The Anti-Reward System of the Adolescent Brain: Part 2

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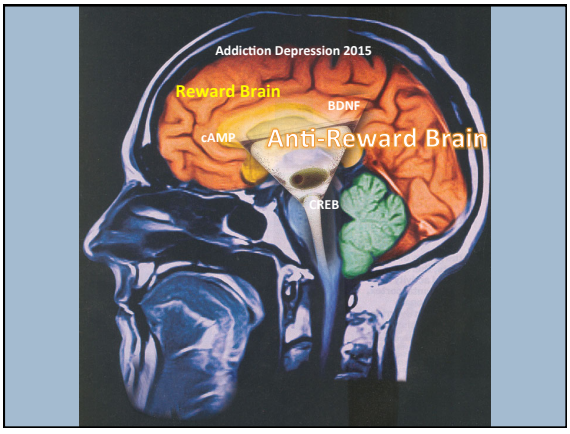
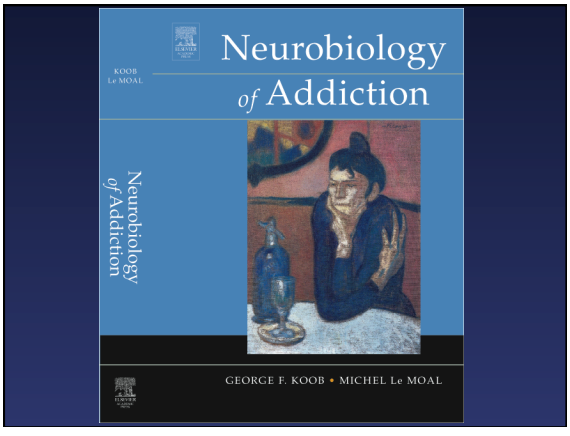
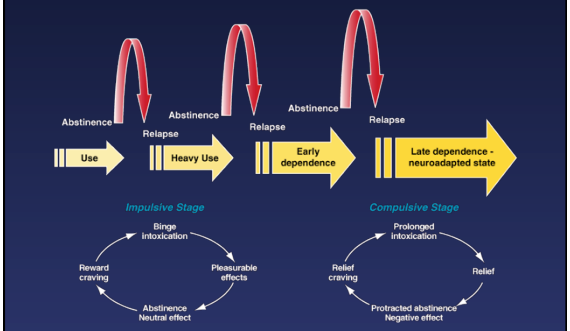


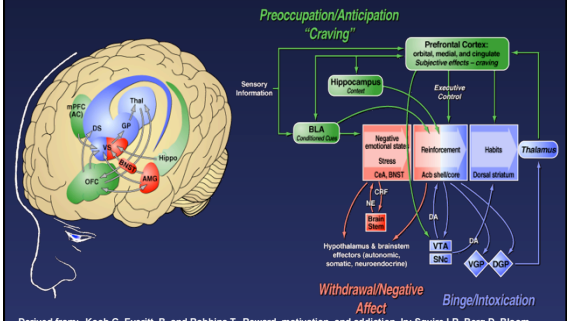


Progression of Drug Dependence



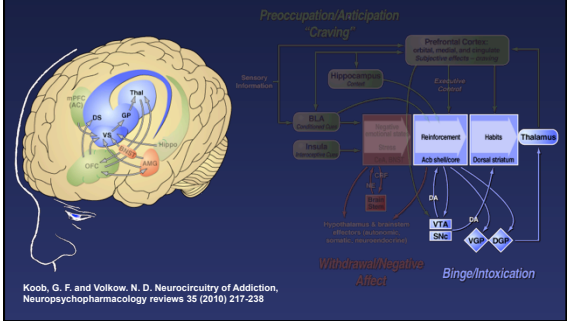
From:Heilig M and Koob GF, Trends Neurosci, 2007, 30:399-406.

Neurocircuitry of Addiction



Derived from: Koob G, Everitt, B and Robbins T, Reward, motivation, and addiction. In: Squire LR, Berg D, Bloom FE, du Lac S, Ghosh A, Spitzer NC (Eds.), Fundamental Neuroscience, 3rd edition, Academic Press, Amsterdam, 2008, pp. 987-1016.

Binge/Intoxication Stage



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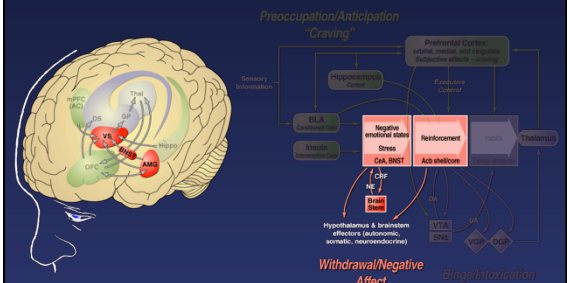
Withdrawal/Negative Affect Stage



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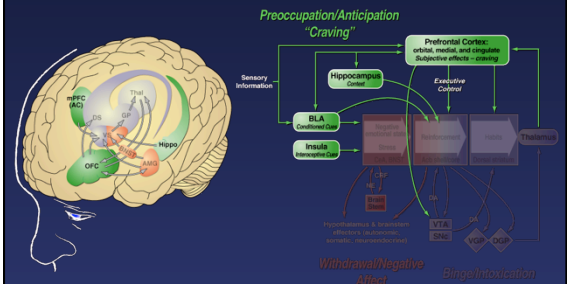
Reward Transmitters Implicated in the Motivational Effects of Drugs of Abuse

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

Preoccupation/Anticipation "Craving" Stage



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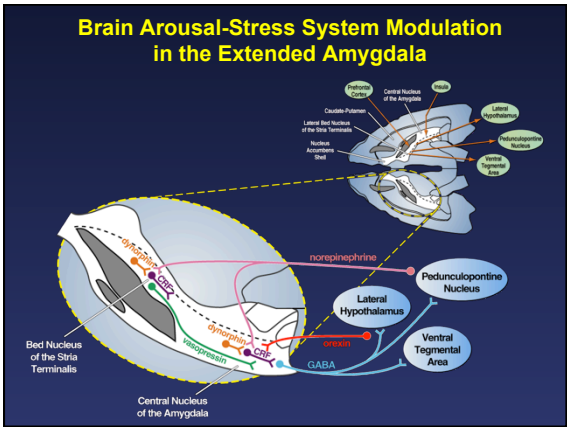
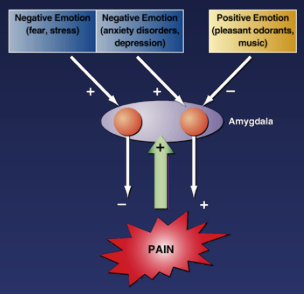
Brain Arousal-Stress System Modulation in the Extended Amygdala

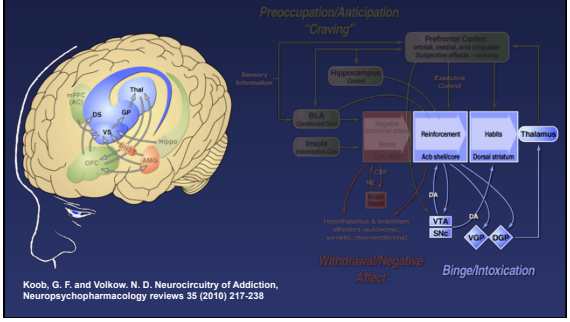


Pain, Emotions, and the Amygdala



From: Neugebauer V, Li W, Gird GC and Han JS, The Neuroscientist, 2004, 10:221-234.

