

Neurobiology of Addiction: A Reward Deficit, Stress Surfeit and Executive Function Disorder

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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), Springer, New York, in press.

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**

Bottom lines

- 1. Addiction is a reward deficit disorder**
- 2. Addiction is a stress surfeit disorder**
- 3. 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)

Positive Reinforcement, Negative Reinforcement, Reward- Definitions

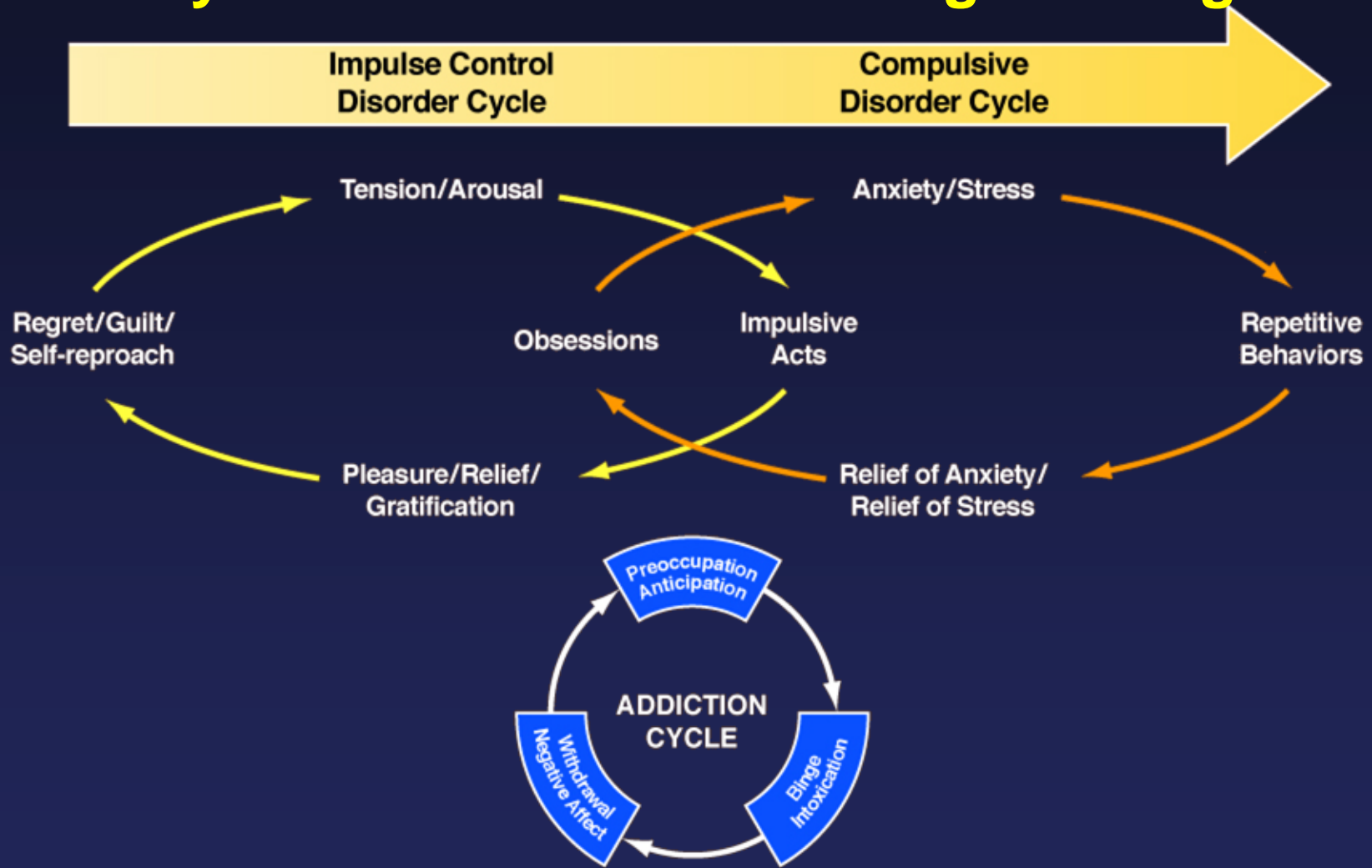
Positive Reinforcement — defined as the process by which presentation of a stimulus (drug) increases the probability of a response (non dependent drug taking paradigms).

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)

Reward — defined as a defined as a stimulus (drug) that increases the probability of a response, but usually includes a positive hedonic connotation

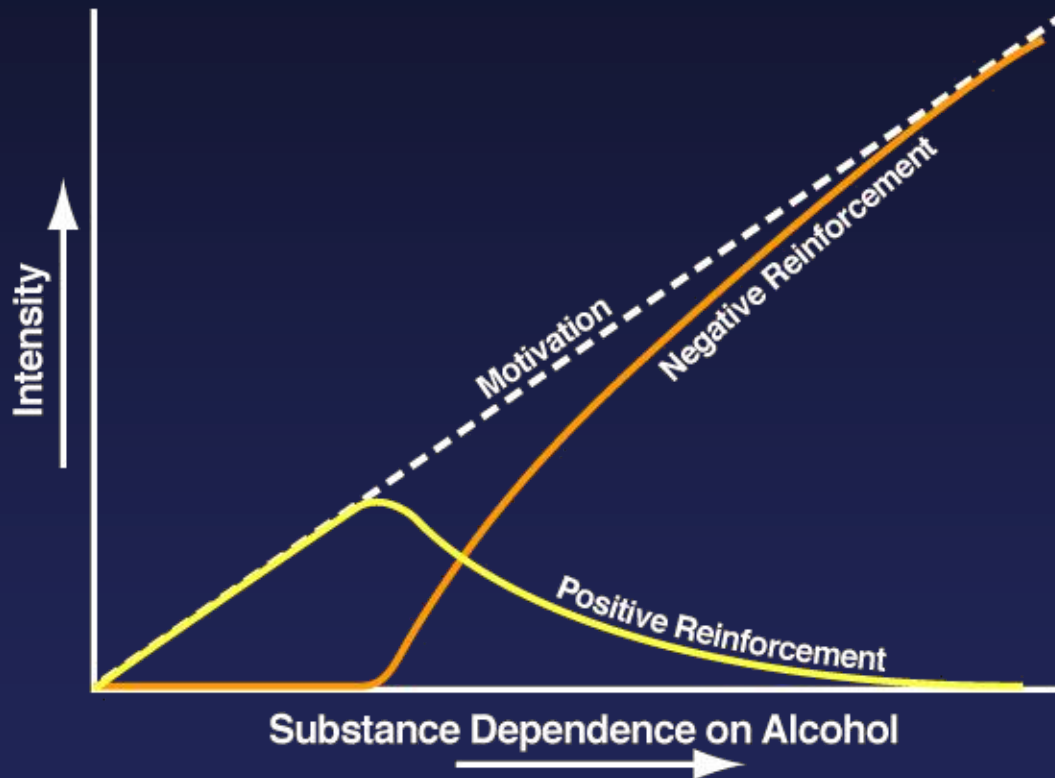
Punishment — defined as a process by which presentation of an aversive stimulus decreases the probability of a response

Theoretical Framework Relating Addiction Cycle to Motivation for Drug Seeking



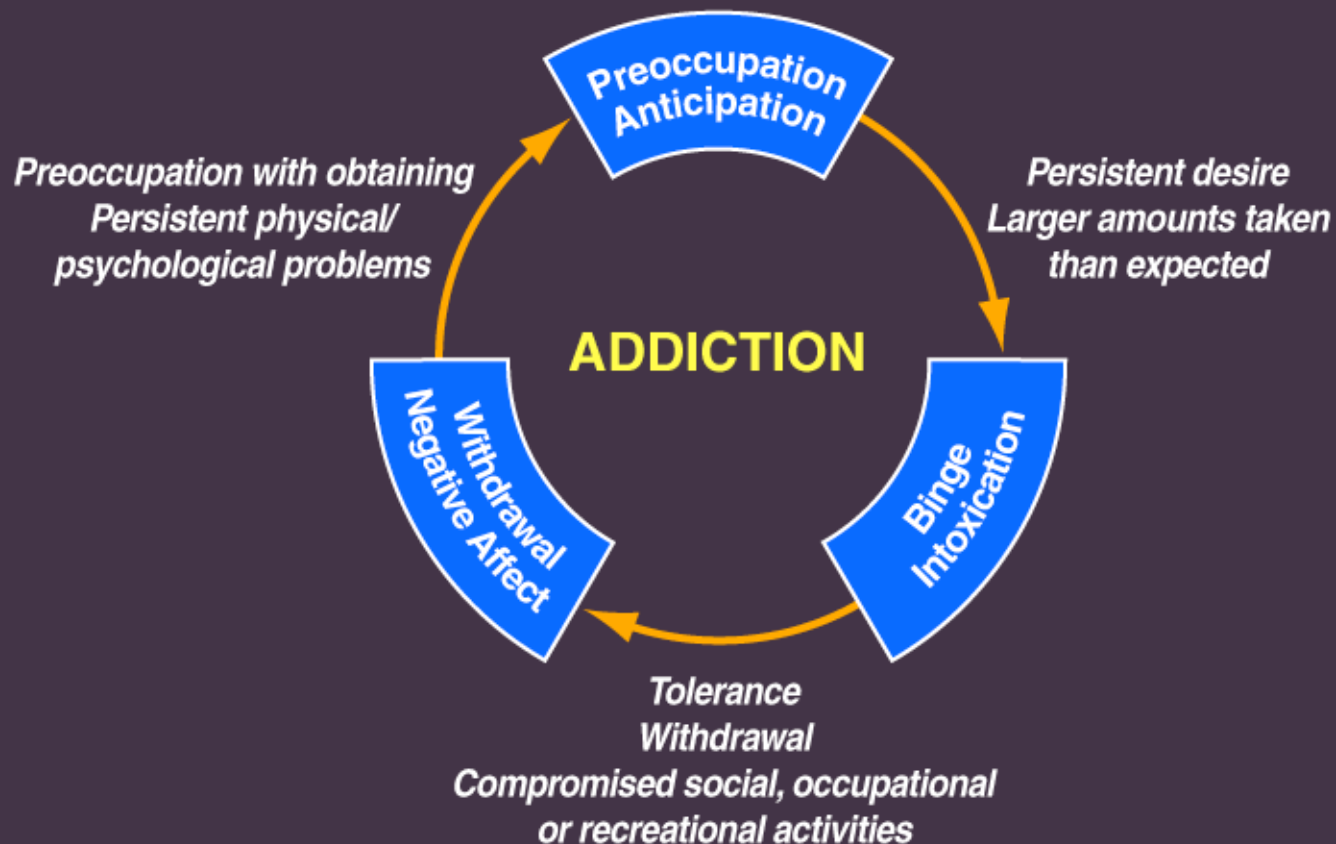
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Theoretical Framework Relating Addiction Cycle to Motivation for Drug Seeking



