The Pain of Pleasure: The Adolescent Brain On Heroin

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Challenges

- While there were 16,235 deaths involving prescription opioids in 2013, an increase of 1% from 2012, the number of deaths involving heroin increased dramatically. There were 8,257 heroin-related deaths in 2013, up 39% from 2012. Total drug overdose deaths in 2013 hit 43,982, up 6% from 2012.

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Challenges- 2016

- Drug overdose is the leading cause of accidental death in the US, with 47,055 lethal drug overdoses in 2014. Opioid addiction is driving this epidemic, with 18,893 overdose deaths related to prescription pain relievers, and 10,574 overdose deaths related to heroin in 2014.

Current Prevention Strategies 2016

- Prescription Monitoring Programs
- Safe Storage
- Avoiding Risky Combos
- Urine Drug Testing
- Overdose Education
- Taking opioids as prescribed
- Mandatory Prescriber Safe Opioid CME
- Treatment agreements "Pain Contracts"
- Naloxone
- Abuse-Deterrent Opioids
- Safe Disposal
- Insurer Lock In Programs-one prescriber/one pharmacy

How Many Strategies Does Georgia Have in Place?

- PDMP- Yes
- Safe Storage- Yes/No
- Avoiding Risky Combos-No
- UDS- Yes
- Overdose Education- No
- Taking opioids as prescribed- No
- Mandatory Prescribing CME- Yes/No
- Treatment Pain Contracts- Yes/No
- Naloxone-Yes
- Abuse Deterrent Opioids- Yes/No
- Safe Disposal-Yes/No
- Insurer Lock Ins-One Physician/One Pharmacy- No
- Multiple Educational Curriculum on Opioids and Addiction- Yes/No

Opioids: Double-edged sword

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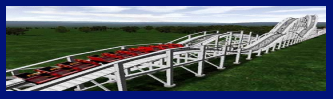
Who is At Risk for Developing An Addiction?

- Young developing brains- 12-26years
- Aging declining brains 50+ years
- Pain brains-acute or chronic
- Trauma brains-physical or emotional
- Stress brains- competition, grades, relationships, $$
- Genetic brains- family history of addiction, mental illness, trauma, suicide
- High use brains- low dose long time or high dose short time
- Mentally disordered brains-ADHD, MDD, GAD, BP I or II, psychosis

Adolescent Brain Development- The Chemistry of Early Adulthood

3 Pathways (rides) through adolescence (Caviola & Kane- Caviola, 1989,) :

(1) The Kiddy Roller Coaster – continuous growth group (23%) - well-adjusted teens who meet the demands of this stage.



(2) Go For a Ride or 2 on the Big Roller Coaster - surgent growth group (35%) comprised of reasonably well-adjusted youngsters, who may have difficulty coping with unexpected trauma.

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3 Pathways (rides) through adolescence (Caviola & Kane- Caviola, 1989,) :

(3) Go For the Biggest, Scariest Roller Coaster You Can Find - tumultuous growth group (42%) characteristic of the adolescent turmoil hypothesized by the 'storm and stress' theorists.

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Which One?

(1) The Kiddy Roller Coaster

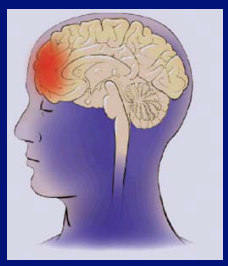
(2) Go For a Ride or 2 on the Big Roller Coaster

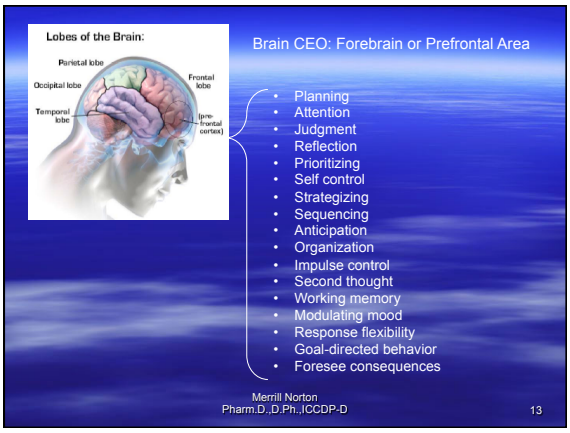
(3) Go For the Biggest, Scariest Roller Coaster

The Prefrontal Cortex is the "Boss" of the brain.