Binge/Intoxication Stage



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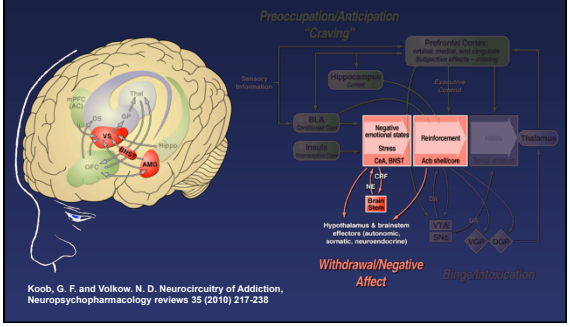
Withdrawal/Negative Affect Stage



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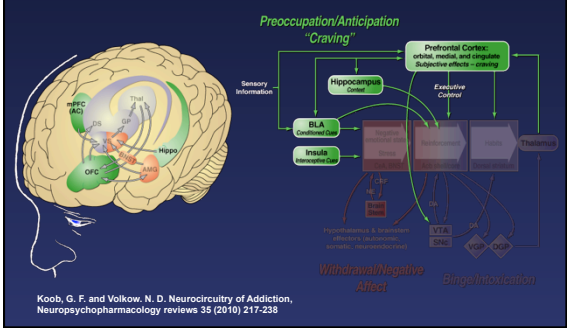
Preoccupation/Anticipation "Craving" Stage



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The Anti-Reward Brain

- 1. A key element of addiction is the development of a negative emotional state during drug abstinence.
- 2. The neurobiological basis of the negative emotional state derives from two sources: decreased reward circuitry function and increased anti-reward circuitry function.
- 3. The anti-reward circuitry function recruited during the addiction process can be localized to connections of the extended amygdala in the basal forebrain.
- 4. Neurochemical elements in the antireward system of the extended amygdala have as a focal point the extrahypothalamic corticotropin-releasing factor system.
- 5. Other neurotransmitter systems implicated in the anti-reward response include norepinephrine, dynorphin, neuropeptide Y, and nociceptin.
- 6. Vulnerability to addiction involves multiple targets in both the reward and anti-reward system, but a common element is sensitization of brain stress systems.
- 7. Dysregulation of the brain reward system and recruitment of the brain anti-reward system are hypothesized to produce an allostatic emotional change that can lead to pathology.
- 8. Nondrug addictions may be hypothesized to activate similar allostatic mechanisms.

ANTI-REWARD

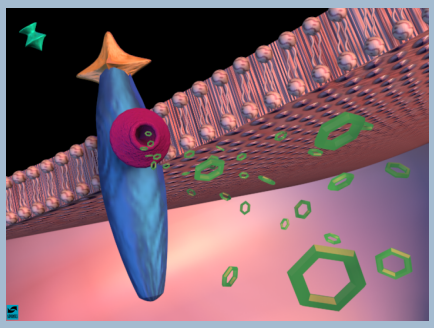
The concept of an anti-reward system was developed to explain one component of time-dependent neuroadaptations in response to excessive utilization of the brain reward system.
The brain reward system is defined as activation of circuits involved in positive reinforcement with an overlay of positive hedonic valence.
The neuroadaptation simply could involve state-shifts on a single axis of the reward system (within- system change; dopamine function decreases).
However, there is compelling evidence that brain stress/emotional systems are recruited as a result of excessive activation of the reward system and provide an additional source of negative hedonic valence that are defined here as the anti-reward system (between-system change; corticotropin-releasing factor function increases). The combination of both a deficit in the reward system (negative hedonic valence) and recruitment of the brain stress systems (negative hedonic valence) provides a powerful motivational state mediated in part by the anti-reward system.
(Koob & Le Moal 2005).

Definitions

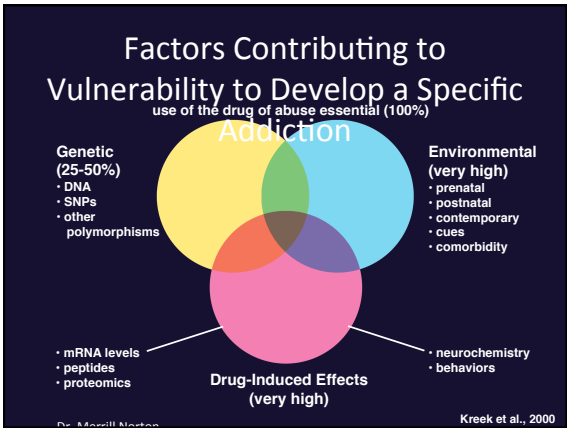
- cAMP- Cyclic adenosine monophosphate used for intracellular signal transduction
- BDNF- Brain-derived neurotrophic factor- encourage the growth and differentiation of new neurons and synapses.
- CREB-(cAMP Response Element Binding)- neuronal plasticity and long-term memory formation in the brain.

A Major Reason People Take a Drug is They Like What it Does to Their Brains

Increased cAMP produced in post-synaptic cell



Factors Contributing to Vulnerability to Develop a Specific Addiction



Molecular Biology of Addiction

Beyond Initial Cellular Targets:

Transcription Factor CREB *(cAMP response element-binding protein)* and its target BNDF

- Brain-derived neurotrophic factor is a member of the nerve growth factor family, which also includes the prototype nerve growth factor as well as neurotrophin-3 and neurotrophin-4.
- These growth factors are involved in the differentiation and growth of many types of neurons in the developing brain as well as the maintenance and survival of neurons in the mature brain.
- Ref: Lo DC. Neurotrophic factors and synaptic plasticity. *Neuron*. 1995;15:979-981.