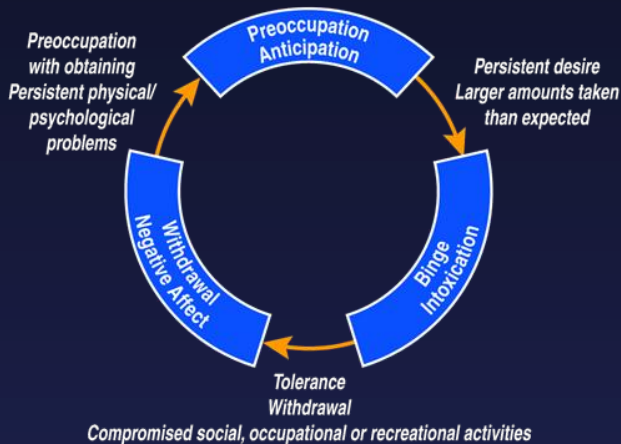
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Stages of the Addiction Cycle

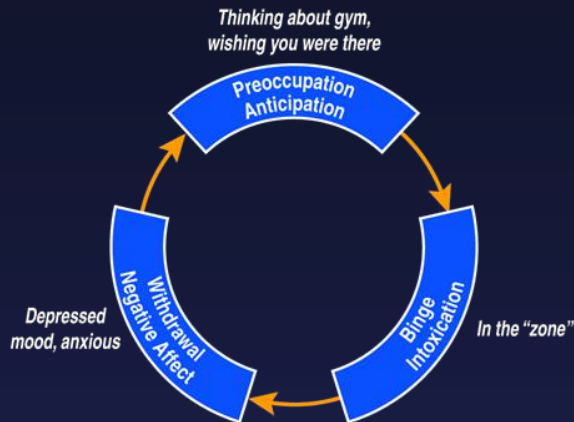


Non Drug “Process” Addiction Cycles

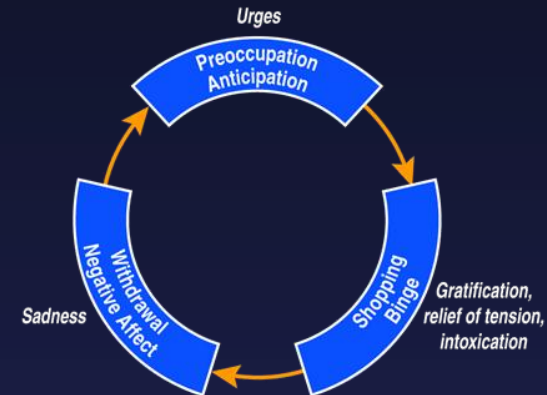
Drug Addiction



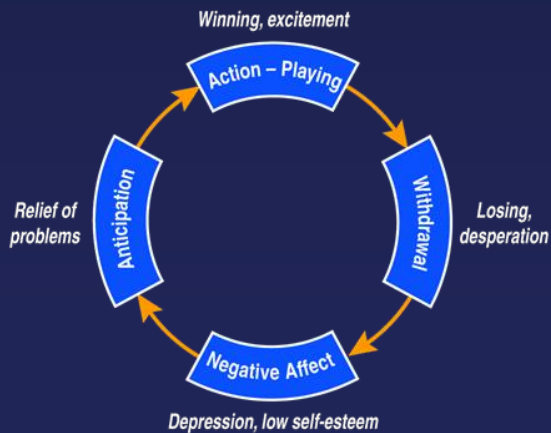
Compulsive Exercise



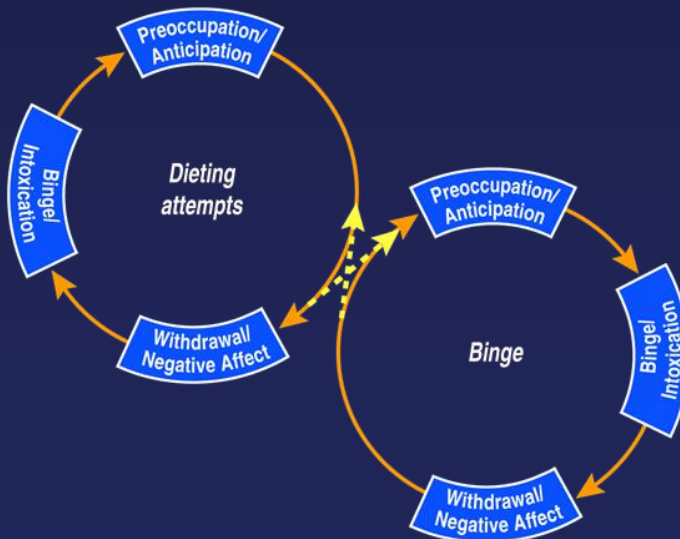