It governs good judgment, complex thinking, decision making, planning and impulse control and in forming of adult personality traits

Majority of prefrontal brain wiring takes place by age 16, and continues to develop until about age 24-26




Lobes of the Brain:
Parietal lobe
Occipital lobe
Temporal lobe
Frontal lobe
(pre-frontal cortex)
Brain CEO: Forebrain or Prefrontal Area
Planning
Attention
Judgment
Reflection
Prioritizing
Self control
Strategizing
Sequencing
Anticipation
Organization
Impulse control
Second thought
Working memory
Modulating mood
Response flexibility
Goal-directed behavior
Foresee consequences
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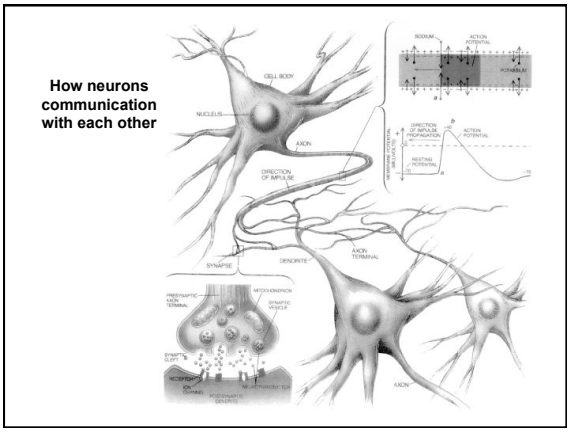
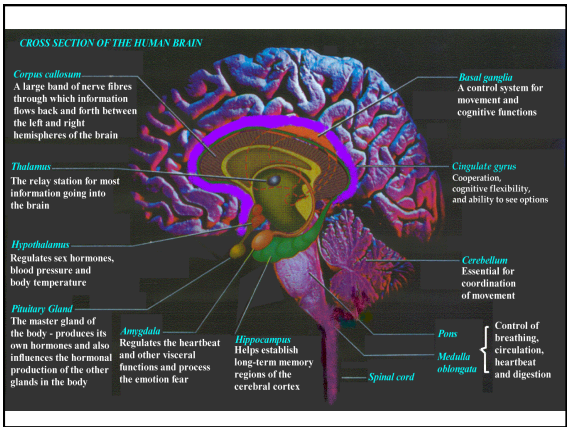
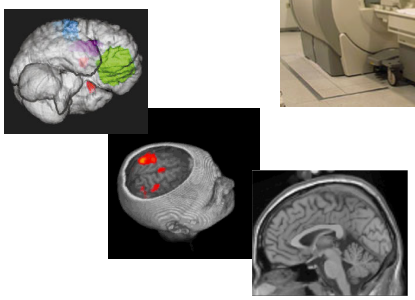

How neurons communication with each other
CELL BODY
NUCLEUS
AXON
DIRECTION OF IMPULSE
DENDRITE
SYNAPSE
AXON TERMINAL


CROSS SECTION OF THE HUMAN BRAIN
Corpus callosum
A large band of nerve fibres through which information flows back and forth between the left and right hemispheres of the brain
Thalamus
The relay station for most information going into the brain
Hypothalamus
Regulates sex hormones, blood pressure and body temperature
Pituitary Gland
The master gland of the body - produces its own hormones and also influences the hormonal production of the other glands in the body
Amygdala
Regulates the heartbeat and other visceral functions and process the emotion fear
Hippocampus
Helps establish long-term memory regions of the cerebral cortex
Basal ganglia
A control system for movement and cognitive functions
Cingulate gyrus
Cooperation, cognitive flexibility, and ability to see options
Cerebellum
Essential for coordination of movement
Pons
Medulla oblongata
Control of breathing, circulation, heartbeat and digestion
Spinal cord