This is your brain

This is your brain
Thanks to BDNF

Think of it like fertilizing and pruning your rose bushes

Molecular Biology of Addiction:

Addiction is a form of drug-induced neural plasticity

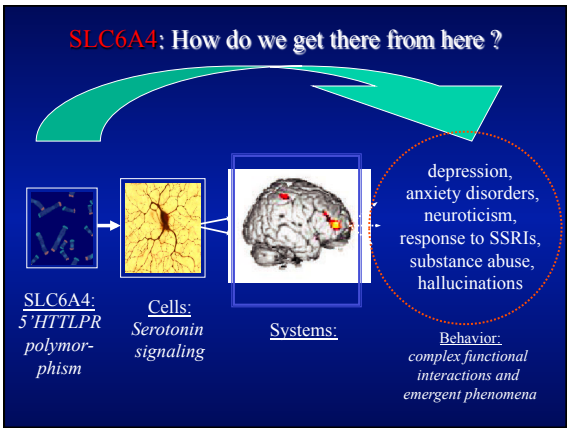
- Upregulation of cAMP pathway
  - Occurs in response to chronic administration of drugs
  - Resulting activation of transcription factor CREB(cAMP response element-binding)
  - Both mediate aspects of tolerance and dependency
- Induction of another transcription factor, d FosB
  - Exerts opposite effects
  - May contribute to sensitized responses to drug exposure

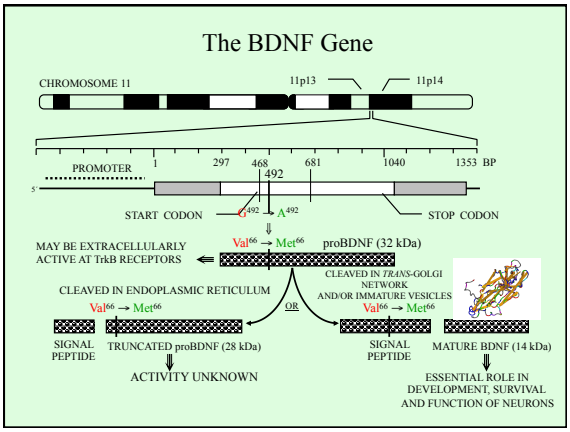
Ref: Nestler, Eric - Molecular Biology of Addiction. Am J of Addictions 10:201-217, 2001

Basis for Plasticity: Summary

- **Drugs enter the brain and bind to an initial protein target**
- **Binding perturbs synaptic transmission which in turn cause the acute behavioral effects of the drug**
- **Acute effects of the drug do not explain addiction by themselves**

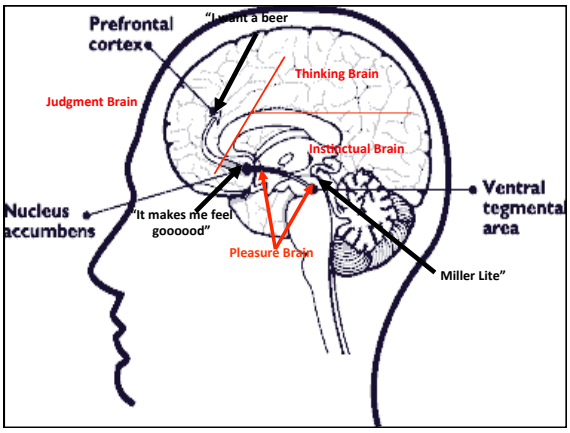
Ref: Nestler, Eric - Molecular Biology of Addiction.
Am J of Addictions 10:201-217, 2001

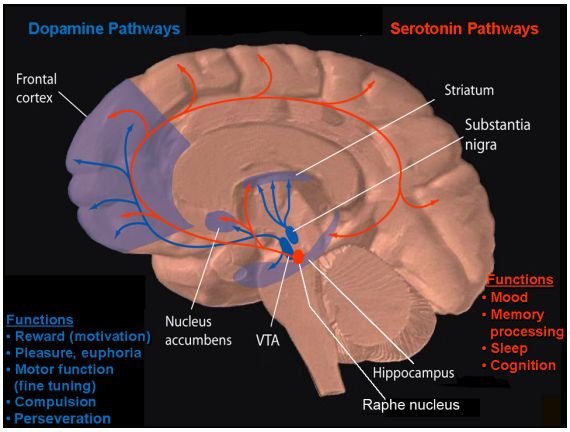


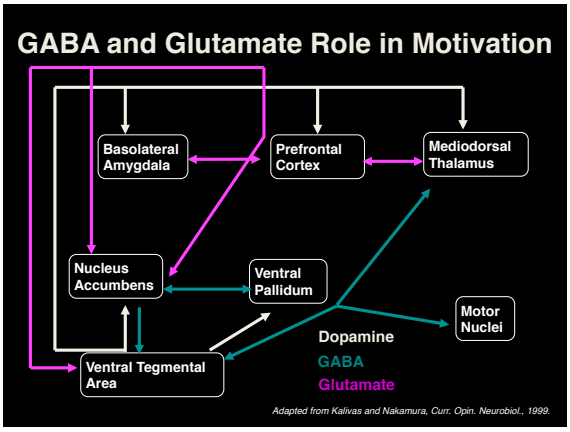


- Addiction produces a change in brain structure and function (adaptation to the drug)
- molecular and cellular changes in particular neurons alter functional neural circuits
- This leads to changes in behavior consistent with addicted states
- Addiction is therefore a form of drug induced neural plasticity

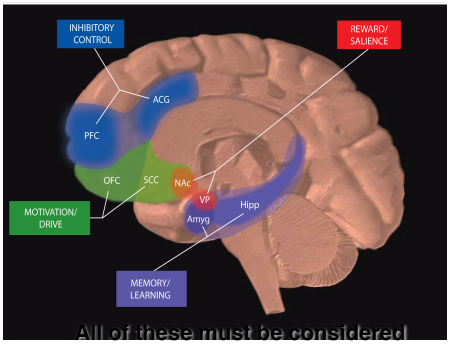
Ref: Nestler, Eric - Molecular Biology of Addiction. Am J of Addictions 10:201-217, 2001


Prefrontal cortex
"I want a beer
Thinking Brain
Judgment Brain
Instinctual Brain
Ventral tegmental area
Nucleus accumbens
"It makes me feel goooood"
Pleasure Brain
Miller Lite"


Dopamine Pathways
Serotonin Pathways
Frontal cortex
Striatum
Substantia nigra
Functions
• Reward (motivation)
• Pleasure, euphoria
• Motor function (fine tuning)
• Compulsion
• Perseveration
Nucleus accumbens
VTA
Hippocampus
Raphe nucleus
Functions
• Mood
• Memory processing
• Sleep
• Cognition

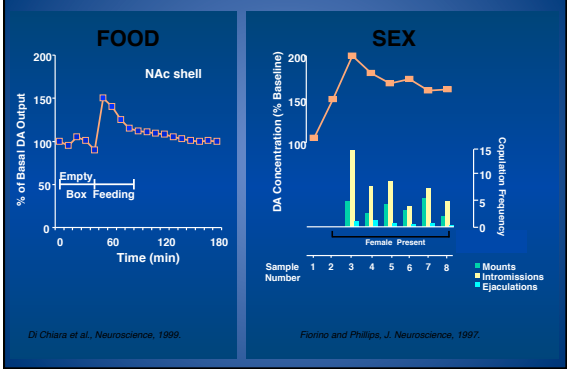

GABA and Glutamate Role in Motivation
Basolateral Amygdala
Prefrontal Cortex
Mediodorsal Thalamus
Nucleus Accumbens
Ventral Pallidum
Motor Nuclei
Dopamine
GABA
Glutamate
Ventral Tegmental Area
Adapted from Kalivas and Nakamura, Curr. Opin. Neurobiol., 1999.