Compulsive Shopping



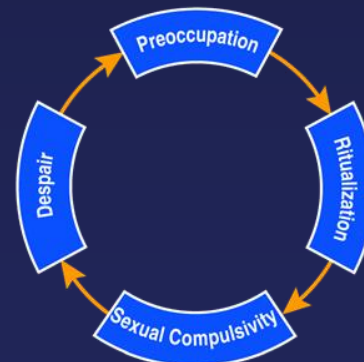
Compulsive Gambling



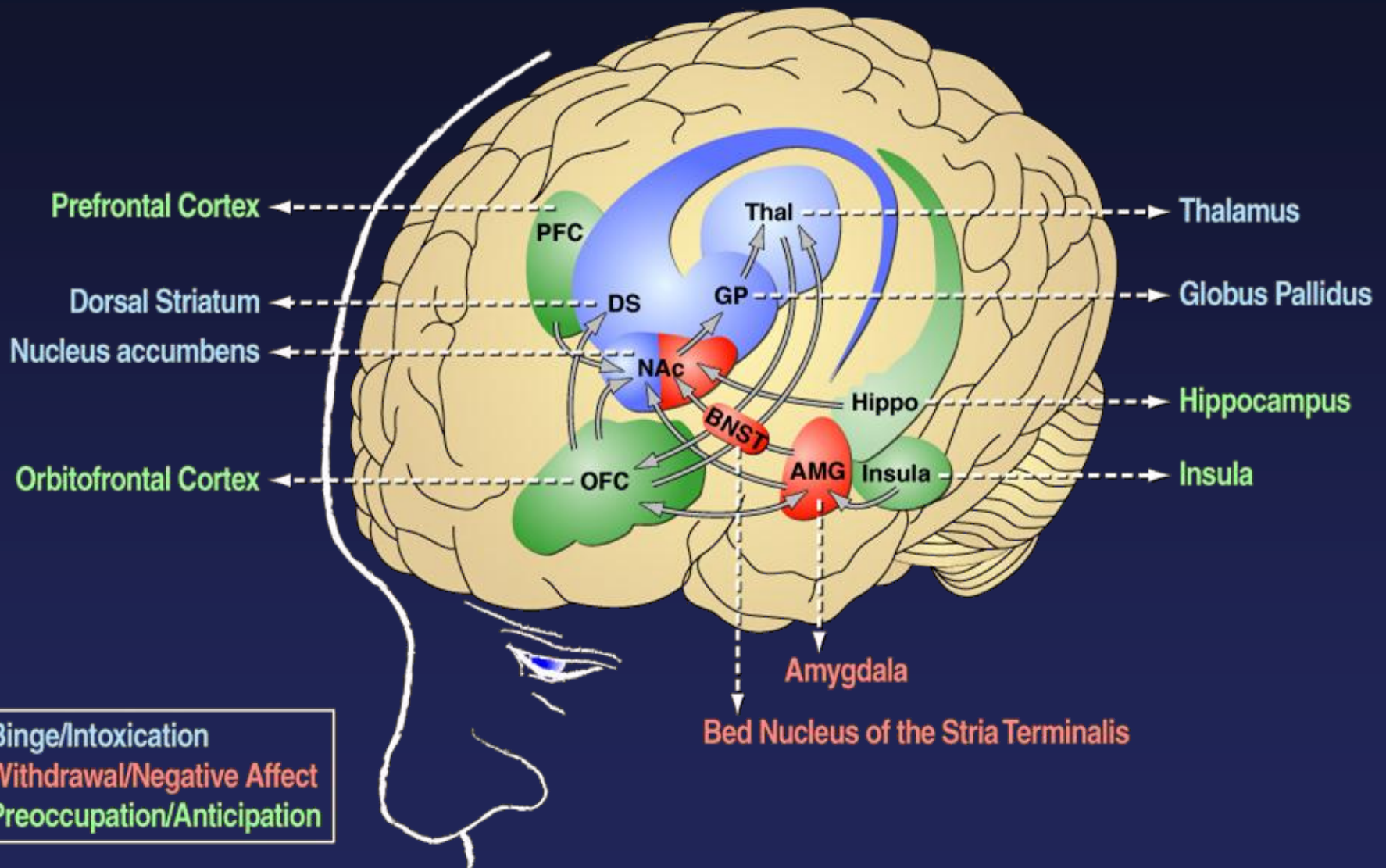
Compulsive Eating



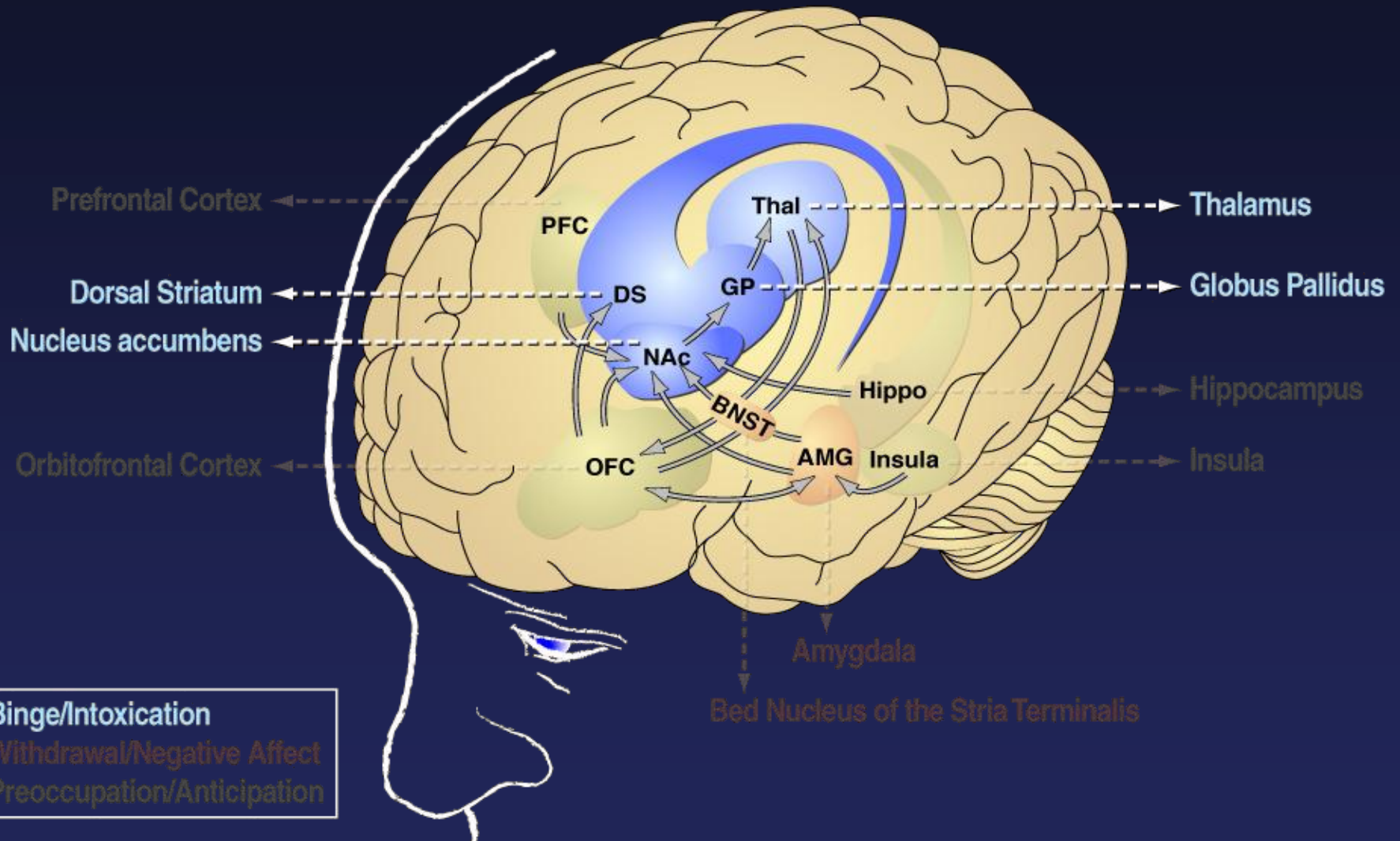
Compulsive Sex



Neurobiology of Addiction



Binge-Intoxication Stage



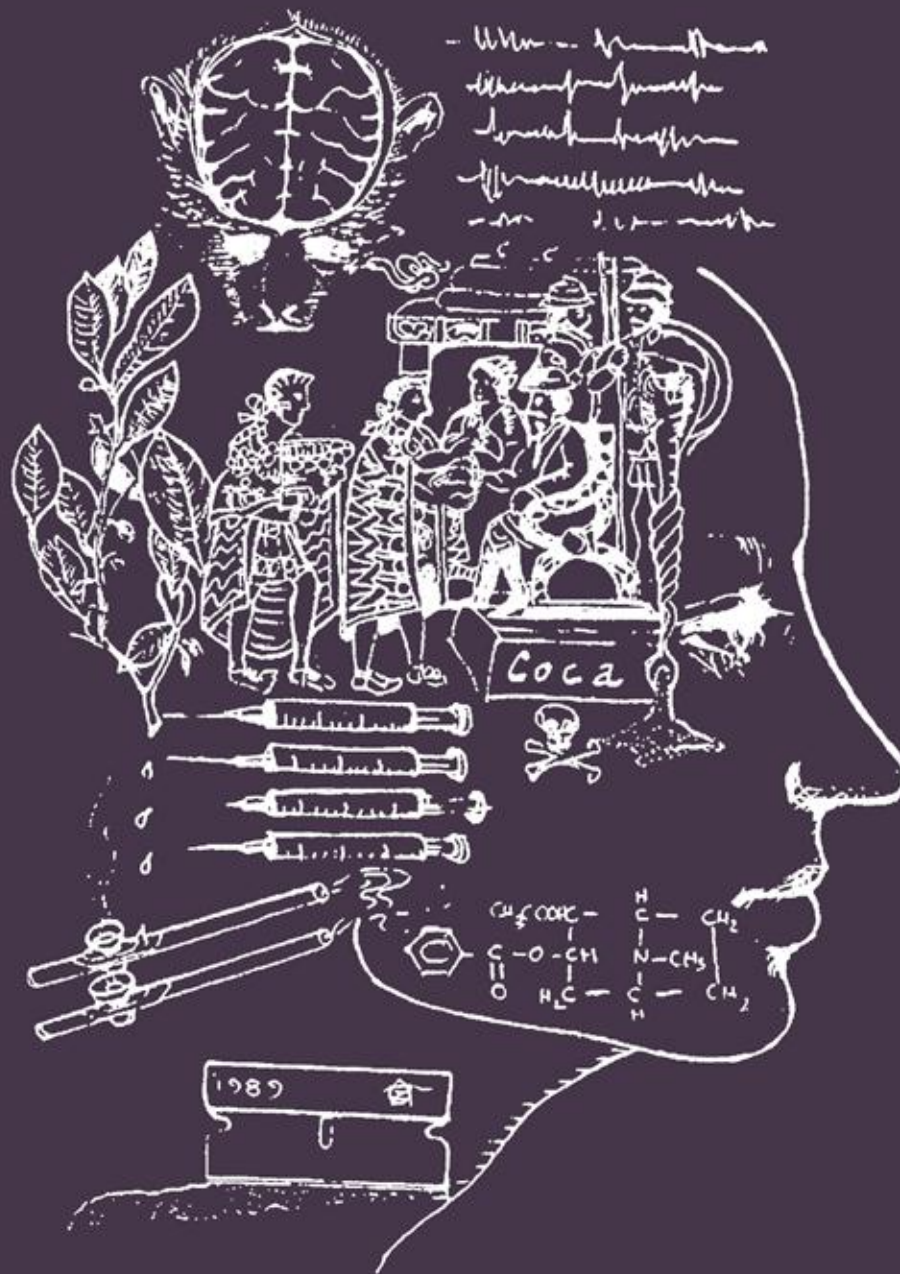


Illustration by J.R. Sanchez-Ramos, M.D.

