The Anti-Reward System of the Adolescent Brain: Part 1

Dr. Merrill Norton Pharm.D.,D.Ph.,ICCDP-D
Clinical Associate Professor
University of Georgia College of Pharmacy
Athens, Geōrgia
mernort@uga.edu

Objectives

- Participants should be able to:
- Recognize the latest neurotransmitter research of psychoactive substance use disorders, anxiety, and depression in the adolescent brain;
- Explain the neurochemical basis of the hijacking of the HPA axis (anti-reward) and its effects on the stress mechanisms of the adolescent brain;
- Describe the neurobiological basis of psychoactive substance use, depressive, and anxiety disorders in the adolescent brain;
- Explain the four types of genetic predispositions of alcoholism in adolescents;
- Provide an educational discussion of current medications use to treat adolescent addiction, anxiety, and depressive disorders.

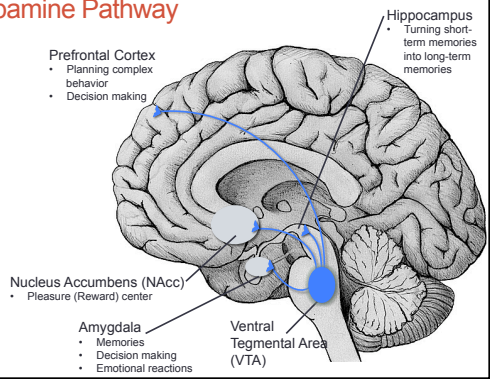
ADDICTION

The Reward Deficit and Stress Disorder

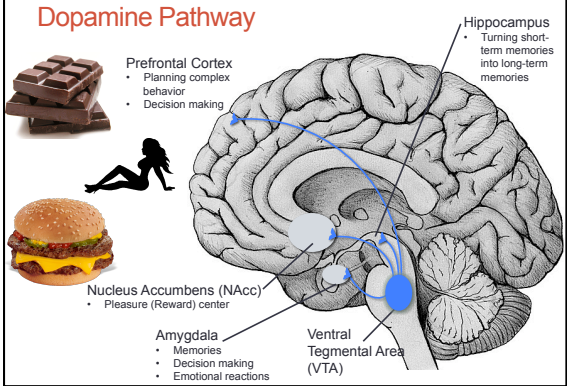
Andrew Popovici, PharmD Candidate
Albert Elakatt, PharmD Candidate
Dr. Merrill Norton, PharmD,D.Ph.,ICCDP-D, Clinical Associate Professor