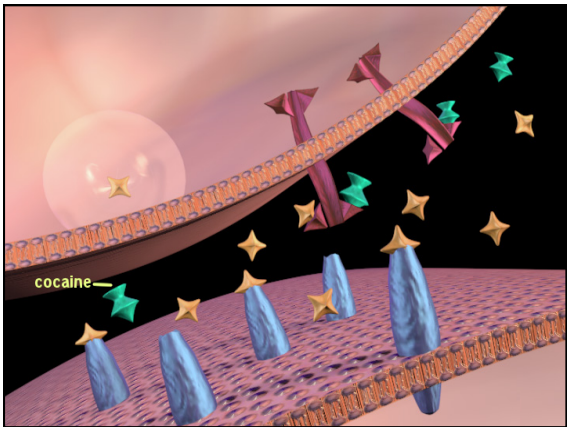
Circuits Involved In Drug Abuse and Addiction



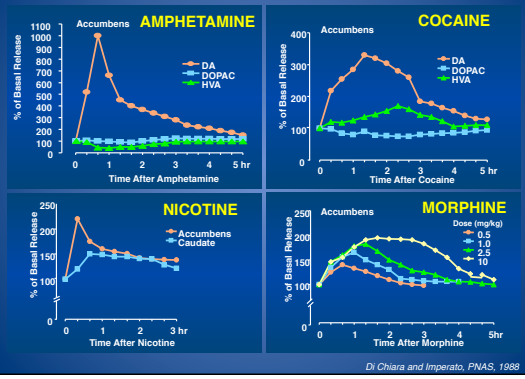
All of these must be considered in developing strategies to effectively treat addiction

Natural Rewards Elevate Dopamine Levels





Effects of Drugs on Dopamine Release



Di Chiara and Imperato, PNAS, 1988

Science has generated much evidence showing that…

prolonged drug use changes the brain in fundamental and long-lasting ways

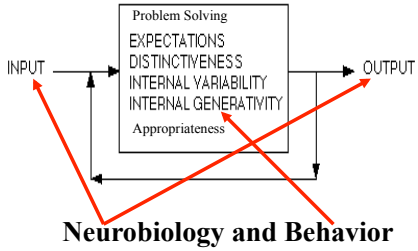
This is your brain

This is your brain After drugs

Think about it as what happens when you fail to fertilize, water, and prune your garden.

The Normal Brain

How are human behaviors and neurobiology related?



Neurobiology and Behavior

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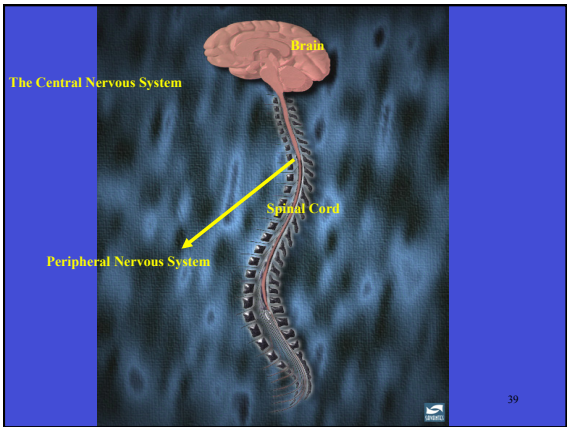

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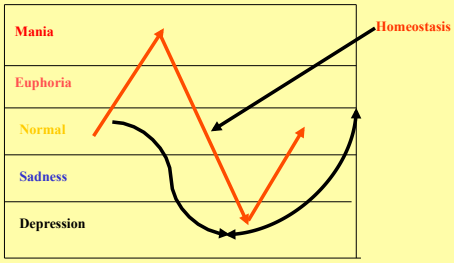
Mood Chart of the Human Brain



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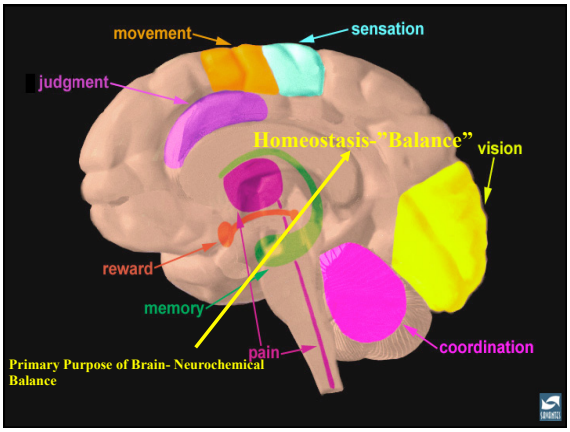

