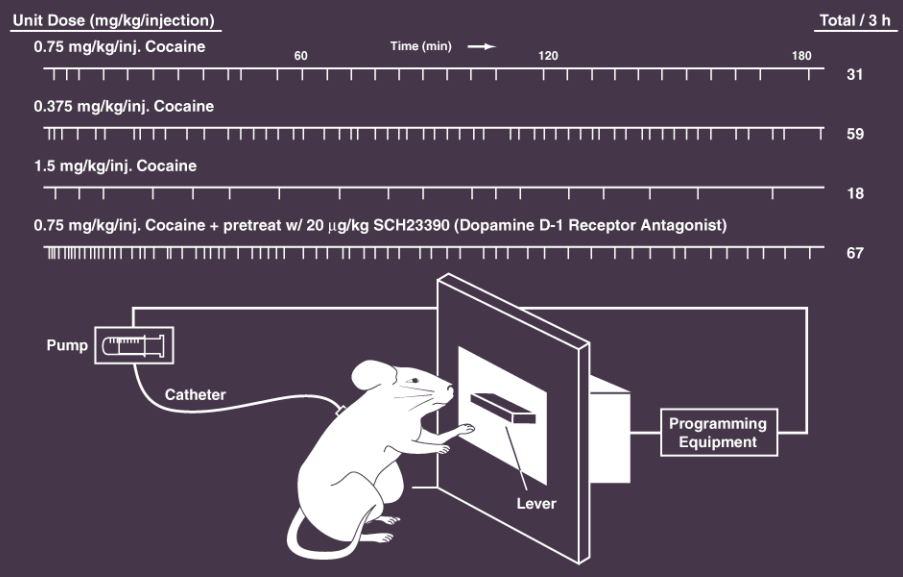
1. **Ventral tegmental area**
2. **Nucleus accumbens**





Ventral Tegmental Area (VTA)

Cocaine Self-Administration



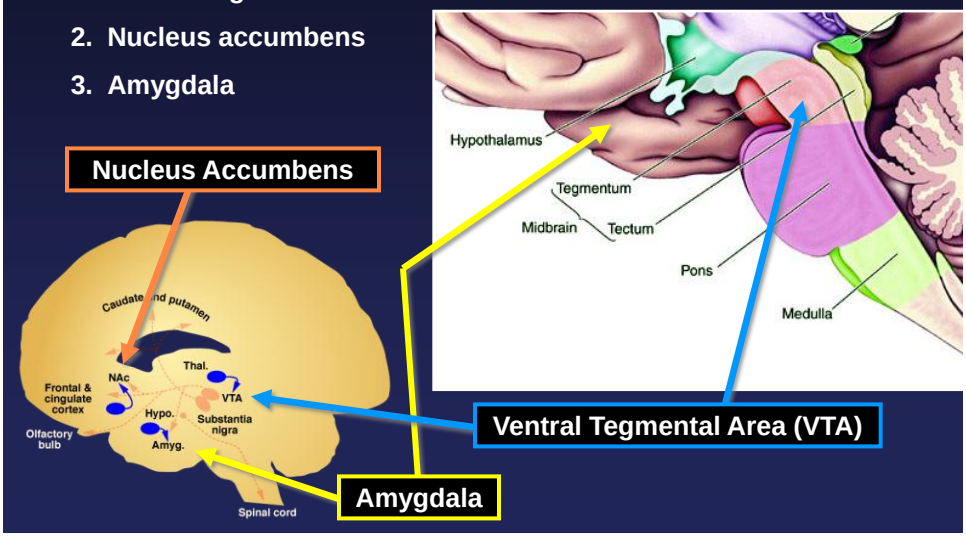
From: Caine SB, Lintz R and Koob GF. in Sahgal A (ed) Behavioural Neuroscience: A Practical Approach, vol. 2, IRL Press, Oxford, 1993, pp. 117-143.