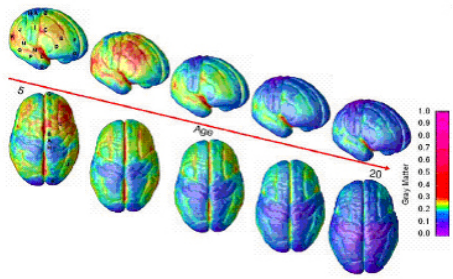
The "Oops" Center- anterior cingulate gyrus

- The cingulate is responsible for helping focus attention
- Links cingulate and emotional hippocampus for integrating reason & emotion to guide decisions
- May involve ability to empathize
- Undergoes high myelination (doubles) during adolescence
- "Oops center" anticipates risk, detects and keeps us from making errors
- Last to area to develop until age 24-26

Functional Magnetic Resonance Imagery (FMRI)



Time-lapse imagery of brain age 5 to 20

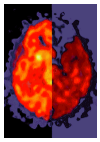


Note: red shows more gray matter while blue shows less gray matter. Gray matter wanes as the brain matures and neurons are pruned. Areas for basic function mature early; higher executive functions later.

Going up in smoke: effects of smoking, alcohol, and drugs

- The reward center in adolescent brains is not as responsive as adult brains
- Lower dopamine levels may take drugs to activate pleasure circuits
- High risk and substance abuse require little effort for greater reward
- Addictions starves cells of dopamine, triggering craving
- Use of addictive substances during adolescence make it more likely to become addicted as an adult– (88% of adult smokers started before 18)
- Adolescents required twice as much nicotine as adults, which continued when they become adults
- Alcohol quickly impairs the hippocampus, reduces its size, and may be long lasting
- Cognitive impairment can persist weeks after stopping drinking and make them more sensitive to impairments later in life

Alcohol damage to the cerebellum



PET scan of non-drug user (left) and Ecstacy user (right) regarding serotonin activity. Suggests permanent brain damage

Heroin and Opioids- Adolescent Pathways

The "Why" Heroin Is So Deadly

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Who is At Risk to Move From Abuse to Addiction

- The reason for this study is to identify potential addiction predictability risk factors in student-pharmacists to create an assessment instrument in pharmacy for determining addiction risk factors in future pharmacists.
- These risk factors are:
- 1.) Age of First use;
- 2.) Family History of Addiction/Mental Illness;
- 3.) Current Alcohol/Drug Use;
- 4.) Trauma History;
- 5.) Impulsivity;
- 6.) Negative Proscriptions;
- 7.)Protective Factors;
- 8.) Genetic Use Patterns.
- 9.) Stress Patterns
- The intent of gathering this information is in effort to develop a model for an effective Alcohol and Drug Education and Intervention Program that may be replicated nationally.

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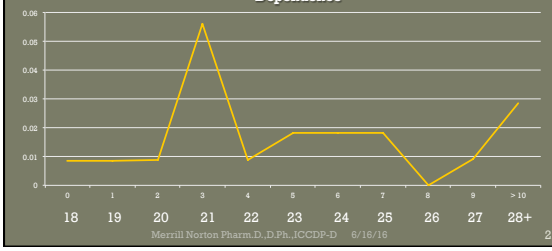
Preliminary Results

The probability of transitioning from alcohol use to dependence is greatest three years after the first use of alcohol

Proportion of At-Risk Respondents Who Transition To Alcohol Dependence



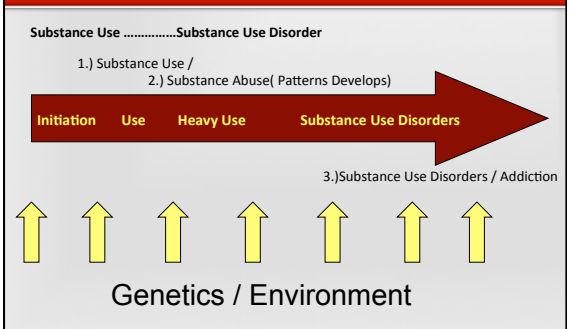
Preliminary results from a cohort of student pharmacists who developed dependence after their first use of alcohol suggest that the probability of transitioning to dependence remains relatively constant at 1% for two years after first use. By the third year the probability of transitioning to dependence peaks at 6% but subsequently decreases to 2% years four through seven. A small but noticeable rise in probability occurs eight to ten years after first use, increasing to approximately 3%. **In short, the probability of transitioning from alcohol use to dependence is greatest three years after first use of alcohol** .