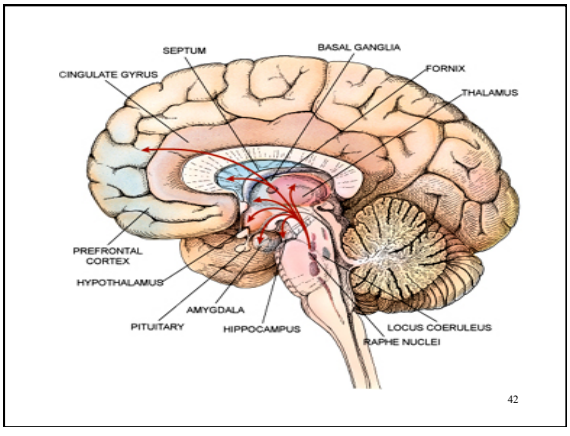

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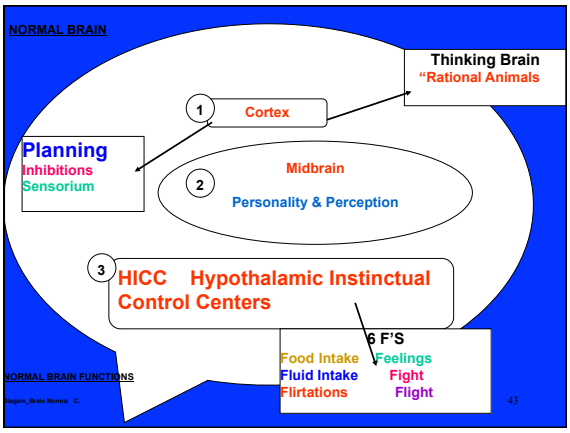
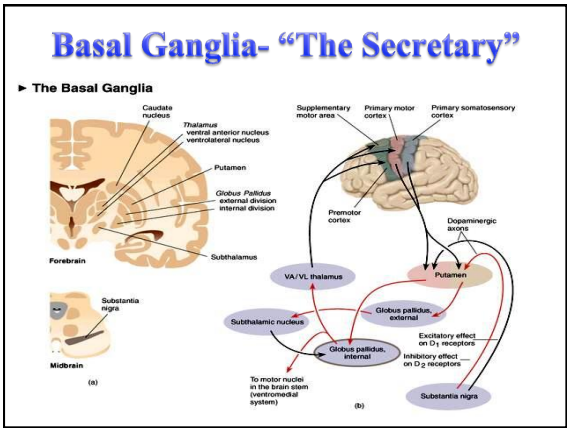
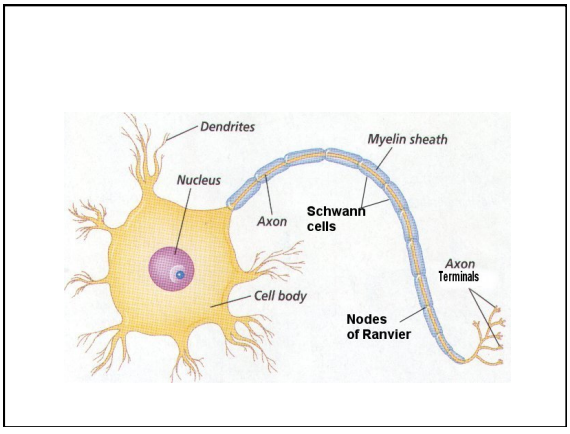
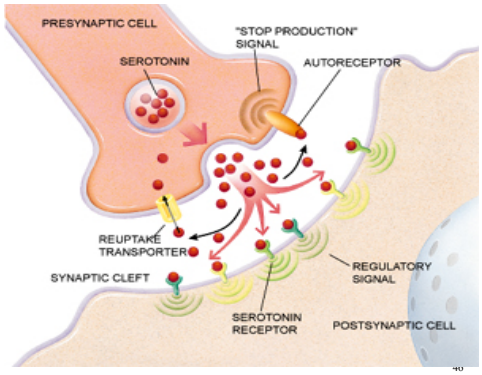

NORMAL BRAIN
Thinking Brain
"Rational Animals
1
Cortex
Planning
Inhibitions
Sensorium
2
Midbrain
Personality & Perception
3
HICC Hypothalamic Instinctual
Control Centers
6 F'S
Food Intake
Fluid Intake
Flirtations
Feelings
Fight
Flight
NORMAL BRAIN FUNCTIONS
43


Basal Ganglia- "The Secretary"
The Basal Ganglia
Caudate nucleus
Thalamus
ventral anterior nucleus
ventrolateral nucleus
Putamen
Globus Pallidus
external division
internal division
Subthalamus
Forebrain
Substantia nigra
Midbrain
(a)
Supplementary motor area
Primary motor cortex
Primary somatosensory cortex
Premotor cortex
Dopaminergic axons
VA/VL thalamus
Putamen
Subthalamic nucleus
Globus pallidus, external
Globus pallidus, internal
Excitatory effect on D1 receptors
Inhibitory effect on D2 receptors
To motor nuclei in the brain stem (ventromedial system)
Substantia nigra
(b)

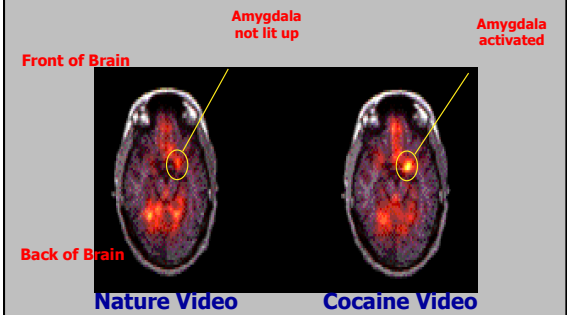

Dendrites
Myelin sheath
Nucleus
Axon
Schwann cells
Axon Terminals
Cell body
Nodes of Ranvier



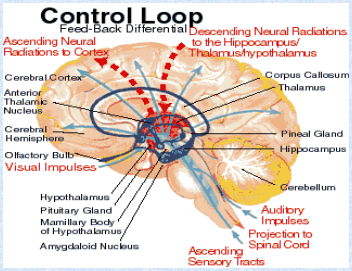
Anatomy of a Neuron

- Cell body – main part
- Dendrite – receives action potential (stimulation) from other neurons
- Axon – branches from cell body, where the action potential occurs
- Axon terminal – end of an axon
- Myelin sheath – lipid layer for protection over neurons that allows for increase in speed of signal transmission; made by Schwann cells
- Nodes of Ranvier – gaps in myelin sheath along the axon, where most Na+ pumps are located
- Synaptic Cleft – gap between neurons; between the axon terminal of 1 neuron and the dendrite of a 2nd neuron

How Long Does the Brain Remember?



The Brain's Regulatory Systems



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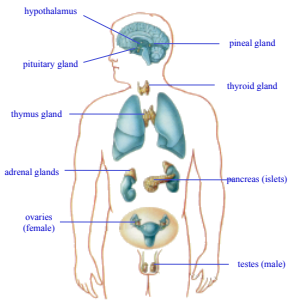
Regulation of hormone secretion

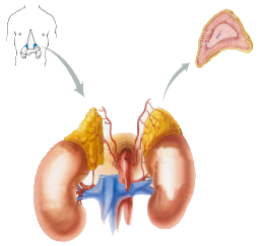
- Sensing and signaling: a biological need is sensed, the endocrine system sends out a signal to a target cell whose action addresses the biological need. Key features of this stimulus response system are:
  - receipt of stimulus
  - synthesis and secretion of hormone
  - delivery of hormone to target cell
  - evoking target cell response
  - degradation of hormone