Pieter Bruegel

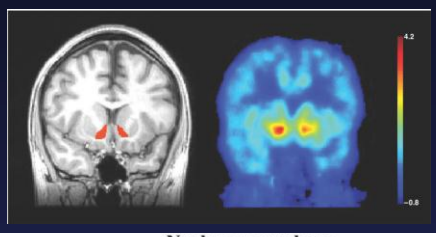
Opioid Peptide Reward System

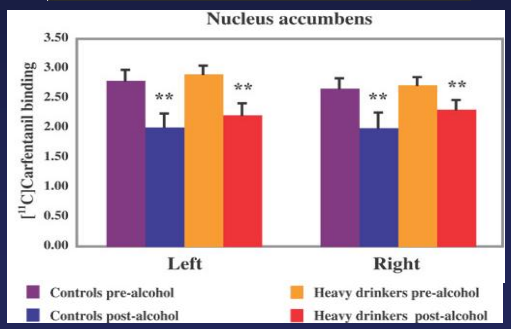
Enkephalin and endorphin reward system

1. **Ventral tegmental area**
2. **Nucleus accumbens**
3. **Amygdala**



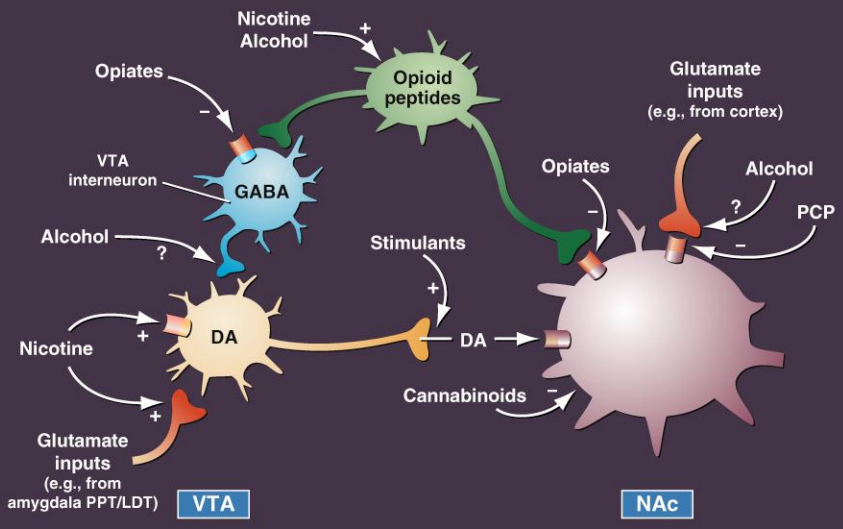
Alcohol Consumption Induces Endogenous Opioid Release in the Human Nucleus Accumbens





From: Mitchell JM, O'Neil JP, Janabi M, Marks SM, Jagust WJ, Fields HL. Sci Transl Med, 2012, 4:116ra6.

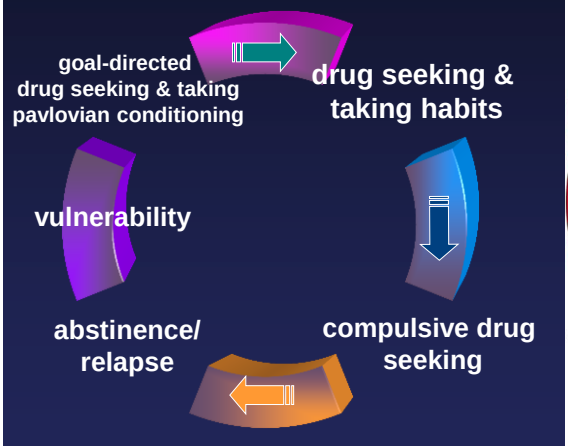
Converging Acute Actions of Drugs of Abuse on the Ventral Tegmental Area and Nucleus Accumbens



From: Nestler EJ, Nat Neurosci, 2005, 8:1445-1449.