"Let's just go in and see what happens."

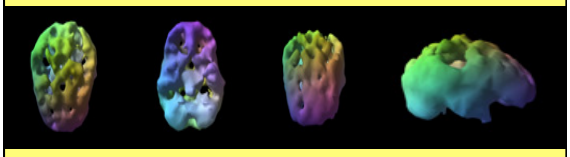
UGA Statistics

- Alcohol Use in last 30 days: 83.4%
- Marijuana Use in last 30 days: 21.4%
- Non medical use Rx drugs: 20.5%
  - University of Georgia Executive Summary Spring 2014
  - American College Health Association National College Health Assessment II ACHA-NCHA II

Predisposition & Progression

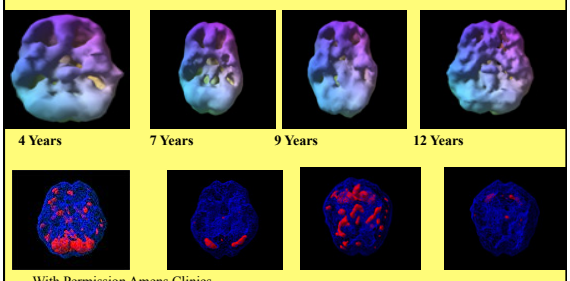


Alcohol Spect Scans



Alcohol Use of 7 Years

Marijuana Spect Scans



4 Years 7 Years 9 Years 12 Years

With Permission Amens Clinics

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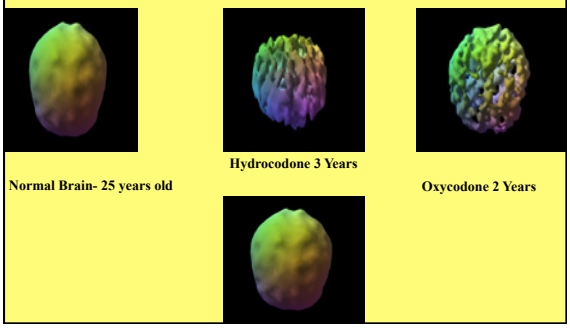
Opioids Spect Scans



Normal Brain- 25 years old

Hydrocodone 3 Years

Oxycodone 2 Years

Opiates (Natural Alkaloids)

Natural alkaloids

- morphine → heroin
- codeine → oxycodone, hydrocodone
- thebaine → buprenorphine, naloxone

OPIOIDS
fully synthetic

OPIATES

Bind to opioid receptors

Morphine-like action

DSM-5: **OPIOIDS**

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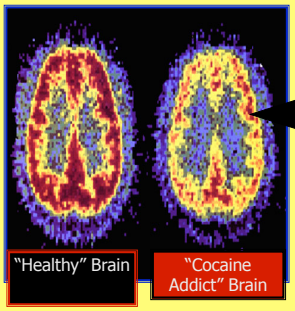
Addiction *is* a Brain Disease



Prolonged Use Changes the Brain in Fundamental and Lasting Ways

The Brain

The brain is the most complex organ in the body. Necessary to do and enjoy daily activities such as to create art, to interpret and respond to experiences, to breath…

We will explain to you

- How different parts of the brain work in a team to coordinate and perform different functions.
- How drugs alter important areas necessary for life sustaining functions.
- How these changes to the brain can drive compulsive drug use that marks addiction.