Brain Reward System

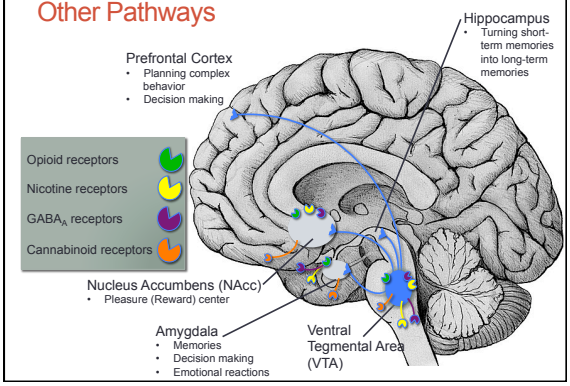
Dopamine Pathway



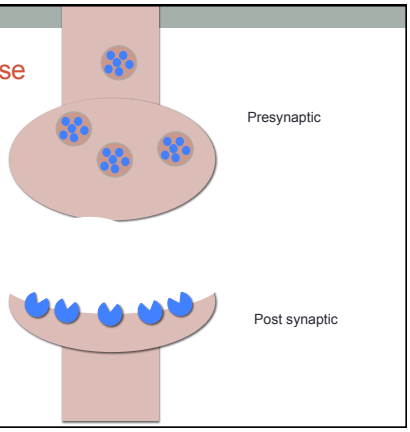
Dopamine Pathway



Other Pathways



The Synapse



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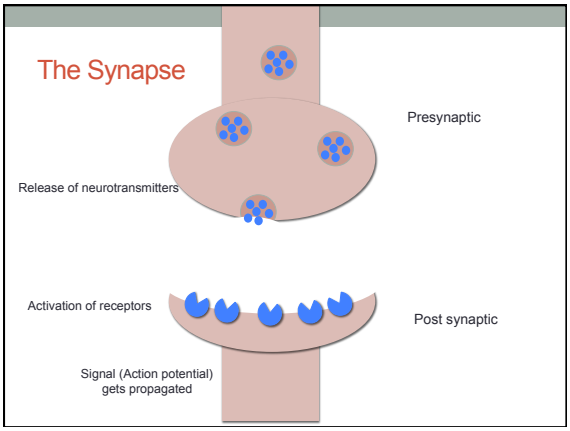

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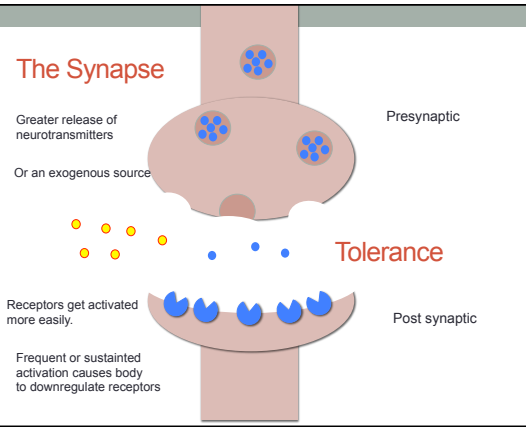
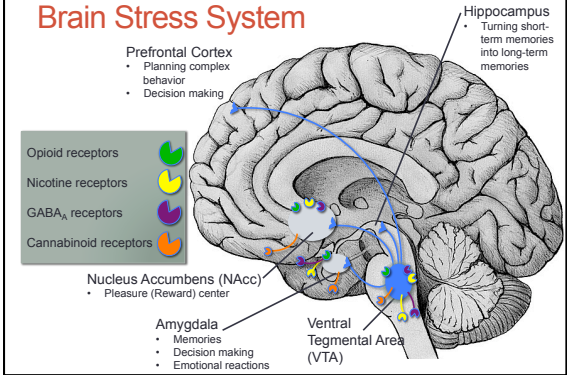
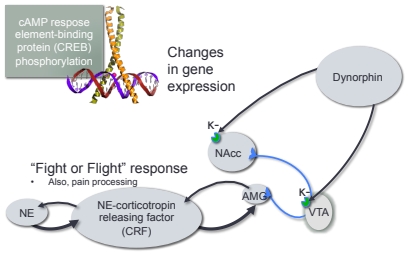


Brain Stress System

Brain Stress System



Brain Stress System



"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**

Human Doing — Neurotransmitters of Substance Use Disorders — Human Being

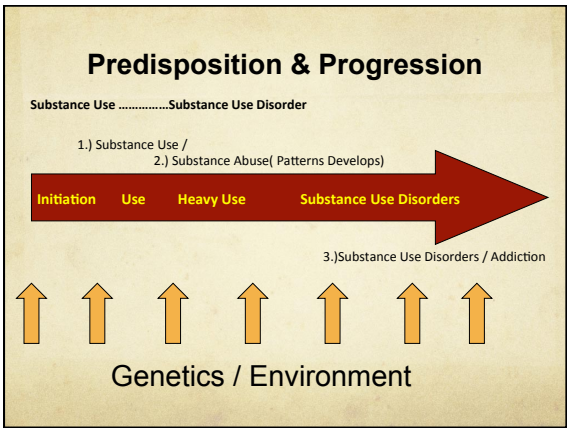
Substance Use Disorders

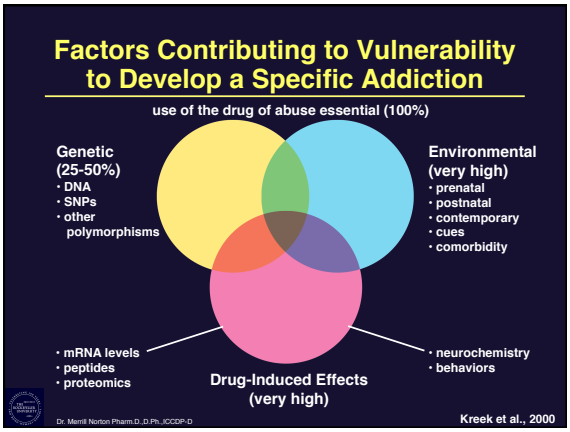
PIP
Dopamine
Glutamate
Acetylcholine
Anandamide
Endorphins / Enkelphins
GABA
Serotonin
Epinephrine / Norepinephrine