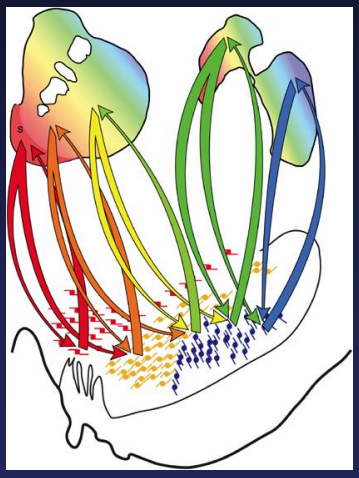
Neurocircuitry of Incentive Salience

The Ventral to Dorsal Striatal Shift: Ascending Spirals of VTA/Nigra-Striatal pathways

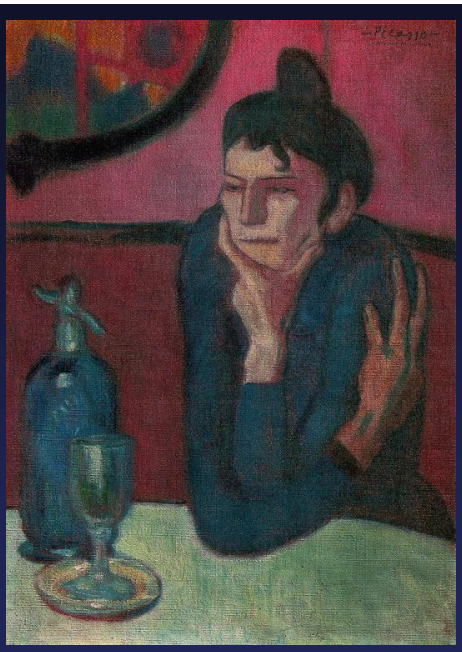


Everitt & Robbins 2005

Ikemoto 2007 - similar organization in rat brain

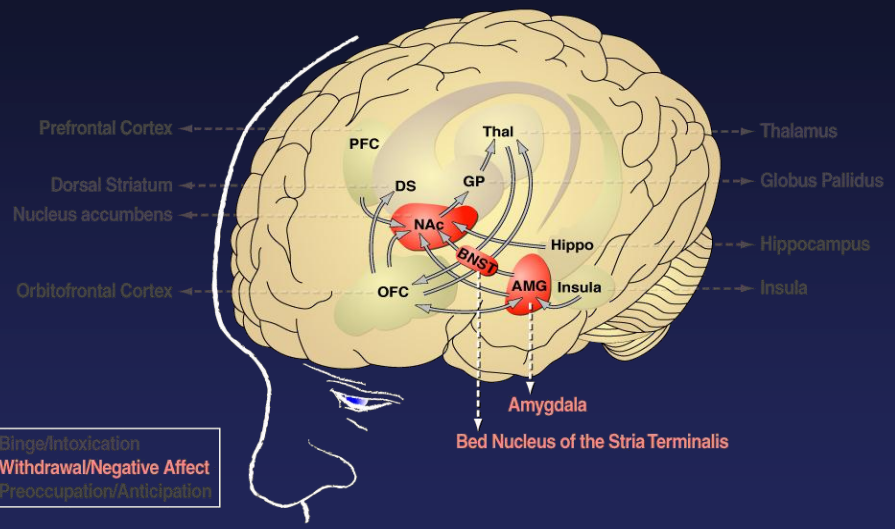


Haber et al. 2000



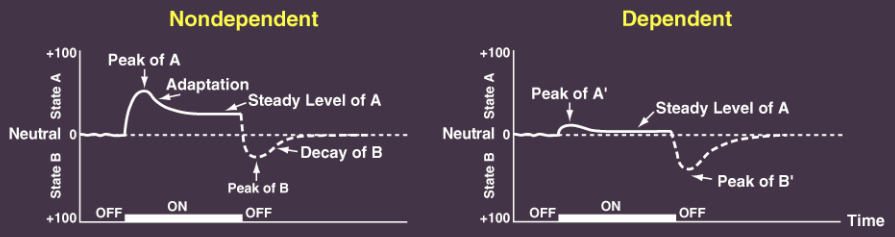
"Absinthe Drinker"
Pablo Picasso (1910)

Withdrawal-Negative Affect Stage



From: Koob, G. F. and Volkow. N. D. Neurocircuitry of Addiction, Neuropsychopharmacology Reviews 35 (2010) 217-238