ENDOCRINE GLANDS

Endocrine vs. exocrine
Hormone
Endocrine gland



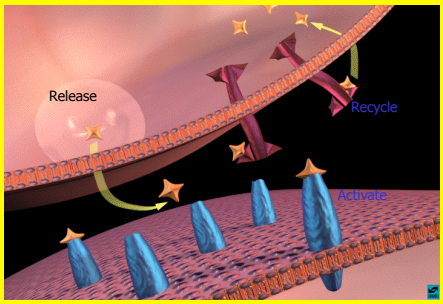
ADRENAL CORTEX (ZONA GLOMERULOSA)



Natural Rewards

- Food
- Sex
- Excitement
- Comfort
- Nurturing

Dopamine Spells REWARD



Behavior Pathways

- Rewarding behaviors can become routine
- "Subconscious" control of the behavior
- Difficult to extinguish behaviors because people are not always aware when they are initiated
- Resistant to change

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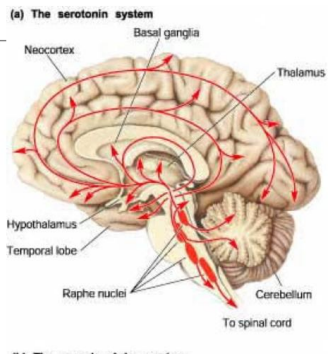
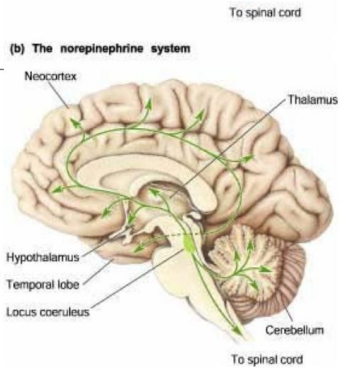
Serotonin (5-HT) is the neurotransmitter of the raphe nuclei

Implicated in control of sleep, and related arousal and attention



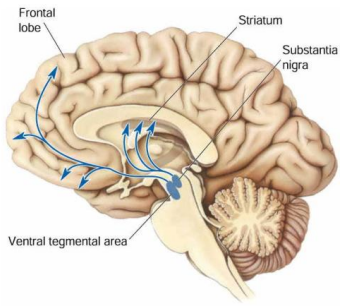
Norepinephrine is transmitter from the locus coeruleus

Implicated in control of attention, arousal, mood, etc.

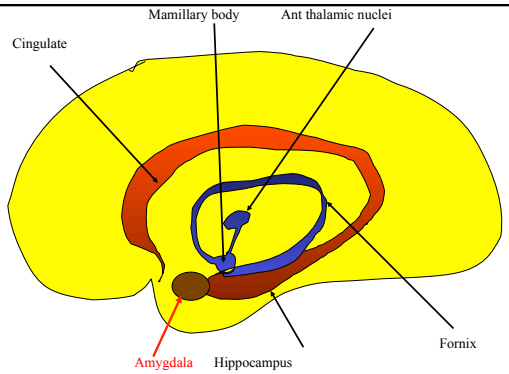


Dopamine projection systems

Important for control of reward and reinforcement



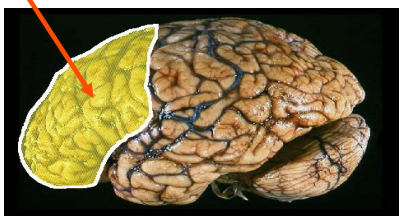
The Mood Brain



The hardware of emotions: The limbic system.

The frontal lobes

Home of Rational Brain



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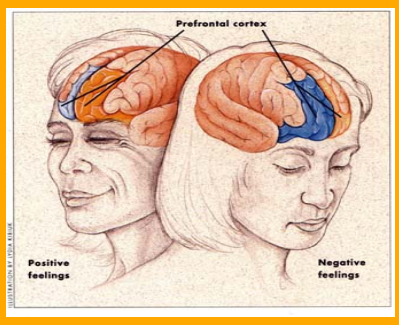
Bliss and the Brain



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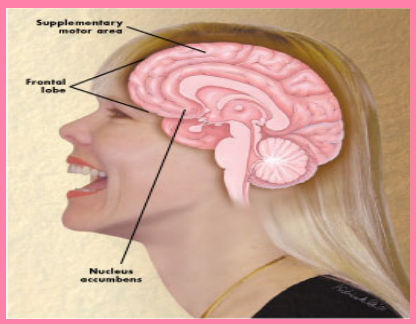
Humor, Laughter and the Brain



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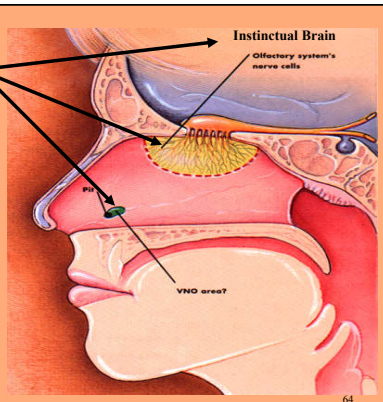
Pheromones

"The Scents of Love"



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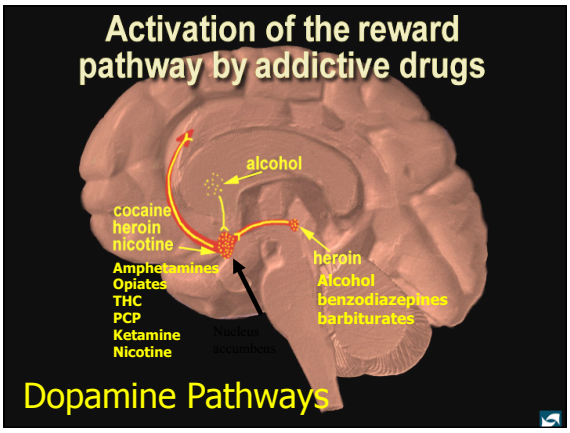
The Addicted Brain