Recovery

Depletion may take less than 12 months

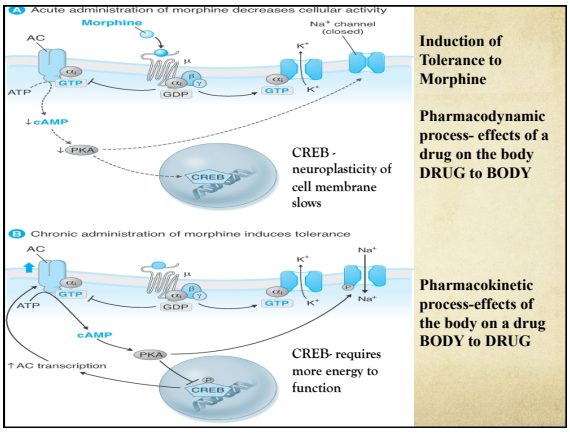
Replenishment may take 5 to 7 years





Basic Pharmacology

- Pharmacodynamics is the study of what the drug does to the body (DRUG to BODY)
- – dynamics = change
- Pharmacokinetics is the study of what a body does with a dose of a drug (BODY to DRUG)
- – kinetics = motion
  – Absorbs, Distributes, Metabolizes, Excretes



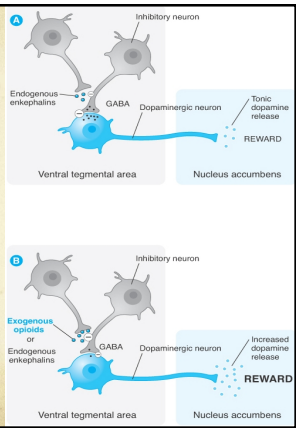
Induction of Tolerance to Morphine

Pharmacodynamic process- effects of a drug on the body DRUG to BODY

Pharmacokinetic process-effects of the body on a drug BODY to DRUG

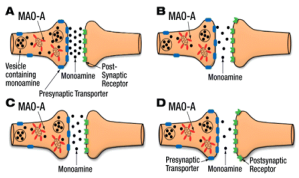
Reward Brain Pathways:
(Dopamine, Endorphins, Serotonin)
Role of Opioids
1.) Pain Management- A Good Thing
2.) Euphoria- Adverse Drug Effect- Not Desired

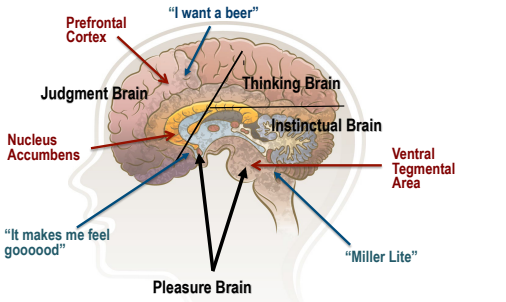
Anti-Reward Brain Pathways:
(Glutamate, GABA)
1.) Withdrawal
2.) Tolerance
3.) Craving



THE RECEPTOR SENSITIVITY HYPOTHESIS

- Supersensitivity and up-regulation of post-synaptic receptors leads to depression
- Suicidal and depressed patients have increased 5HT-α_2 receptors





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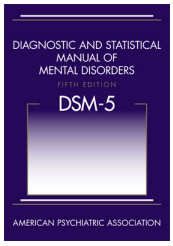
Addiction

- A chronic, relapsing disorder characterized by:
  - A **compulsion** to seek and take drugs
  - The **loss of control** over drug intake
  - And the emergence of a **negative emotional state** (dysphoria, anxiety, and irritability) when access to the drug is prevented