Standard Pattern of Affective Dynamics Produced by Novel and Repeated Unconditioned Stimulus or "Opponent Process: What Goes Up Must Come Down"

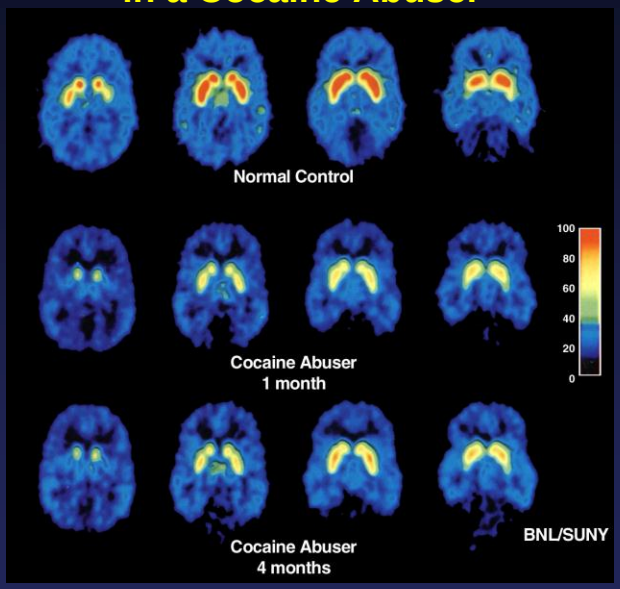


From: Solomon RL, American Psychologist, 1980, 35:691-712.

Reward Transmitters Implicated in the Motivational Effects of Drugs of Abuse

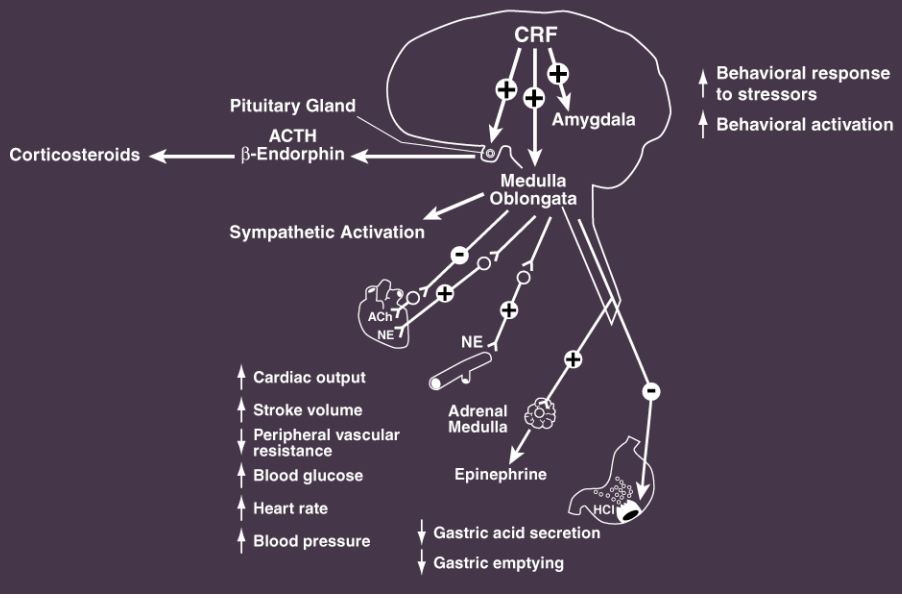
Positive Hedonic Effects	Negative Hedonic Effects of Withdrawal
↑ Dopamine	↓ Dopamine … "dysphoria"
↑ Opioid peptides	↓ Opioid peptides ... pain
↑ Serotonin	↓ Serotonin … "dysphoria"
↑ GABA	↓ GABA … anxiety, panic attacks

Decreased Dopamine D_2 Receptor Activity in a Cocaine Abuser



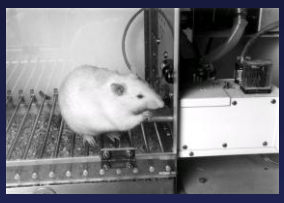
From: Volkow ND, Fowler JS, Wang GJ, Hitzemann R, Logan J, Schlyer DJ, Dewey S and Wolf AP, Synapse, 1993, 14:169-177.