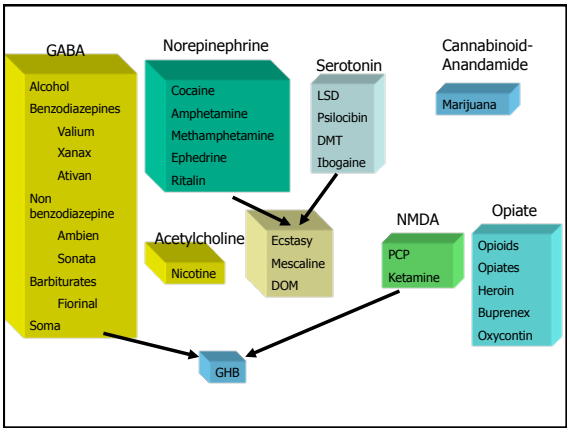
How Drugs Work

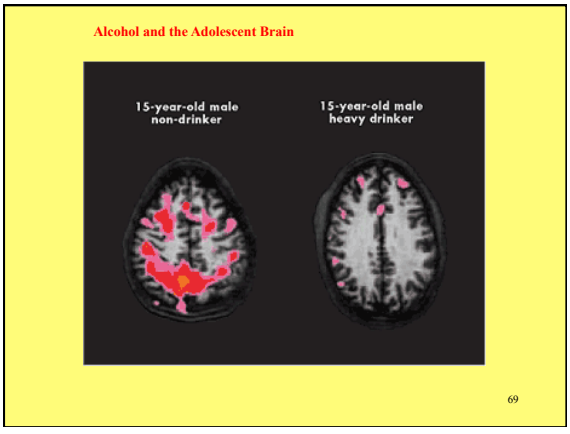
- Interact with neurochemistry

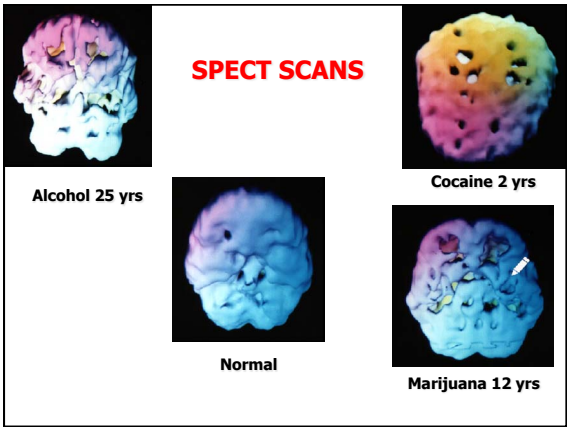
⇨ **Results:**

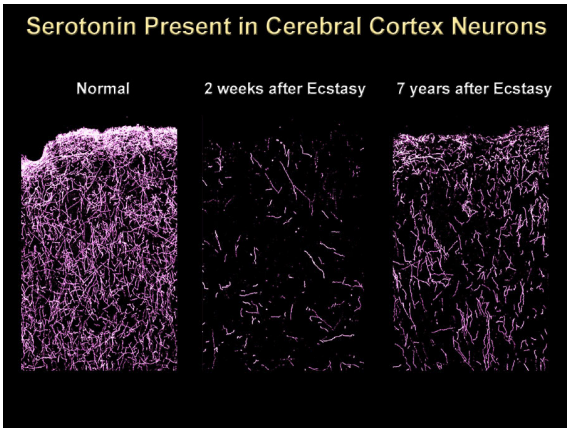
- Feel Good – Euphoria/reward
- Feel Better – Reduce negative feelings

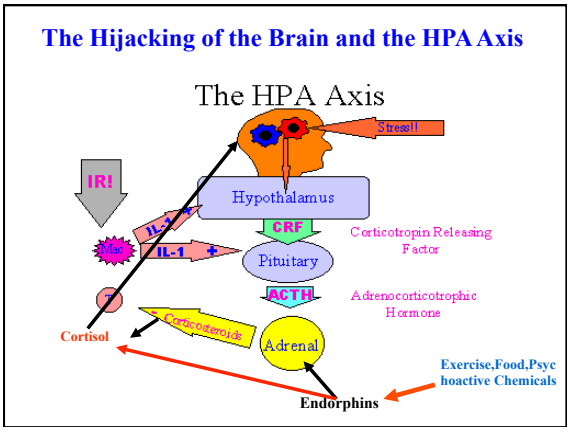

Activation of the reward pathway by addictive drugs
alcohol
cocaine
heroin
nicotine
Amphetamines
Opiates
THC
PCP
Ketamine
Nicotine
heroin
Alcohol
benzodiazepines
barbiturates
Nucleus accumbens
Dopamine Pathways


GABA
Alcohol
Benzodiazepines
Valium
Xanax
Ativan
Non benzodiazepine
Ambien
Sonata
Barbiturates
Fiorinal
Soma
Norepinephrine
Cocaine
Amphetamine
Methamphetamine
Ephedrine
Ritalin
Serotonin
LSD
Psilocibin
DMT
Ibogaine
Cannabinoid-Anandamide
Marijuana
Acetylcholine
Nicotine
Ecstasy
Mescaline
DOM
NMDA
PCP
Ketamine
Opiate
Opioids
Opiates
Heroin
Buprenex
Oxycontin
GHB


Alcohol and the Adolescent Brain
15-year-old male non-drinker
15-year-old male heavy drinker
69

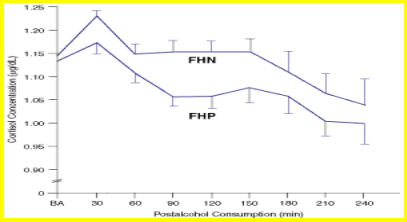

SPECT SCANS
Alcohol 25 yrs
Cocaine 2 yrs
Normal
Marijuana 12 yrs


Serotonin Present in Cerebral Cortex Neurons
Normal
2 weeks after Ecstasy
7 years after Ecstasy


The Hijacking of the Brain and the HPA Axis
The HPA Axis
Stress!!
IR!
Hypothalamus
CRF
Corticotropin Releasing Factor
Mac
IL-1
IL-1
Pituitary
ACTH
Adrenocorticotrophic Hormone
Cortisol
Corticosteroids
Adrenal
Exercise,Food,Psychoactive Chemicals
Endorphins

Cortisol Research in Families

The illustration below is from Vol. 19, No. 3, 1995 of the Journal *Alcohol Health & Research World.*



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"The Necessary Nine"

- Norepinephrine/Epinephrine-stimulant,anger,fear,anxiety,fight,flight
- Serotonin-depressant,sleep,calm,pleasure
- GABA-relaxant,stress reduction,seizure threshold
- Endorphins-pain relief,pleasure
- Acetylcholine-involutary actions,memory,motivation
- Anandamide-memory,new learning,calmness
- Glutamate-organization of brain signaling,memory,pain
- Dopamine-perception,movement,pleasure
- PIP- loving of one's self,others,GOD

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"Human Doing" "Human Being"

Neurotransmitters of Dependence

Dependence

Recovery

PIP
Dopamine
Glutamate
Acetylcholine
Anandamide
Endorphins / Enkelphins
GABA
Serotonin
Epinephrine / Norepinephrine