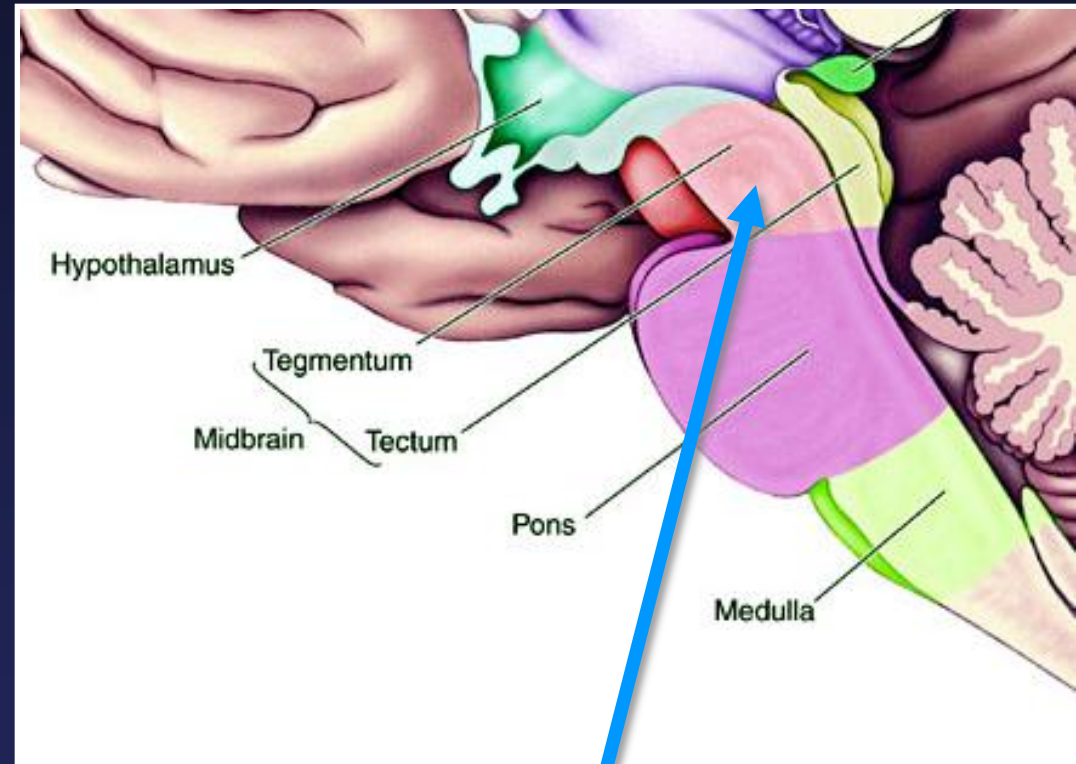
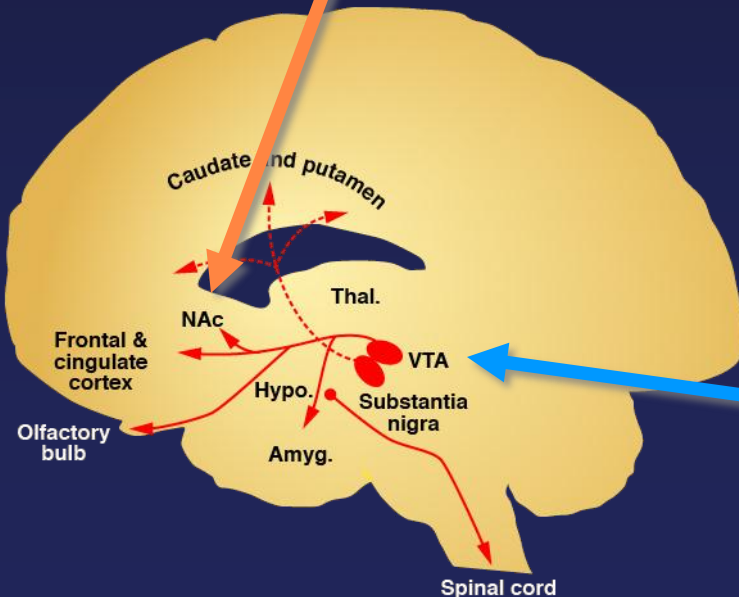
from: *The Psychiatric Times*, February (1990) 20-22.

Mesolimbic Dopamine System

Mesolimbic dopamine system

1. Ventral tegmental area
2. Nucleus accumbens

Nucleus Accumbens



Ventral Tegmental Area (VTA)



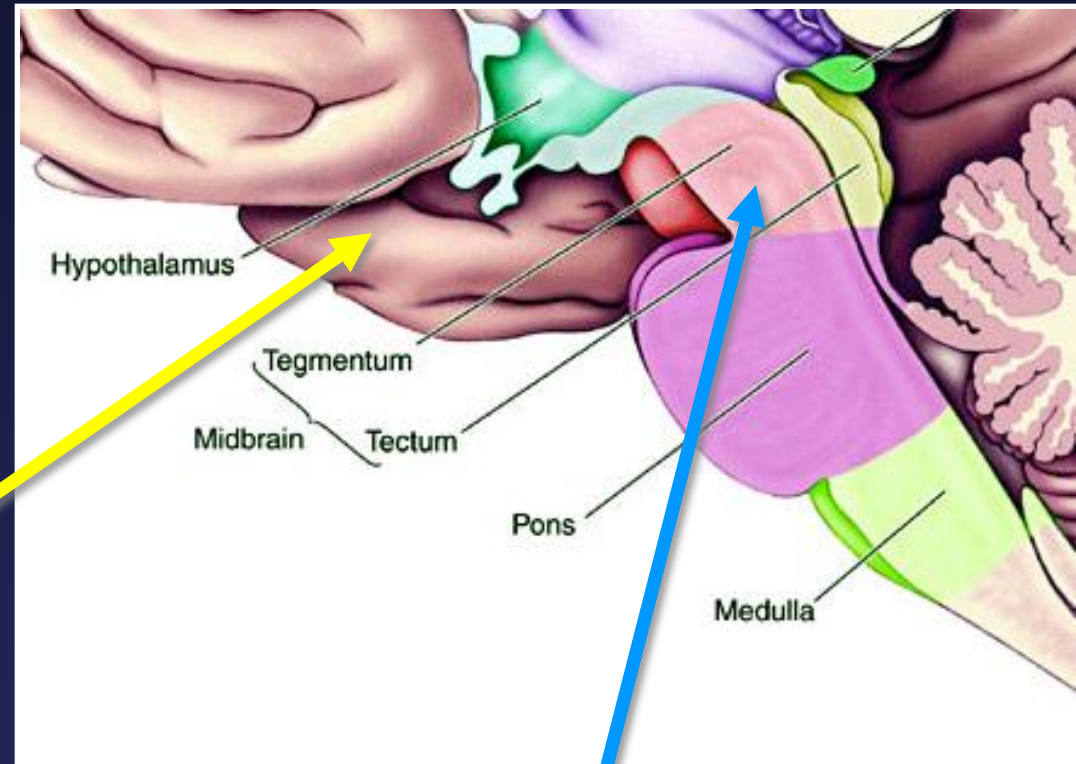
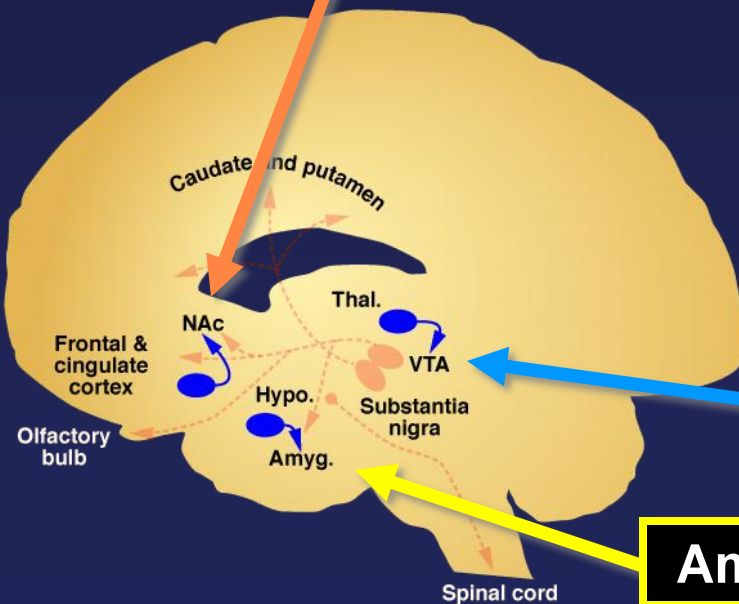
Pieter Bruegel

Opioid Peptide Reward System

Enkephalin and endorphin reward system

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

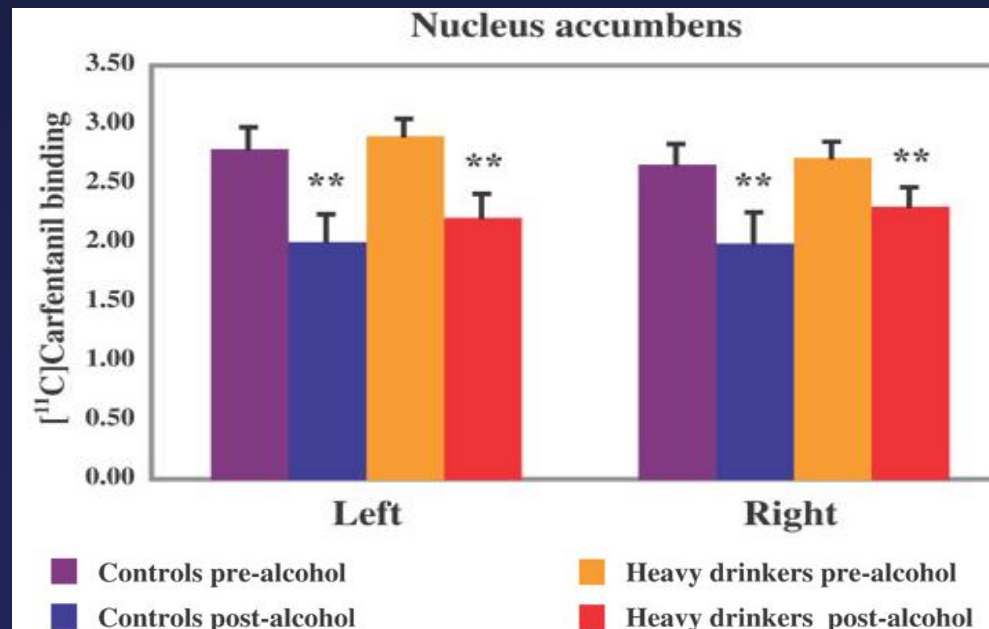
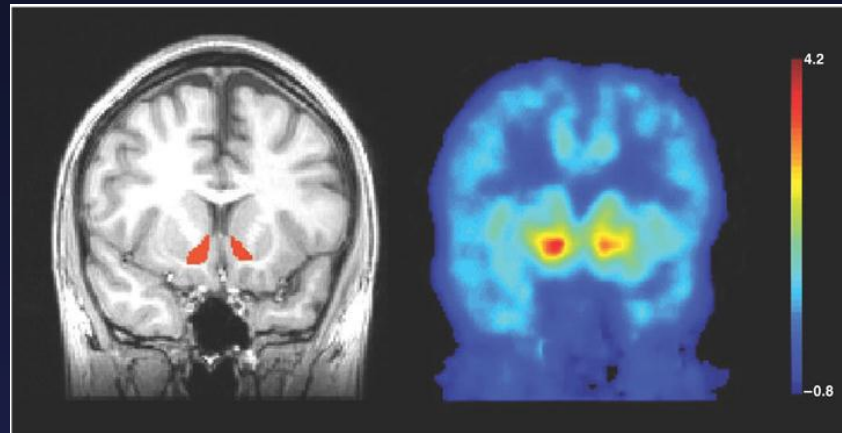
Nucleus Accumbens