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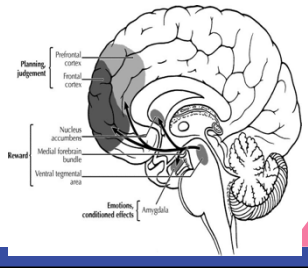
Brain Region Overview

Prefrontal (choices/good/bad) → nucleus accumbens (reward pathways) --> Ventral Tegmental Area (memory)



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Opioid Receptors

- μ (mu):
  - Activated by morphine: analgesia
  - Primary action site of all opioids
  - Distribution: primarily in CNS and also GI
  - Linked to substance use disorders
- κ (kappa): analgesia, endocrine changes and dysphoria (brain-amygdala, spinal cord)
- δ (delta): for endogenous peptides

(brain, hypothalamus, spinal cord)

Opioid Receptors (I)

- **Five classes of opioid receptor**
  - **Mu(μ), Delta(δ), Kappa(κ) Nociceptin Subtypes (σ, ε receptors**
- **Subtype of μ, δ, κ receptor**
- **Structural characteristics** (The more characteristics- the higher addiction liability)**
  - **Typical G-protein-coupled receptor**
    - **Seven hydrophobic region**
    - **Three intracellular loops**
    - **Three extracellular loops**
    - **Intracellular carboxy-terminal tail**
    - **Extracellular amino-terminal tail**

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Opioid Receptors (II)

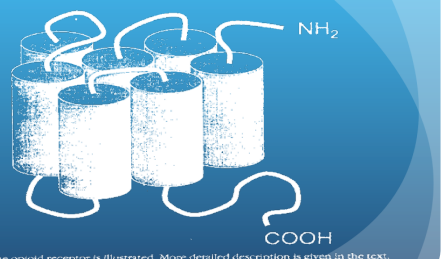
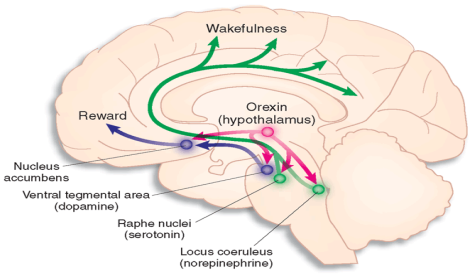


Fig. 1. The opioid receptor is illustrated. More detailed description is given in the text.

The Basic Pharmacology of the Endogenous Opioids



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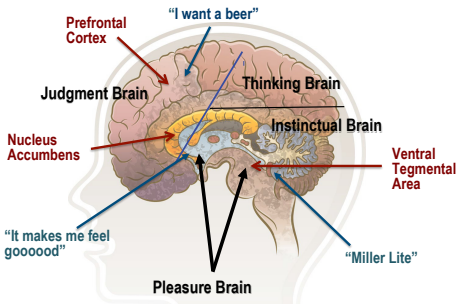

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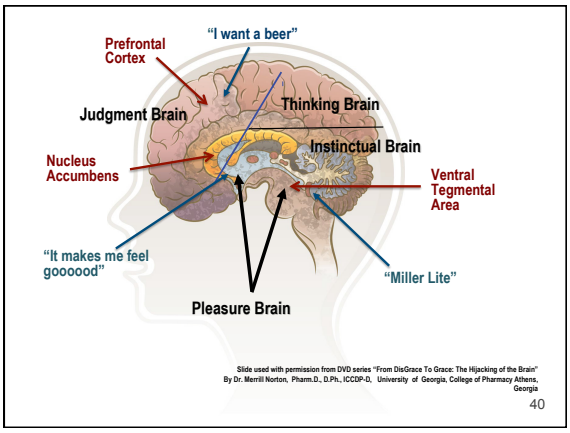
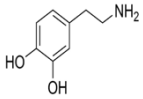


Dopamine

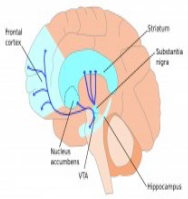


Primary chemical in the brain responsible for activating the reward pathway

During the preoccupation phase of addiction, dopamine is being released stimulating desire for a drug

During the intoxication phase, all the dopamine in the brain is released giving the user a euphoric feeling

During the withdrawal phase, the brain has run out of dopamine and can not function properly until more is made



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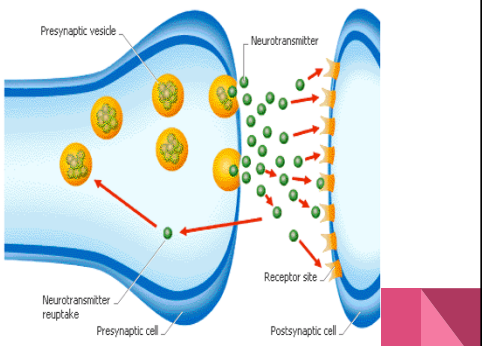