New Classification: Substance Use Disorder

DSM-5



- Combines previous categories of substance abuse and substance dependence into a single disorder
- Each substance is categorized as its own disorder (alcohol use disorder, stimulant use disorder), but nearly all substances are diagnosed based on the same overarching criteria
- Clarification with the term dependence:
  - Often confused with "addiction"
  - Dependence can be a normal body response to a substance

New Classification: Addictive Disorder DSM-5

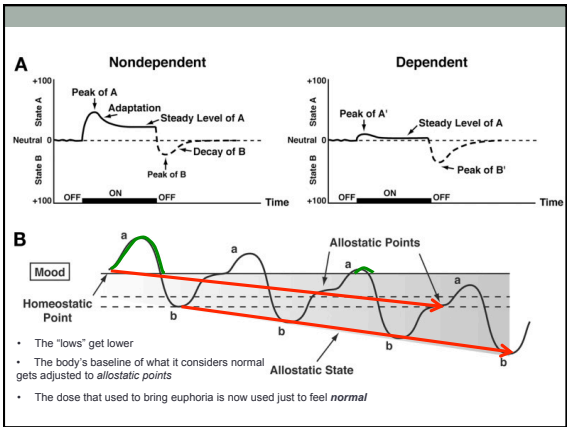
- New category of behavioral addictions
- Currently only includes gambling disorder
- New findings show similarity to substance-related disorders in:
  - Clinical expression
  - Brain origin
  - Comorbidity
  - Physiology
  - And Treatment

The Addiction Cycle

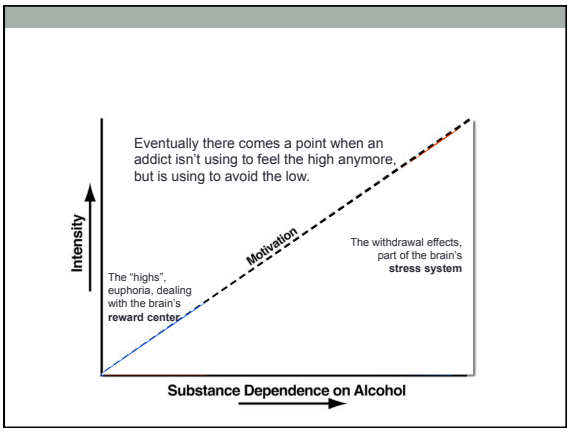
Binge/ Intoxication

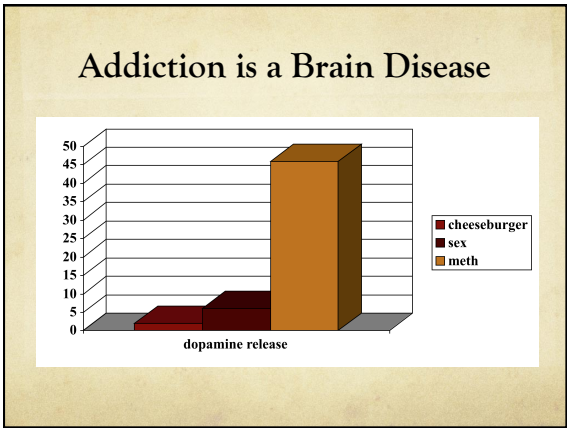
Withdrawal/ Negative Effect

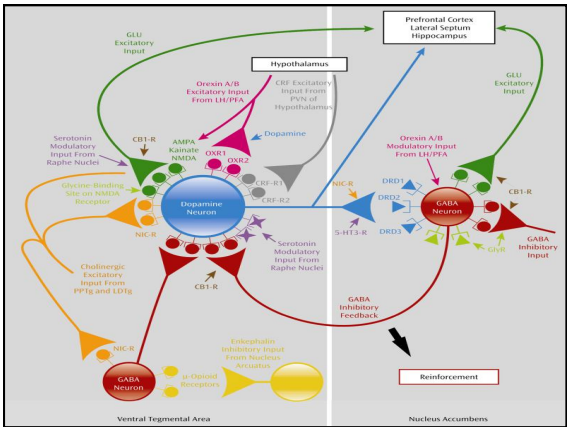
Preoccupation/ anticipation



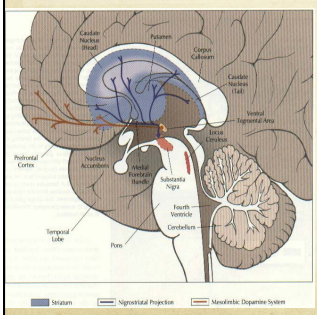
- The "lows" get lower
- The body's baseline of what it considers normal gets adjusted to *allostatic points*
- The dose that used to bring euphoria is now used just to feel ***normal***