Depletion may take less than 12 months

Replenishment may take 5 to 7 years

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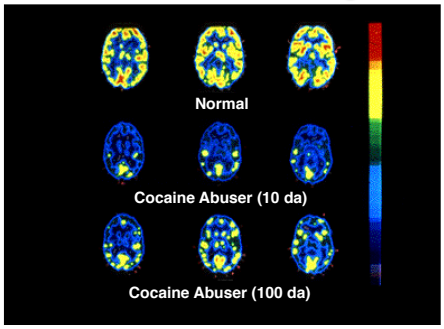
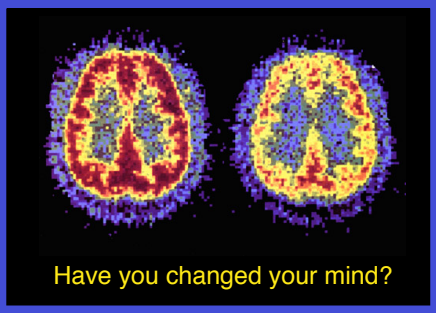
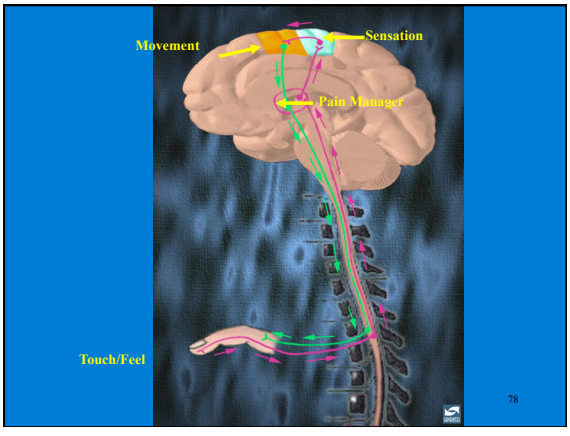
Your Brain After Drugs







Brain Reward Cascade

Serotonin

↓

Enkephalins

↓

Dopamine

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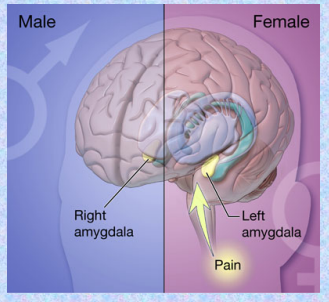
The Pain Brain



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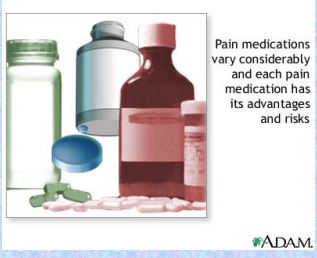
Pain and Addiction



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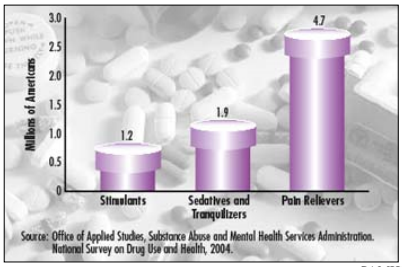
More than 10 Million Americans Reported Current Use of Prescription Drugs for Nonmedical Purposes in 2013

When used in ways other than they are prescribed, prescription drugs have the potential for **abuse** and **addiction**



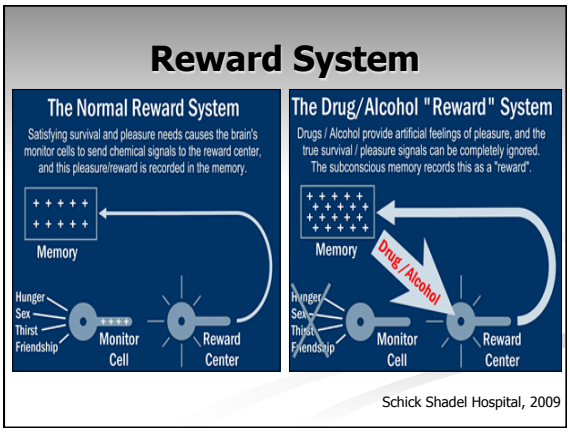
SAMHSA 2009

Opiates/Opioids Potency

- **Opiates(Opium Poppy Extracts/ Modifed Extracts)**
- **Morphine(Various) = 1.0**
- **Codeine(Tylenol #3) = 0.4**
- **Opium(Paregoric) = 0.8**
- **Diacetylmorphine(Heroin) = 1.5**
- **Hydrocodone(Vicodin) = 3.0**
- **Oxycodone(Oxycontin, Percodan) = 4.0**
- **Hydromorphone(Dilaudid) = 5.0**

Opioids Potency

- **Meperidine(Demerol) = 1.0**
- **Propoxyphene(Darvon) = 0.7**
- **Pentazocine(Talwin) = 0.5**
- **L acetyl alpha methadol(LAAM)= 2.0**
- **Methadone (Dolophine) = 3.0**
- **Levomethadyl acetate HCl (Orlaam) = 3.0**
- **Fentanyl(Sublimase) = 50.0**
- **Sufentanyl(Various) = 100.0**
- **Alpha Sufentanyl (Various) = 200.0**



Schick Shadel Hospital, 2009

The Anti-Reward Brain

- 1. A key element of addiction is the development of a negative emotional state during drug abstinence.
- 2. The neurobiological basis of the negative emotional state derives from two sources: decreased reward circuitry function and increased anti-reward circuitry function.
- 3. The anti-reward circuitry function recruited during the addiction process can be localized to connections of the extended amygdala in the basal forebrain.
- 4. Neurochemical elements in the antireward system of the extended amygdala have as a focal point the extrahypothalamic corticotropin-releasing factor system.
- 5. Other neurotransmitter systems implicated in the anti-reward response include norepinephrine, dynorphin, neuropeptide Y, and nociceptin.
- 6. Vulnerability to addiction involves multiple targets in both the reward and anti-reward system, but a common element is sensitization of brain stress systems.
- 7. Dysregulation of the brain reward system and recruitment of the brain anti-reward system are hypothesized to produce an allostatic emotional change that can lead to pathology.
- 8. Nondrug addictions may be hypothesized to activate similar allostatic mechanisms.

ANTI-REWARD

The concept of an anti-reward system was developed to explain one component of time-dependent neuroadaptations in response to excessive utilization of the brain reward system.
The brain reward system is defined as activation of circuits involved in positive reinforcement with an overlay of positive hedonic valence.
The neuroadaptation simply could involve state-shifts on a single axis of the reward system (within- system change; dopamine function decreases).
However, there is compelling evidence that brain stress/emotional systems are recruited as a result of excessive activation of the reward system and provide an additional source of negative hedonic valence that are defined here as the anti-reward system (between-system change; corticotropin-releasing factor function increases). The combination of both a deficit in the reward system (negative hedonic valence) and recruitment of the brain stress systems (negative hedonic valence) provides a powerful motivational state mediated in part by the anti-reward system.
(Koob & Le Moal 2005).