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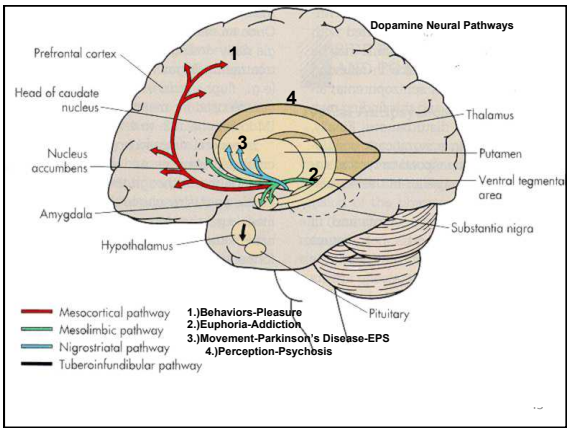
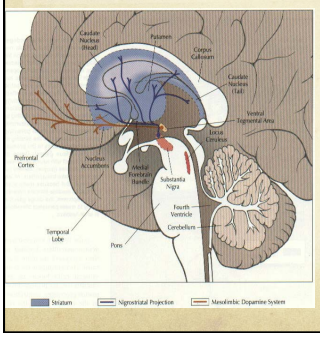


MESOLIMBIC DOPAMINE SYSTEM



- Circuit #1 Use- Dopamine
  - **Relief/Like**
    - Pleasure/Pain circuit
      Meso-accumbens
- Circuit #2 Abuse-Endorphins
  - **Repeat/Want**
    - Desire and urge circuit
      Basolateral n. of amygdala
- Circuit #3 Addiction-Dynorphin A/B
  - **Need/Craving**
    - Pathologic desire & demand circuit
      Periaqueductal gray of brain stem
      Stimulation of the periaqueductal gray matter of the midbrain activates enkephalin-releasing neurons that project to the raphe nuclei in the brainstem.
      Enkephalin (endogenous opioid neurotransmitter), binds to mu opioid receptors.

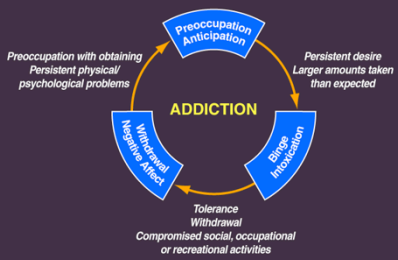
Heroin Addiction is Greater Than a Mother's Love

- The reason for the that addicts can not stop using is once the dopaminergic system is deactivated (depleted) due to multiple neurobiological reasons- the reinforcing effects(dynorphin) of the drug becomes more powerful than a mother's love(dynorphin) for her children. In 2016, the potencies of most street drugs (marijuana/heroin) has increased. This increased potency creates the increased reinforcing effects of dopamine thus increasing the addiction liability of the drug on the brain.

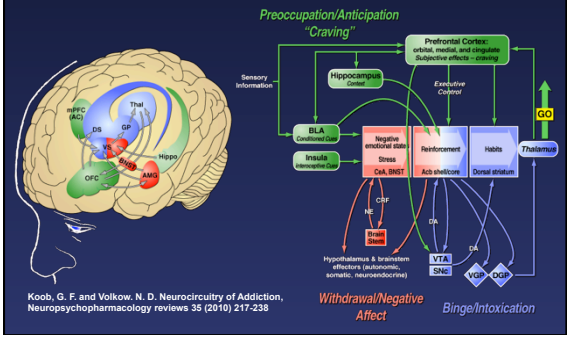
The "Why" Heroin is So Deadly

- Heroin crosses the blood-brain barrier one-hundred faster than morphine. This rapid diffusion is due to heroin being highly soluble in lipids.
- Heroin's short-term effects will last over a period of three to six hours.
- Pinpoint pupils. Nausea and vomiting. Constipation or explosive diarrhea. Urinary retention due to activity on GIT sphincter muscle systems (plus anticholinergic activity-dry mouth, blurred vision)
- Depression of medulla oblongata creates bradycardia (heart rate below 60 BPM) and abnormal low respirations (less than 8 per minute)