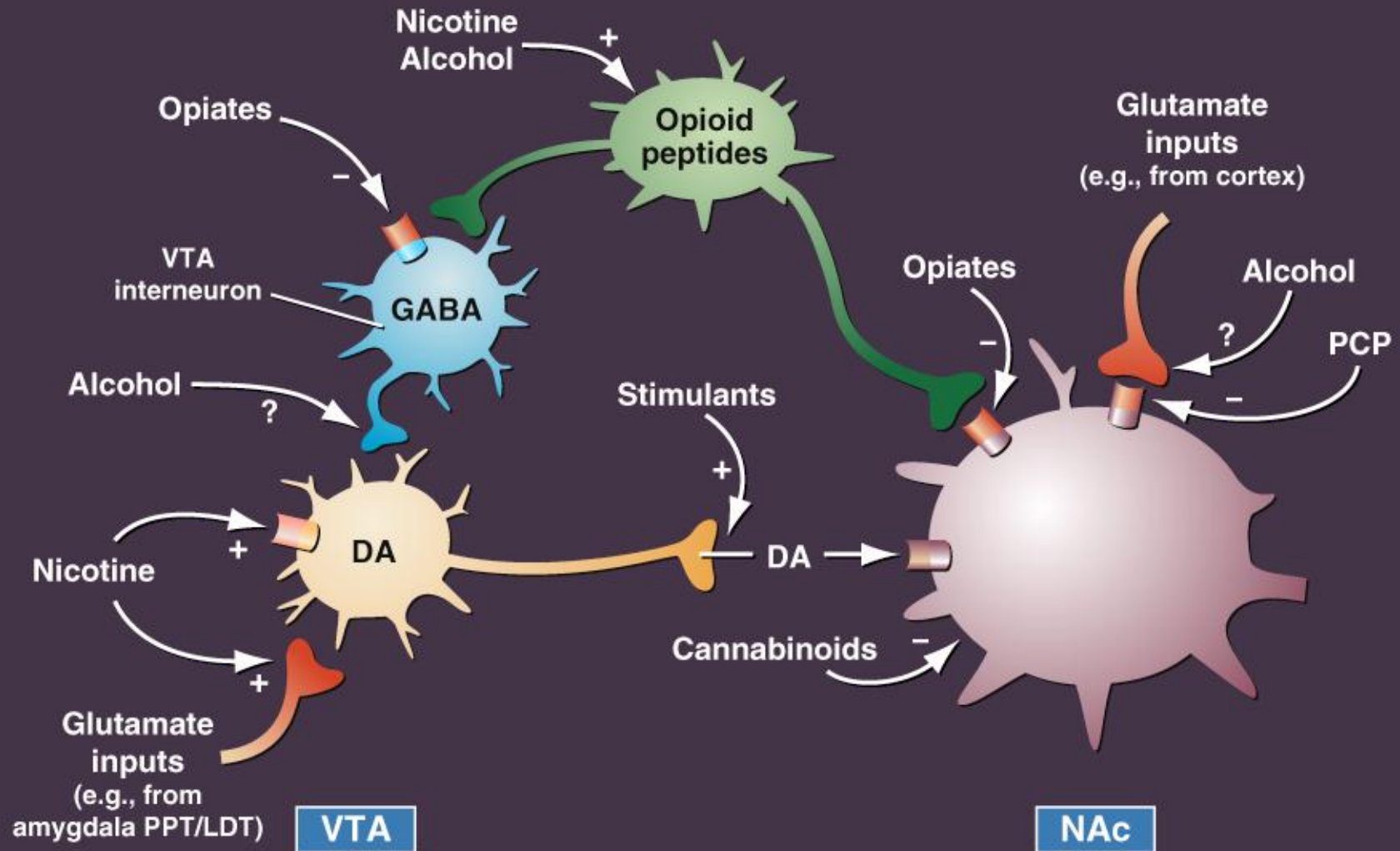
Ventral Tegmental Area (VTA)

Amygdala

Alcohol Consumption Induces Endogenous Opioid Release in the Human Nucleus Accumbens



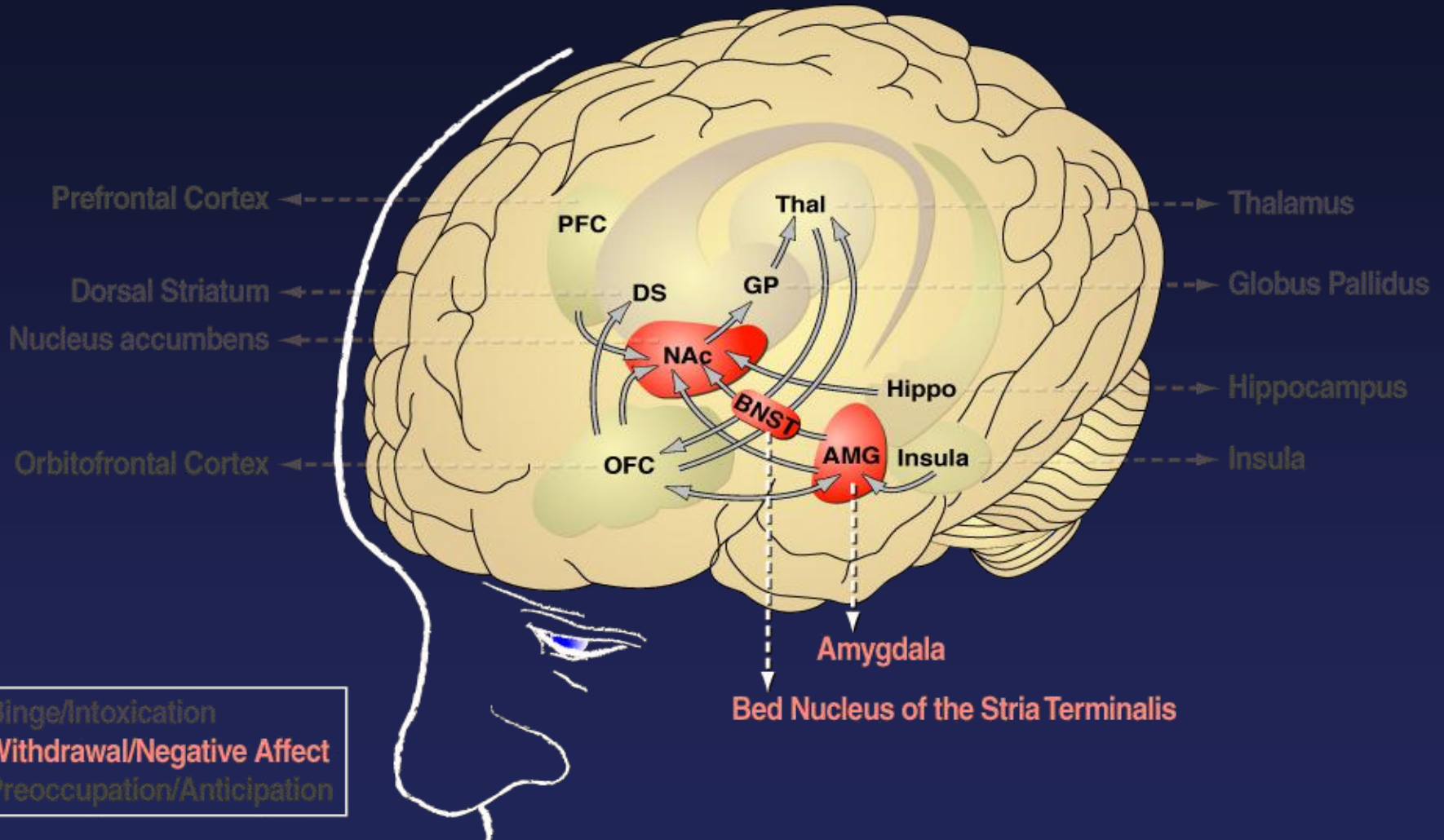
Converging Acute Actions of Drugs of Abuse on the Ventral Tegmental Area and Nucleus Accumbens