CNS Actions of Corticotropin-Releasing Factor (CRF)



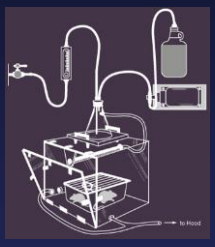
Rodent Model of Excessive Drinking During Withdrawal

Self-administration training → **Dependence induction** → **Withdrawal from alcohol vapors**



Sweetened solution fading used to train animals to lever press for:

10%w/v EtOH vs **Water**



Chronic intermittent alcohol vapors (4+ wks)

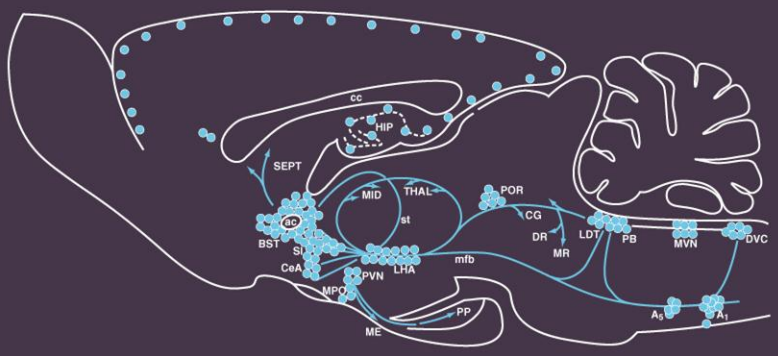
Target blood alcohol levels (BALs): 0.125-0.250 g%

Negative emotional state:
- Anxiety-like behavior
- Reward threshold deficits
- Increased CRF release in the extended amygdala

Excessive drinking:
- 2-3 fold higher alcohol intake
- Increased progressive ratio breakpoints
- Relapse following prolonged abstinence

Methods from:
Roberts AJ, Cole M and Koob GF, Alcohol Clin Exp Res, 1996, 20:1289-1298.
Roberts AJ, Heyser CJ, Cole M, Griffin P and Koob GF, Neuropsychopharmacology, 2000, 22:581-584.
O'Dell LE, Roberts AJ, Smith RT and Koob GF, Alcohol Clin Exp Res, 2004, 28:1676-1682.

Summary of Drugs of Abuse Interactions with Corticotropin-Releasing Factor Systems