Stages of the Addiction Cycle



Neurobiology of Addiction



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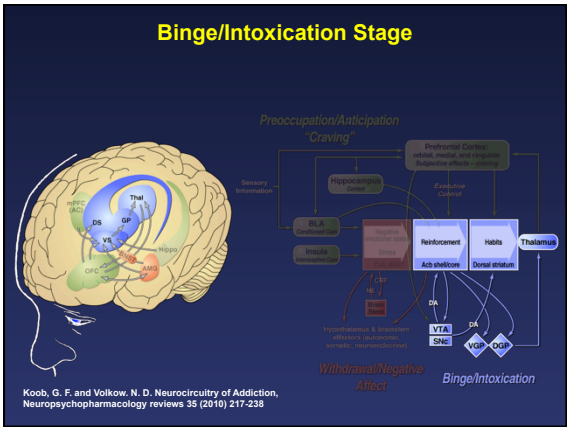
Binge/Intoxication Stage



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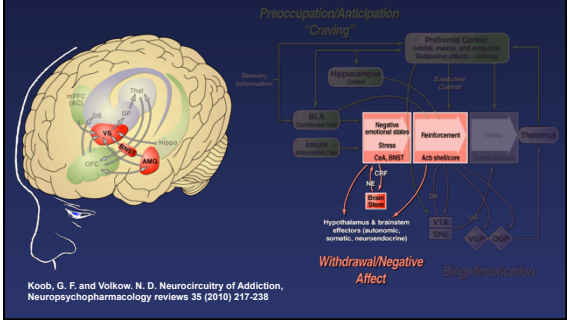
Withdrawal/Negative Affect Stage



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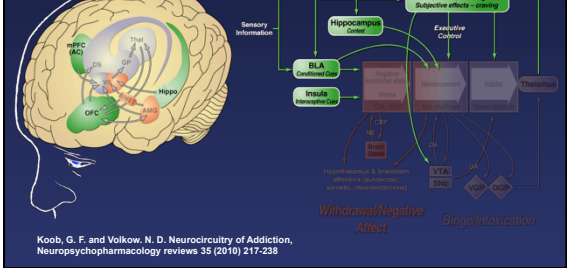
Preoccupation/Anticipation "Craving" Stage



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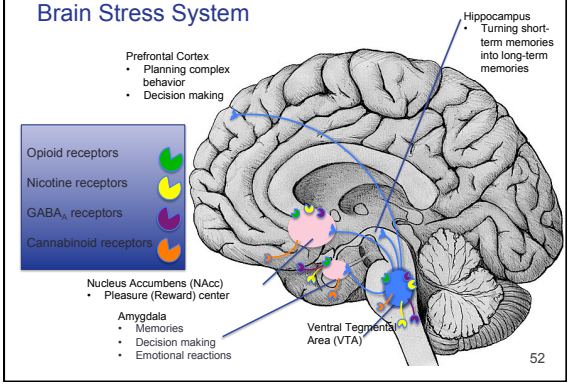
Brain Stress System



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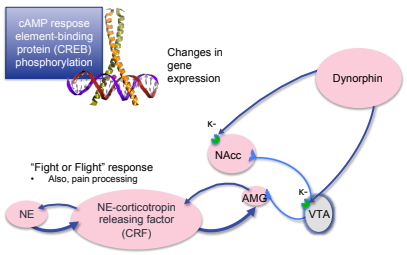
Brain Stress System



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Neuroadaptation

The more a drug is used, the more the brain gets accustomed to its effects. This can cause long term changes in the nervous system. The begins to change the mesolimbic dopaminergic system circuits.

This ultimately leads to increased tolerance to the drug.