Eventually there comes a point when an addict isn't using to feel the high anymore, but is using to avoid the low.
Intensity
Motivation
The withdrawal effects, part of the brain's stress system
The "highs", euphoria, dealing with the brain's reward center
Substance Dependence on Alcohol

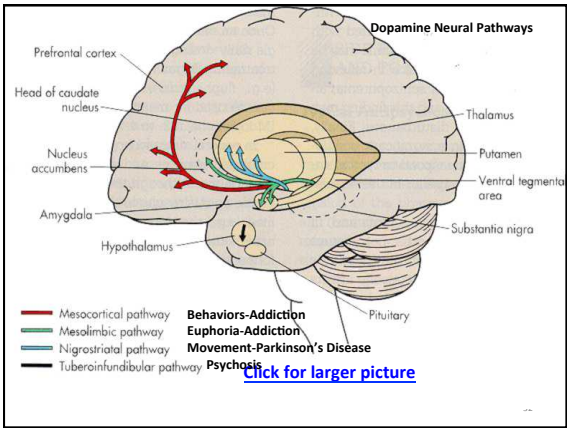

Addiction is a Brain Disease
50
45
40
35
30
25
20
15
10
5
0
cheeseburger
sex
meth
dopamine release


Prefrontal Cortex
Lateral Septum
Hippocampus
Hypothalamus
GLU Excitatory Input
Orexin A/B Excitatory Input From LH/PFA
CRF Excitatory Input From PVN of Hypothalamus
Dopamine
Serotonin Modulatory Input From Raphe Nuclei
CB1-R
AMPA
Kainate
NMDA
OXR1
OXR2
Glycine-Binding Site on NMDA Receptor
CRF-R1
CRF-R2
Dopamine Neuron
NIC-R
Cholinergic Excitatory Input From PPTg and LDTg
Serotonin Modulatory Input From Raphe Nuclei
GABA Inhibitory Feedback
Orexin A/B Modulatory Input From LH/PFA
DRD1
DRD2
DRD3
5-HT3-R
GABA Neuron
CHR
GABA Inhibitory Input
Encephalin Inhibitory Input From Nucleus Accumbens
μ-Opioid Receptors
Reinforcement
Ventral Tegmental Area
Nucleus Accumbens

MESOLIMBIC DOPAMINE SYSTEM



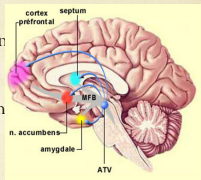
- Circuit #1
  - **Relief/Like**
    - Pleasure/Pain circuit
      Meso-accumbens
- Circuit #2
  - **Repeat/Want**
    - Desire and urge circuit
      Basolateral n. of amygdala
- Circuit #3
  - **Need**
    - Pathologic desire & demand circuit
      Periaqueducal gray of brain stem
      Stimulation 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.



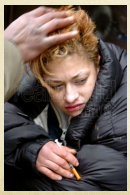
Click for larger picture

Addiction creates a powerless state because of *where and how* the brain is altered

- Pathways include projections from the ventral tegmental area (VTA) of the brain through the median forebrain bundle (MFB), and terminating in the nucleus accumbens (Nuc Acc), in which dopamin neurons are prominent
- These centers near the brainstem and hypothalamus areas are not very responsive to the cerebral cortex



Addiction Drivers



- The same neural circuitry that drives aggression for defense of territory or obtaining food, or desiring sex, also drives addiction.
  - Craving equates with hunger (starvation level) and mortal fear (impending doom).
- The thinking part cannot "just say no": the thinking part must be cleaver to carry out
  - Finding
  - Obtaining
  - Using
  - Hiding
- The thinking part is subservient.
- The species survival role of the mesolimbic dopaminergic system will *sacrifice the individual* for the sake of the species.