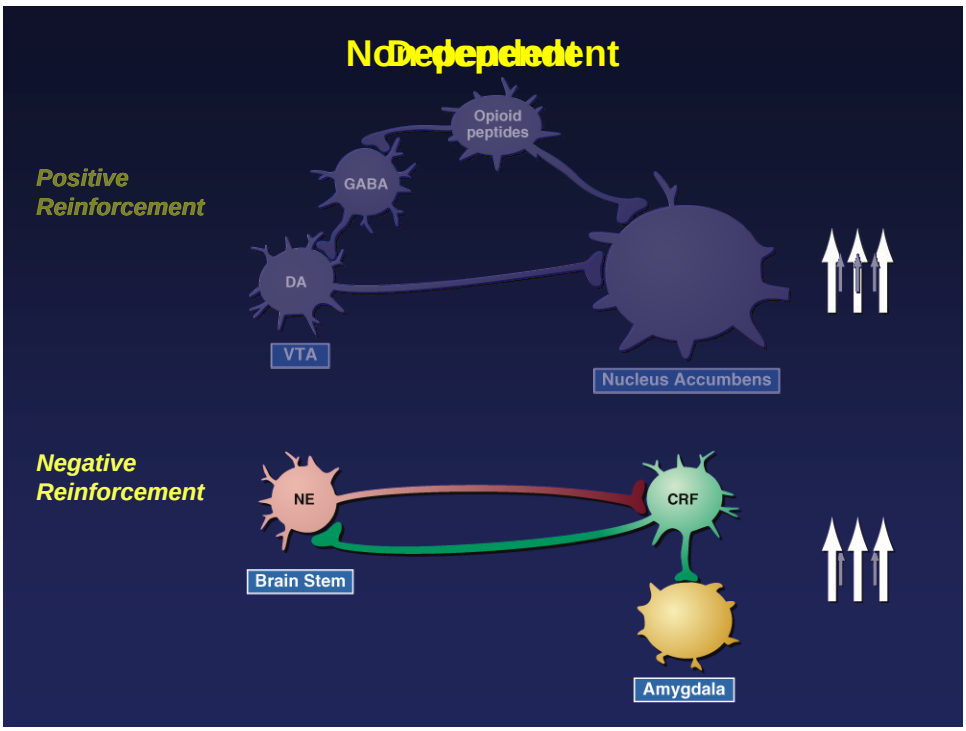


	CRF Antagonist Effects			
Withdrawal-induced changes in extracellular CRF in CeA	Withdrawal-induced anxiety-like or aversive responses	Baseline self-administration or place preference	Dependence-induced increases in self-administration	Stress-induced reinstatement
↑	↓	–	↓	↓

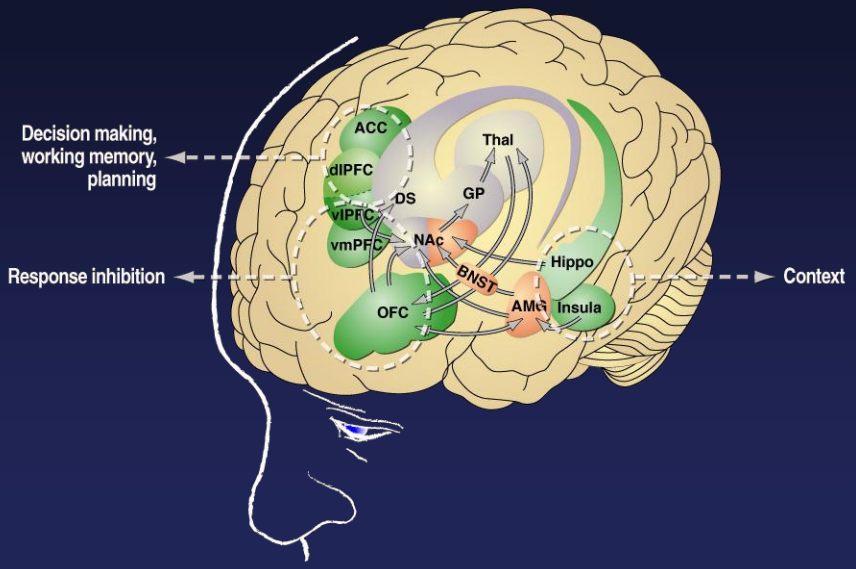
Modified from: Swanson LW, Sawchenko PE, Rivier J and Vale W, Neuroendocrinology, 1983, 36:165-186.
Koob GF, Neuron, 59:11-34

Anti-Reward Transmitters Implicated in the Motivational Effects of Drugs of Abuse