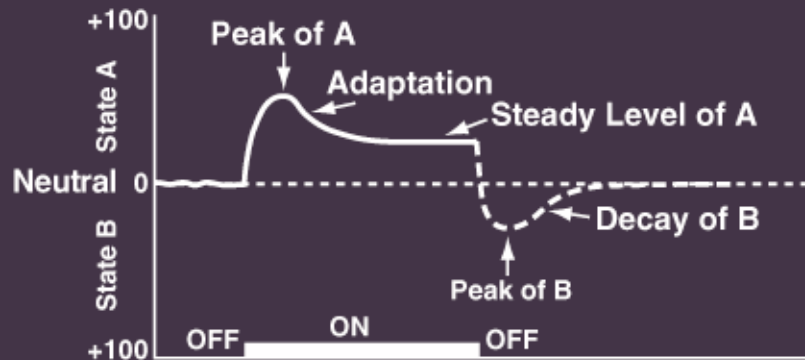
SUAYASAMIN

Withdrawal-Negative Affect Stage

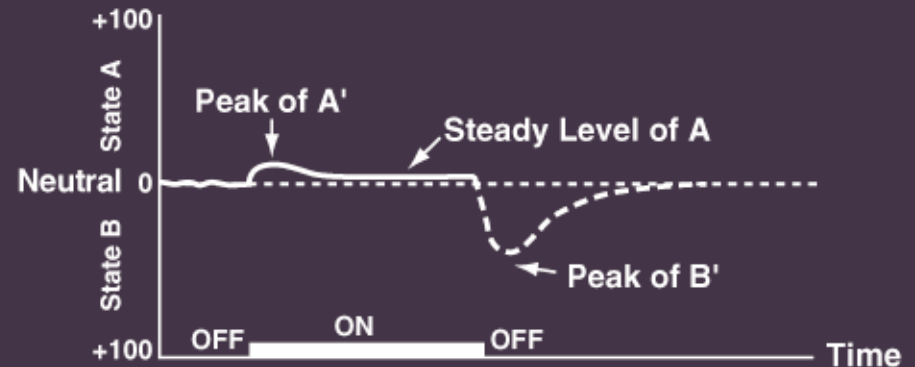


Standard Pattern of Affective Dynamics Produced by Novel and Repeated Unconditioned Stimulus or “Opponent Process: What Goes Up Must Come Down”

Nondependent



Dependent



Reward Transmitters Implicated in the Motivational Effects of Drugs of Abuse

Positive Hedonic Effects

↑ Dopamine

↑ Opioid peptides

↑ Serotonin

↑ GABA

Negative Hedonic Effects of Withdrawal

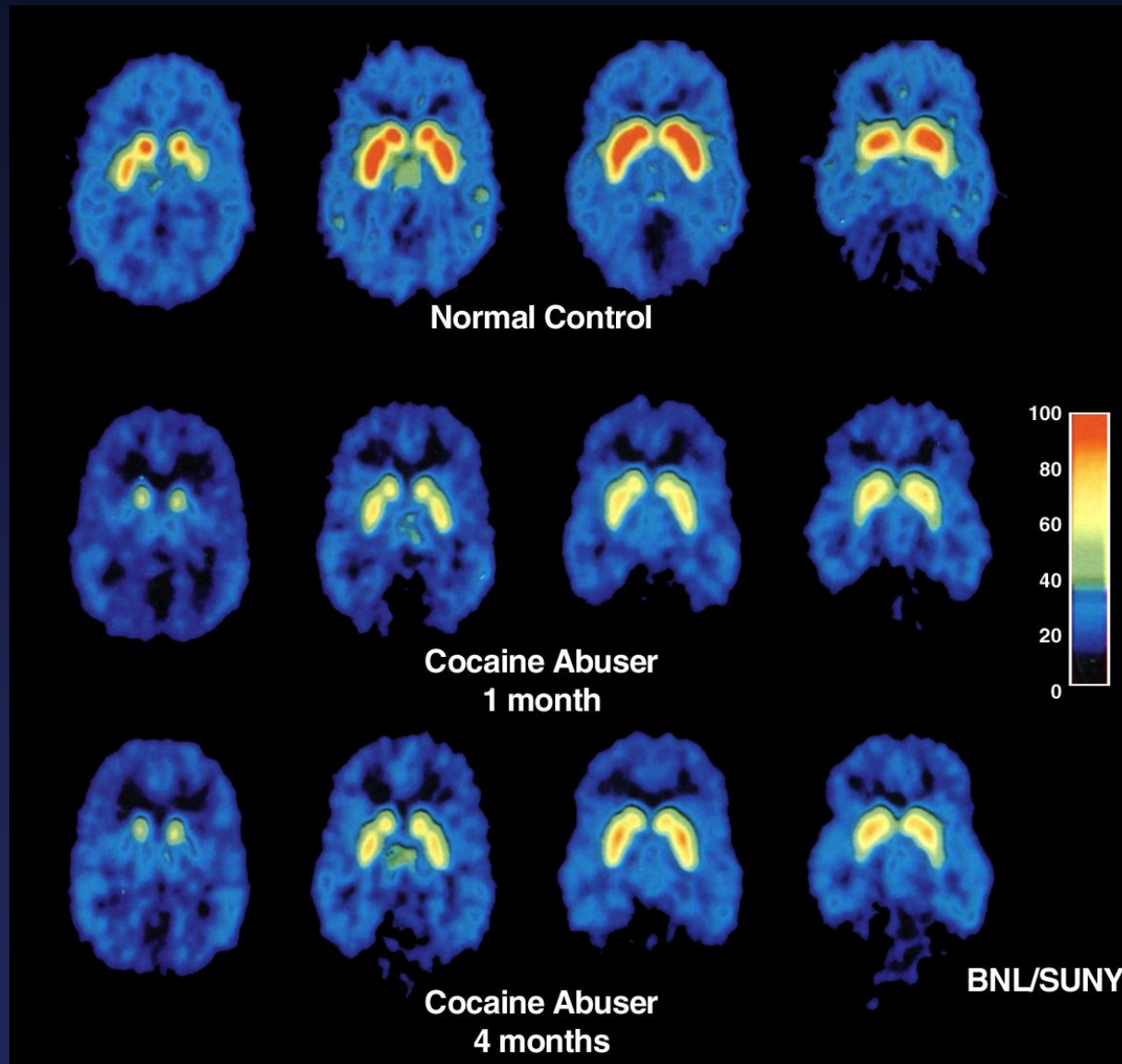
↓ Dopamine ... “dysphoria”

↓ Opioid peptides ... pain

↓ Serotonin ... “dysphoria”

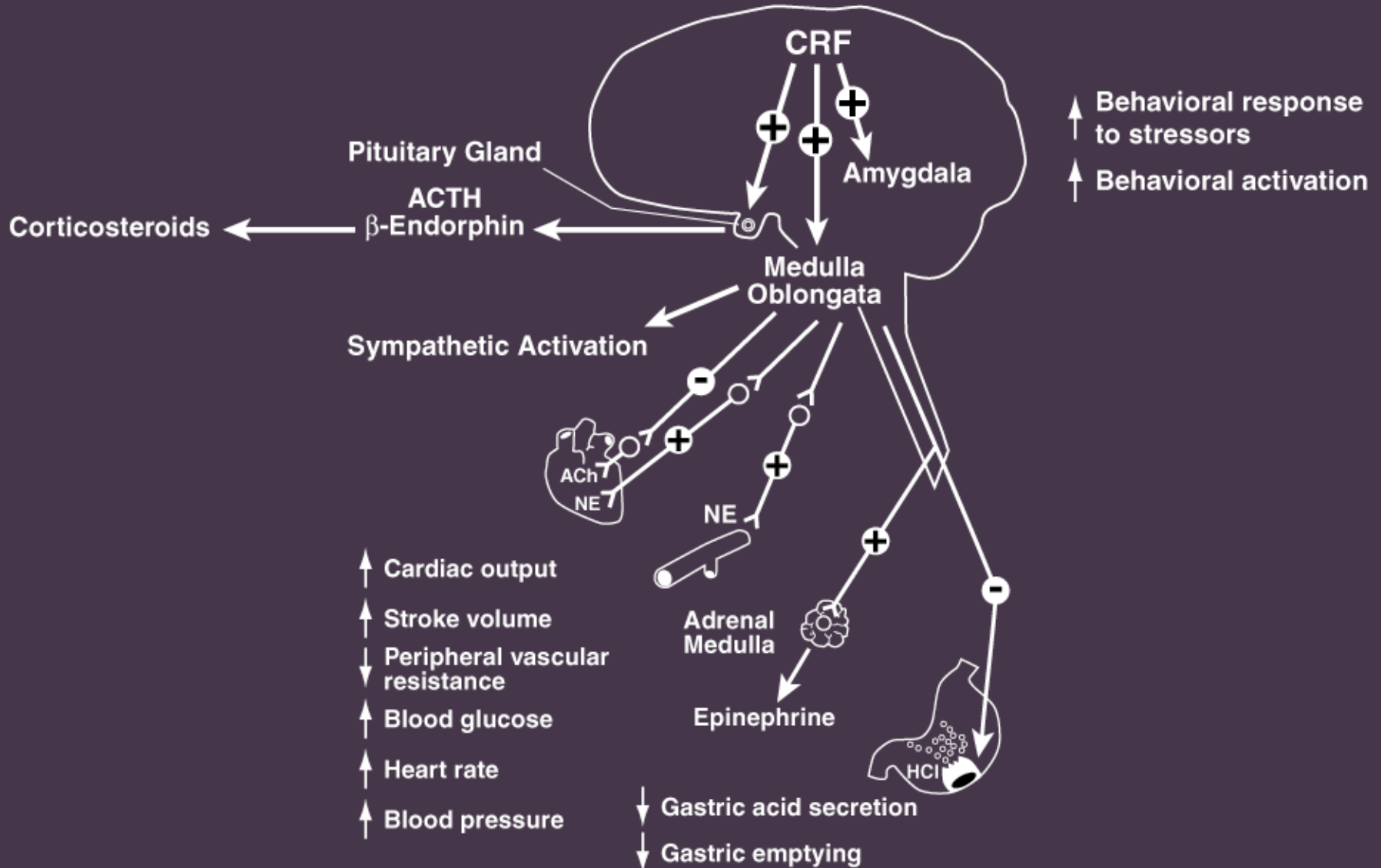
↓ GABA ... anxiety, panic attacks

Decreased Dopamine D₂ 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)