Receptor Sensitization

Liking

Wanting

Craving

The neurobiology of reward

- The neurobiology of reward has been well understood for decades, whereas the neurobiology of addiction is still being explored.
- Most clinicians have learned of reward pathways including projections from the ventral tegmental area (VTA) of the brain, through the median forebrain bundle (MFB), and terminating in the nucleus accumbens (Nuc Acc), in which dopamine neurons are prominent.

The neurobiology of reward

- Current neuroscience recognizes that the neurocircuitry of reward also involves a rich bi-directional circuitry connecting the nucleus accumbens and the basal forebrain.
- It is the reward circuitry where reward is registered, and where the most fundamental rewards such as food, hydration, sex, and nurturing exert a strong and life-sustaining influence.

The neurobiology of reward

- Alcohol, nicotine, other drugs and pathological gambling behaviors exert their initial effects by acting on the same reward circuitry that appears in the brain to make food and sex, for example, profoundly reinforcing.
- Other effects, such as intoxication and emotional euphoria from rewards, derive from activation of the reward circuitry.

The neurobiology of reward

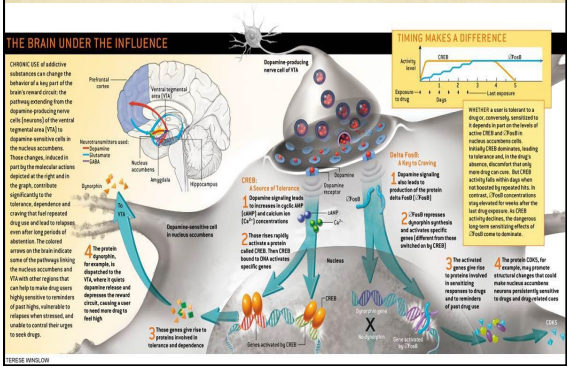
- While intoxication and withdrawal are well understood through the study of reward circuitry, understanding of addiction requires understanding of a broader network of neural connections involving forebrain as well as midbrain structures.
- Selection of certain rewards, preoccupation with certain rewards, response to triggers to pursue certain rewards, and motivational drives to use alcohol and other drugs and/or pathologically seek other rewards, involve multiple brain regions outside of reward neurocircuitry itself.

The neurobiology of need

- UNDERSTANDING THE ADDICTED MIND.

- In this MRI of a brain (side view), the green, yellow and red areas indicate bundles of neurons involved in addiction. Red represents reward pathways; green and yellow signify habitual responses.

Brain Under the Influence



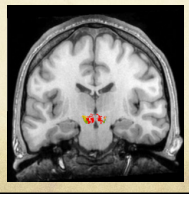
Unforgettable

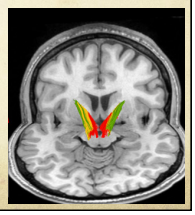
- There are things you don't forget, and there are things you can't. For people who become drug addicts, the drug experience — the substance, but the entire "scene" too — is not only unforgettable but indelibly etched into the physiological brain circuitry that drives us onward through the obstacle course of existence.
- And much of that memory is false. Because all addictive drugs appear to share a rather mysterious property: They're "better than the real thing." Better, that is, than the real things our reward circuitry was designed by evolution to reward: food, sleep, sex, friendship, novelty, etc.

Dope fires up your dopamine

- These dopamine-squirting neurons constitute a tiny fraction of all neurons. But each of them can network with up to 10,000 or more other neurons stretching to the far corners of the brain.

In this rear view of the brain, the colored areas show the origin of the dopamine neurons in the midbrain