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Tolerance vs. Reverse Tolerance

Tolerance

Drug/Alcohol effectiveness has decreased due to chronic administration

Consumption of larger quantity of abused substance → more tolerance

- Larger Dose is needed to achieve same effects
- Diminishes over time with abstinence

Reverse Tolerance

The more often you consume drugs and/or alcohol, the greater the positive effects appear to be

More frequent consumption of abused substance → more tolerance

- Same dose is needed, but more frequently, to achieve same effects
- Continues long after the use of alcohol or drug of choice has been stopped
- Environmental/social influence

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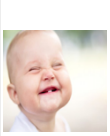
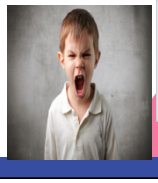
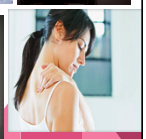
Positive Reinforcers Negative Reinforcers







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Receptor Sensitization

Liking- Occassional Use- → Circuit # 1

Wanting- Use with a Pattern → Circuit # 2

Craving- Compulsive Use Circuit # 3

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Addiction

- A state of periodic and chronic intoxication.
  - An overpowering desire or need to obtain the drug at any means necessary.
  - A tendency to increase the dose.
  - A psychological and physical dependence on the effects of the drug.
  - A negative affect when in abstinence state.

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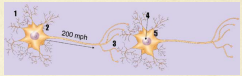
The Anti-Reward Brain

- **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.**

Merrill Norton Pharm.D.,D.Ph.,ICCDP-D 59

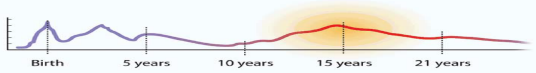
Peaks of Brain Plasticity

The word "plasticity" is a term used to describe the brain's ability to physically change its internal structure (by making more dendrites) when we learn new things or have new experiences.



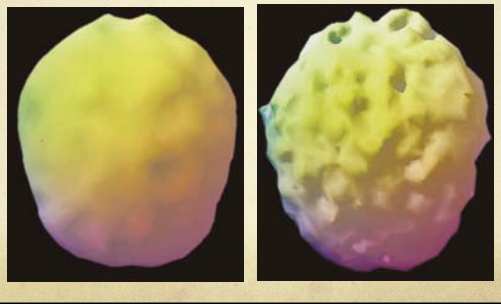
During peaks of plasticity the brain must make key neural connections to wire us to become a responsible, thoughtful, intelligent adults

Drinking alcohol during peak periods of plasticity can seriously damage brain wiring



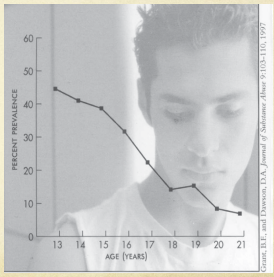
Levels in the brain of a healthy non-drinker (left).....and that of a sober 21-year old with a 4 year history of heavy alcohol use (right).

*The "holes" indicate areas of significantly reduced brain activity



40% of kids who begin drinking at age 15 will become alcoholics.

Only 7% of those who begin drinking at age 21 become alcoholics.



Alcohol acts like a computer virus in a teen brain

- Slows or shuts down brain activity
- Damages neuro-connections
- Decreases the ability to learn
- Hinders brain wiring that a teen needs to become a responsible,

thoughtful adult.

The Pain of Pleasure- Rx Drug Abuse and Its Implications

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Katy Janousek, MS, CHES

#dawgstakeasdirected

- **8 key messages**
- **Webpage to explain messages and provide more information**
  - **https://www.uhs.uga.edu/dawgstakeasdirected/**
- **Poster and Cup Campaign**

The Partnership for Safer Medication Use Initiative on UGA Campus

The Fontaine Center
Prevention. Early Intervention. Support Services.

UGA Student Affairs | University Health Center

THE UNIVERSITY OF GEORGIA COLLEGE OF PHARMACY

RX for Safer Medication Use Initiative

1. Dawgs take Rx as directed
2. Dawgs don't mix Rx pills with alcohol
3. Dawgs use Rxs responsibly
4. Dawgs call 911 for Rx emergencies
5. Dawgs don't share Rxs
6. Dawgs ask professionals about Rxs
7. Dawgs study Rx safe
8. Dawgs drop box the Rx leftovers

Thank You For Your Time

Any Questions?

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