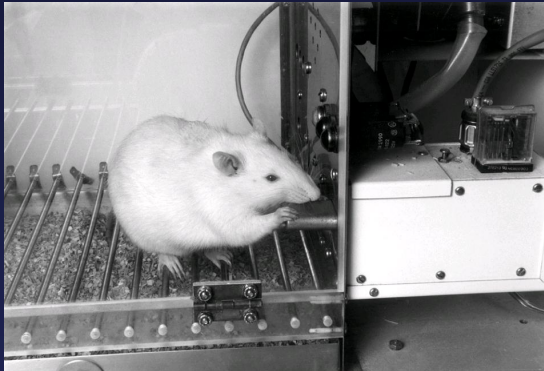


Rodent Model of Excessive Drinking During Withdrawal

Self-administration training

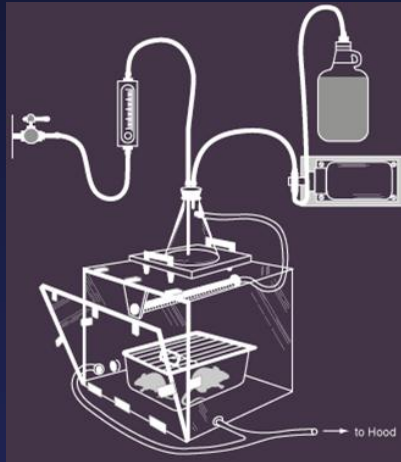
Dependence induction

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.

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

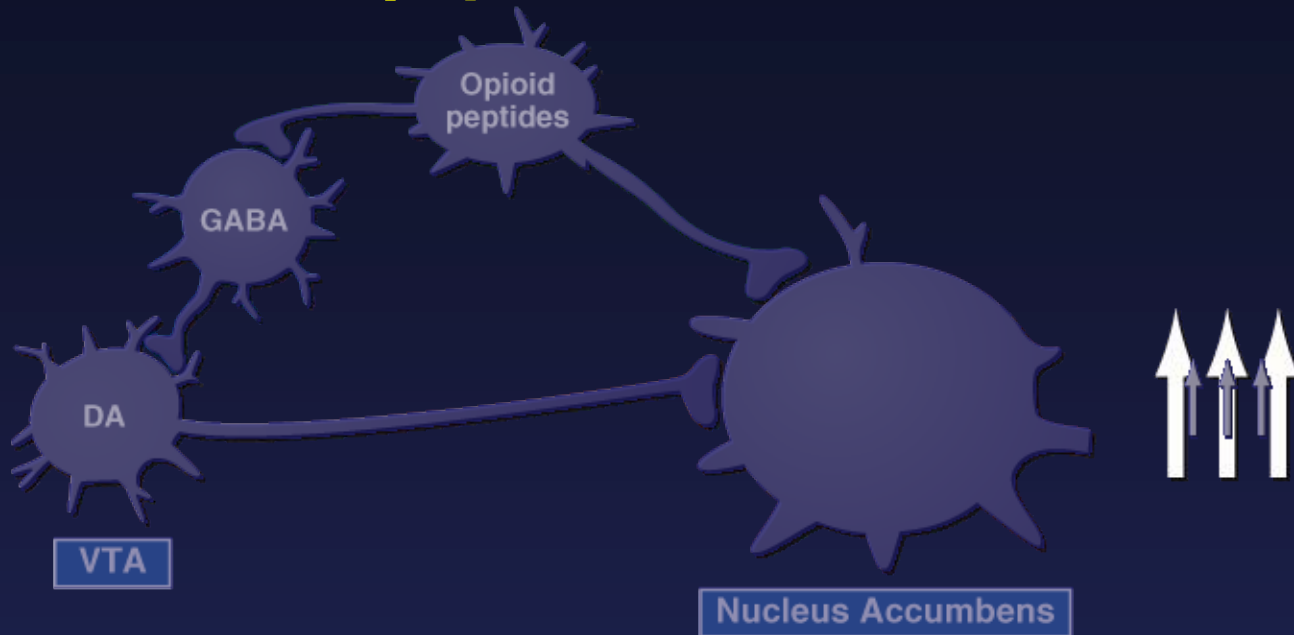
↑ Dynorphin ... “dysphoria”