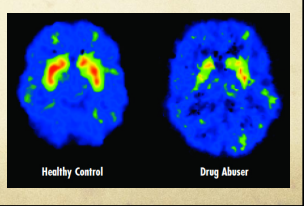


Downward spiral of reward

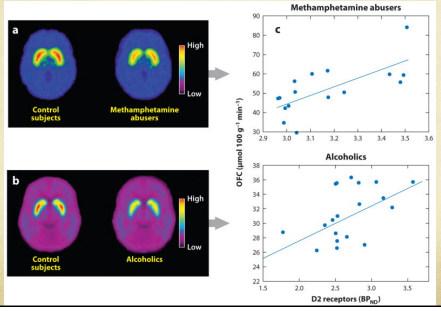
- With normally rewarding things like food and sex, we usually have a pretty good idea of how good it will be. It's when the reward exceeds our expectations that the dopamine circuitry really lights up big time. Conversely, if our expectations aren't met, dopamine activity drops off.
- But cocaine, heroin, alcohol and nicotine directly activate the circuit – they goose dopamine secretion – regardless of how high the expectation was. "Every time you take it, you activate that dopamine activity, so you're getting a readout that says, 'Wow, this was even better than I thought it would be,'
- The experience is remembered as always getting better – even if, paradoxically, it's actually not so great anymore. ("Tolerance mechanisms" within the brain can cause a drug's pleasant effect to diminish with repeated use.)

Downward spiral of reward

- Dopamine's impact on the reward circuit of a drug abuser's brain can become abnormally low, and the ability to experience any pleasure is reduced. This is why the abuser eventually feels flat, lifeless, and depressed, and is unable to enjoy things that previously brought them pleasure.
- Now, they need to take drugs just to try and bring their dopamine function back up to normal. And, they must take larger amounts of the drug than they first did to create the dopamine high - an effect known as tolerance.



Brain dopamine D2 receptors (D2R) in controls and in methamphetamine abusers and alcoholics and association between D2R in the striatum and metabolism in the orbitofrontal cortex.

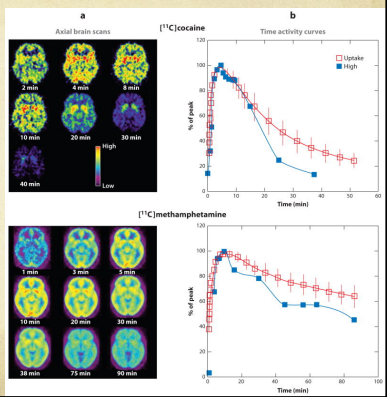


The needle and the damage done

- In susceptible individuals, repeated drug use creates the same kind of lasting changes in the connections among neurons that we get from learning to ride a bike.
- One important way our brains snap an experience into long-term memory is by strengthening the synaptic contacts between neurons in the network that encodes this experience. This involves a number of biochemical changes in both the bulb protruding from a neuron's axon and the brush-like extension of a nearby neuron.
- Drug abuse can also cause neurons to sprout brand-new synapses – for example in the nucleus accumbens.
- It can weaken synapses, too. Nora Volkow, MD, of the National Institute on Drug Abuse has shown that the plan-oriented prefrontal cortex functions poorly in cocaine addicts.

Nora Volkow, MD

Pharmacokinetics of cocaine and methamphetamine in the human brain and relationship to the drug-induced "high."



The needle and the damage done

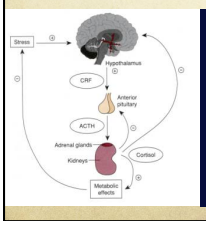
- The long-term strengthening of drug-associated memory circuits, combined with that "even better than expected" illusion addictive drugs foist on users, goes a long way toward explaining what is probably the biggest problem addicts and those who treat them face: a pronounced tendency to slide back into the habit.
- Long-term treatment is vital.

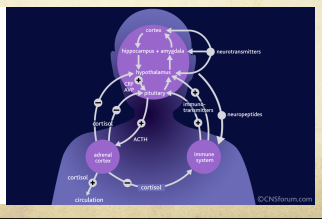
The needle and the damage done

- If you are an addict, not just the drug but also all the associated physical, geographical and social cues exert a powerful effect, even decades after the last time you were anywhere near the drug: You walk past the bar you used to get drunk in and see your buddies in there, or you smell cigarette smoke — or, if you used to inject cocaine or heroin, all it may take is seeing a spoon — and you experience a craving and risk a relapse.
- Stress — you lose your job, suffer a divorce, undergo a financial crisis — can mimic drugs' influence on the reward circuitry, and is therefore another major cause of relapse.

Relapse mechanisms

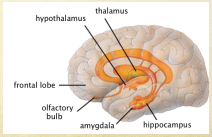
- **Relapse triggered by exposure to stressful experiences involves brain stress** circuits beyond the hypothalamic-pituitary-adrenal axis that is well known as the core of the endocrine stress system.