- ↑ Dynorphin … "dysphoria"
- ↑ CRF … stress
- ↑ Norepinephrine … stress



Neurobiology of Addiction: Preoccupation-Anticipation ("Craving") Stage



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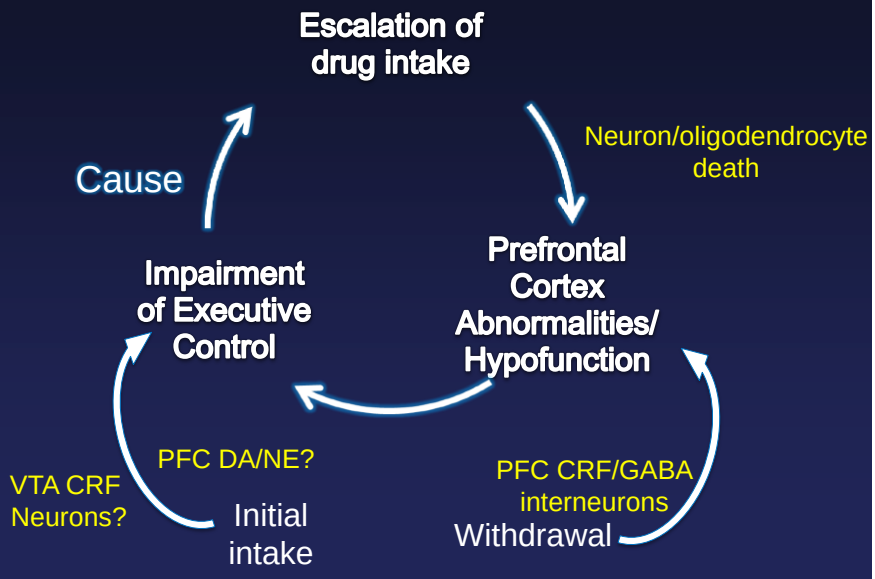
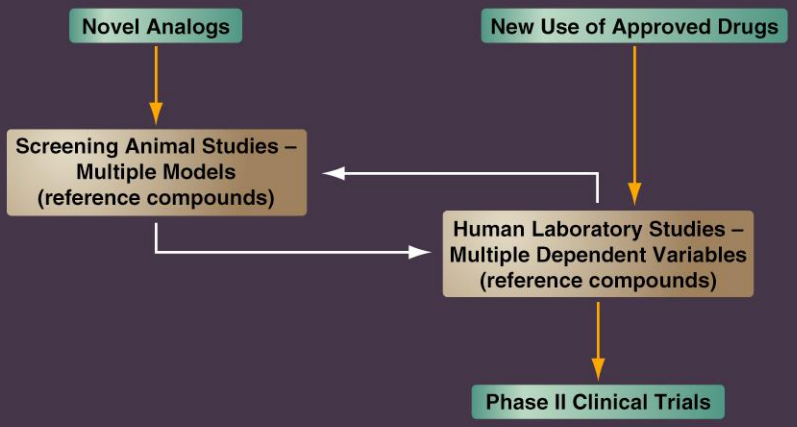
Loss of Control Over Intake — Self-medication



Medications Development- A Rosetta Stone Approach



From: Koob GF, Lloyd GK, Mason BJ. Nat Rev Drug Discovery, 2009, 8:500-515.

Future Targets for Medications Development Derived from Preclinical Basic Research

Class	Target
Dopamine receptor partial agonists	D_2 receptor partial agonist (aripiprazole) D_3 receptor partial agonist
Modulators of γ-aminobutyric acid	Gabapentin
Modulators of brain stress systems	CRF_1 receptor antagonist Dynorphin antagonist Neurokinin-1 receptor antagonist
Modulators of glutamate	AMPA receptor antagonist NMDA receptor antagonist Metabotropic glutamate receptor agonist Glutamate-5 receptor antagonist Topiramate

From: Koob GF, Lloyd GK, Mason BJ. Nat Rev Drug Discov, 2009, 8:500-515.

Bottom lines

1. Addiction is a facilitation of incentive salience - compulsive drug taking is associated with engagement of associative (stimulus response) mechanisms involving cortico-striatal-pallidal-thalamic loops that converge in the basal ganglia

2, Addiction is a reward deficit disorder- all drugs of abuse compromise reward function and decrease dopamine activity

3. Addiction is a stress surfeit disorder- all drugs of abuse sensitize brain stress systems such as CRF

4. Addiction is an executive system disorder- all drugs of abuse compromise frontal cortical executive function which disinhibits impulsivity and disinhbits the brain stress systems

Learning Objectives

1. Understand a conceptual framework of addiction that goes beyond the acute rewarding effects of drugs

2. Understand the neuroplasticity in the brain reward, stress systems and executive function systems associated with the transition to addiction

3. Understand how such knowledge may predict vulnerability and novel treatments for addiction

Neurobiology of Drug Addiction
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Prefrontal Cortex, c-Fos, CRF, and executive function

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Support from:

National Institute on Alcohol Abuse and Alcoholism
National Institute on Drug Abuse
National Institute of Diabetes and Digestive and Kidney Diseases
Pearson Center for Alcoholism and Addiction Research