↑ CRF ... stress

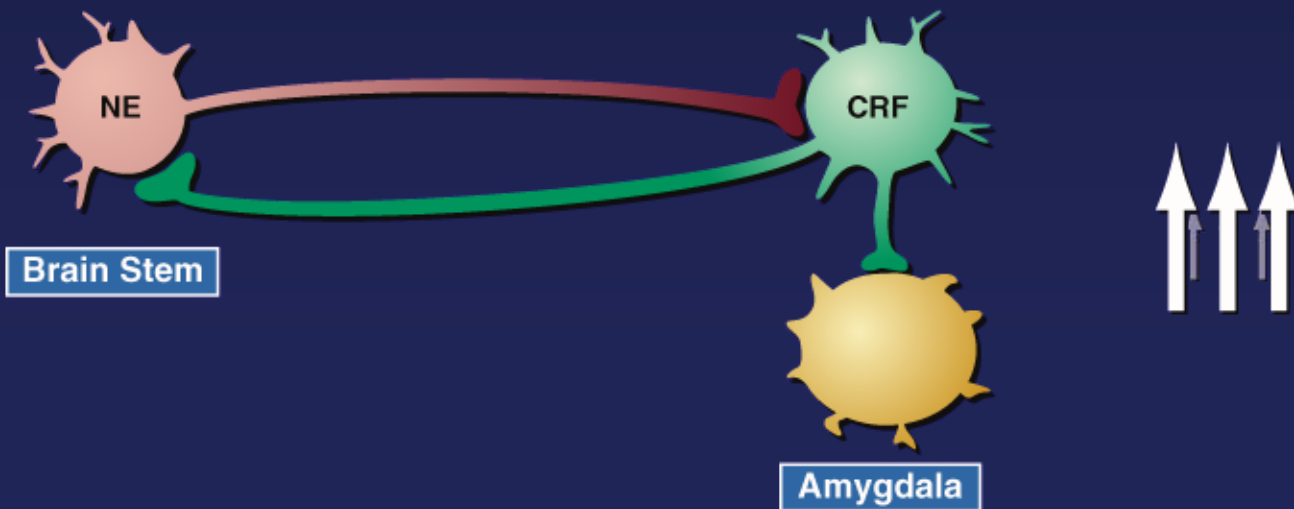
↑ Norepinephrine ... stress

Not Dependent

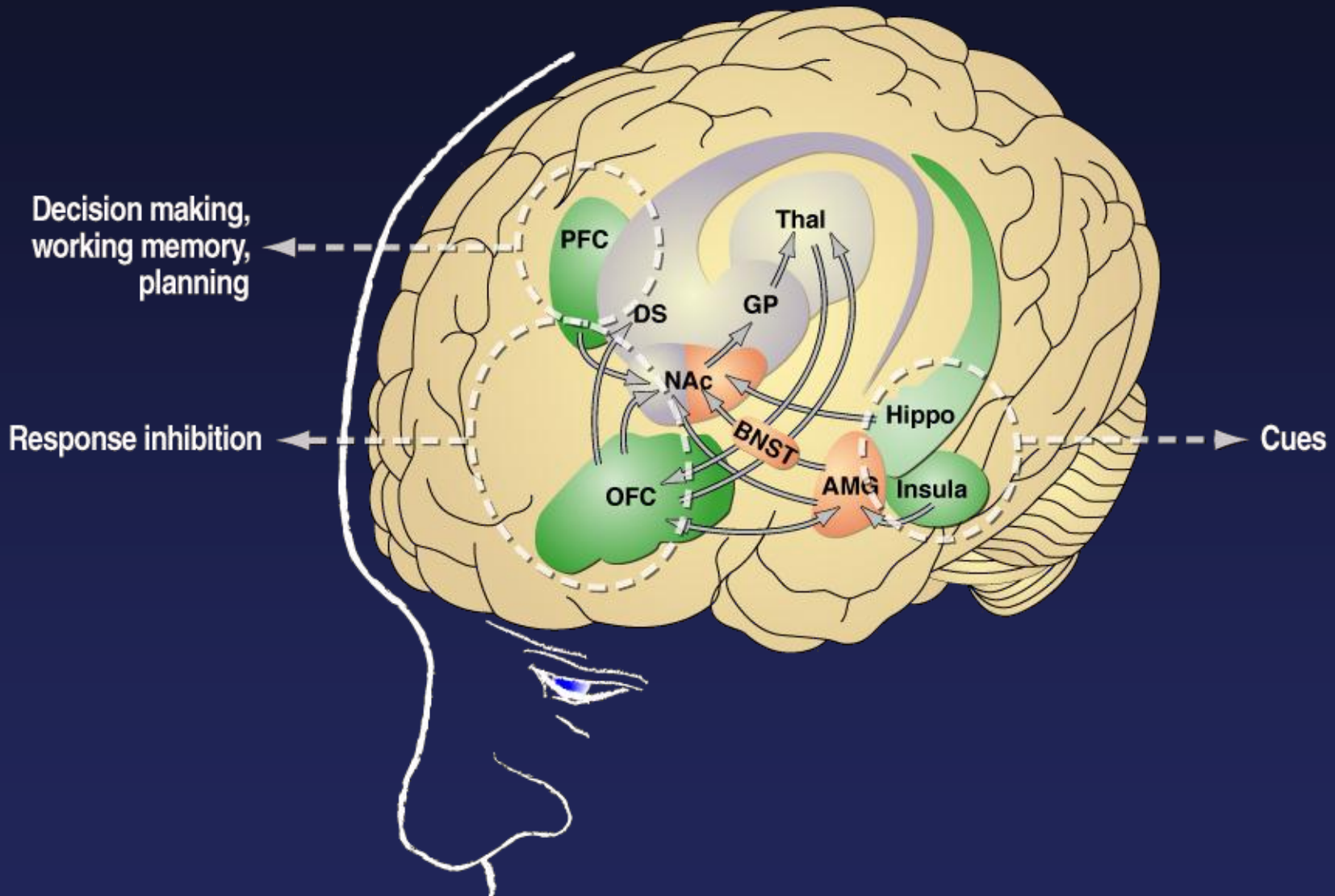
Positive Reinforcement



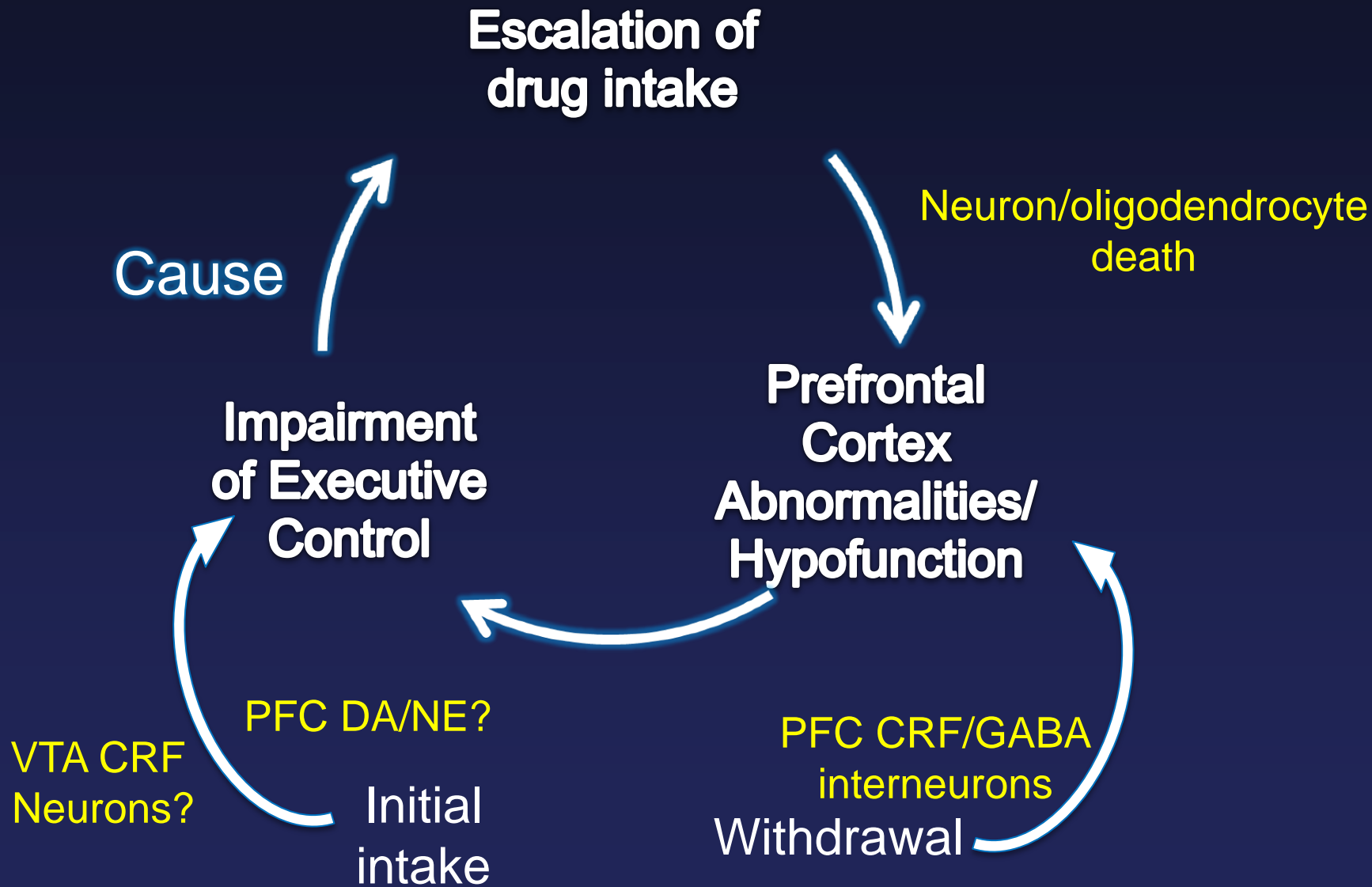
Negative Reinforcement



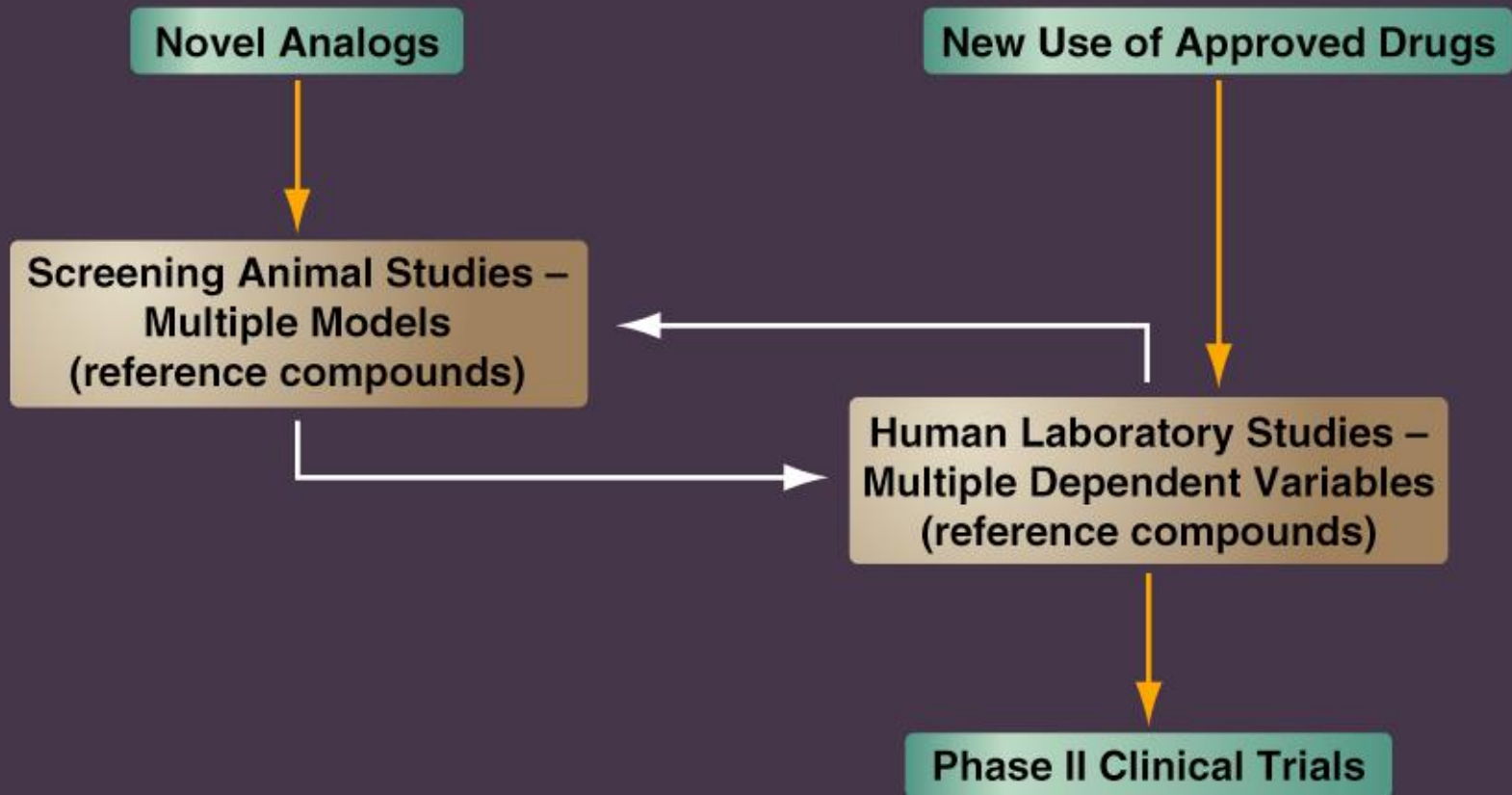
Neurobiology of Addiction: Preoccupation-Anticipation (“Craving”) Stage



Loss of Control Over Intake — Self-medication



Medications Development- A Rosetta Stone Approach



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

Bottom lines

1. Addiction is a reward deficit disorder- **all drugs of abuse compromise reward function and decrease dopamine activity**
2. Addiction is a stress surfeit disorder- **all drugs of abuse sensitize brain stress systems**
3. Addiction is a self-regulation disorder- **all drugs of abuse compromise frontal cortical executive function which disinhibits impulsivity and the brain stress systems**

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Neurobiology of Drug Addiction

Koob Laboratory

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Carrie Wade
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Special Mention

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Prefrontal Cortex, c-Fos,
CRF, and executive function

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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