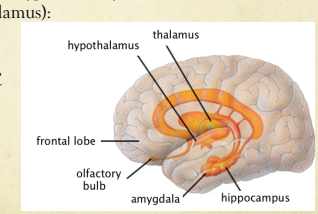
The Limbic System

- The limbic system is a complex set of structures that lies on both sides of the thalamus, just under the cerebrum.
- It includes the hypothalamus, the hippocampus, the amygdala, and several other nearby areas.
- It appears to be primarily responsible for our emotional life, and has a lot to do with the formation of memories.
- Emotional memory is super-fast.



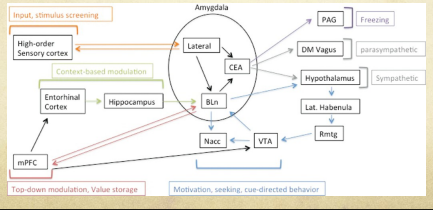
The Limbic System

- In this drawing, you are looking at the brain cut in half, but with the brain stem intact. The part of the limbic system shown is that which is along the left side of the thalamus (hippocampus and amygdala) and just under the front of the thalamus (hypothalamus):



The Amygdala

- The amygdala sends projections to the hypothalamus, the dorsomedial thalamus, the thalamic reticular nucleus, the nuclei of the trigeminal nerve and the facial nerve, the ventral tegmental area, the locus coeruleus, and the laterodorsal tegmental nucleus.



The Amygdalae

- The amygdalae perform primary roles in the formation and storage of memories associated with emotional events, especially fear.
- Research indicates that, during fear conditioning, sensory stimuli reach the basolateral complexes of the amygdalae, particularly the lateral nuclei, where they form associations with memories of the stimuli.
- The association between stimuli and the aversive events they predict may be mediated by long-term potentiation, a sustained enhancement of signaling between affected neurons.
- The amygdalae are crucially engaged in the emotional and motivational modulation of cognition and behavior.

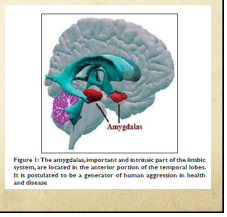
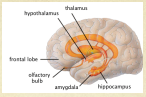


Figure 1: The amygdalas,important and intrinsic part of the limbic system, are located in the anterior portion of the temporal lobes. It is postulated to be a generator of human aggression in health and disease

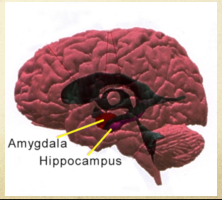
Hypothalamus



- The hypothalamus is a small part of the brain located just below the thalamus on both sides of the third ventricle. It sits just inside the two tracts of the optic nerve, and just above (and intimately connected with) the pituitary gland.
- The hypothalamus is one of the busiest parts of the brain, and is mainly concerned with **homeostasis**. Homeostasis is the process of returning something to some "set point."
- The hypothalamus is responsible for regulating your hunger, thirst, response to pain, levels of pleasure, sexual satisfaction, anger and aggressive behavior, and more.
- It is neurally and chemically connected to the pituitary, the "master gland," which in turn pumps hormones called releasing factors into the bloodstream.

Relapse mechanisms

- **Relapse triggered by exposure to conditioned cues from the environment** involves glutamate circuits, originating in frontal cortex, insula, hippocampus and amygdala projecting to mesolimbic incentive salience circuitry.



Relapse mechanisms

- **Relapse triggered by exposure to stressful experiences involves brain stress** circuits beyond the hypothalamic-pituitary-adrenal axis that is well known as the core of the endocrine stress system.
- There are two of these relapse-triggering brain stress circuits – one originates in noradrenergic nucleus A2 in the lateral tegmental area of the brain stem and projects to the hypothalamus, nucleus accumbens, frontal cortex, and bed nucleus of the stria terminalis, and uses norepinephrine as its neurotransmitter; the other originates in the central nucleus of the amygdala, projects to the bed nucleus of the stria terminalis and uses corticotrophin-releasing factor (CRF) as its neurotransmitter.

Sources

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