Introduction to the Neurobiology of Addiction

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Disclosures

- I have no relevant financial interests to disclose

Learning Objectives

After this talk, participants should

- Be able to define tolerance, withdrawal, dependence and addiction
- Know how the reward circuit functions in opioid use disorder, including major neurotransmitter systems and their associated structures.
- Explain two ways that substance use disorders undermine executive functioning in the brain

Outline

- Tolerance, withdrawal & dependence
- Review of addiction definition & models
- Neuroanatomy of the reward circuit
- Two models of cognitive impairment

Tolerance

- The reduced reaction to a drug following its repeated use
- The need to take more of a drug to get the same effect
- Produced by several different mechanisms
  - Receptor desensitization
  - Receptor downregulation
  - Changes in cellular signaling (heroin/morphine)
  - Increased induction of [hepatic] enzymes involved in drug metabolism (alcohol)

Withdrawal

- Body develops compensatory strategies to manage drug effects, when drug is removed these compensatory strategies present as withdrawal symptoms

Example:

- Locus ceruleus (LC) produces norepinepherine (NE) to stimulate wakefulness, breathing, blood pressure, alertness
- Opioids suppress LC release of NE, producing drowsiness, slow respiration, hypotension
- With repeated opioid exposure, LC increases baseline level of activity to compensate
- The suppressive impact of opioids is offset by the increased LC activity and person feels more or less “normal”
- When opioid removed and can no longer balance the increased LC activity, excessive NE results in jitters, anxiety, hypertension, muscle cramps, diarrhea, tachypnea

Tolerance
+
Withdrawal
Dependence

Is dependence the same as addiction?

Patients can be come tolerant to clonidine and require higher doses, but don't *crave* it.

Venlafaxine discontinuation can cause significant withdrawal symptoms, but patients don't ignore their social responsibilities and engage in criminal activities to obtain their antidepressant.

Models of Addiction

- Moral: hedonists with lack of will
- Criminal: the war on drugs & punishment as solution
- Recovery: a personal journey
- Reinforcement: withdrawal-avoidant, pleasure-seeking
- Medical: neurobiological basis of disease

What is addiction?

American Society of Addiction Medicine

Addiction is a primary, **chronic disease of brain reward, motivation, memory and related circuitry**. Dysfunction in these circuits leads to characteristic **biological, psychological, social and spiritual manifestations**. This is reflected in an individual pathologically pursuing reward and/or relief by substance use and other behaviors.

Addiction is characterized by **inability to consistently abstain**, **impairment in behavioral control**, **craving**, diminished recognition of **significant problems** with one's behaviors and interpersonal relationships, and a dysfunctional emotional response. Like other chronic diseases, addiction often involves **cycles of relapse and remission**. Without treatment or engagement in recovery activities, addiction is **progressive** and can result in **disability or premature death**.

Conceptual Model of Addiction

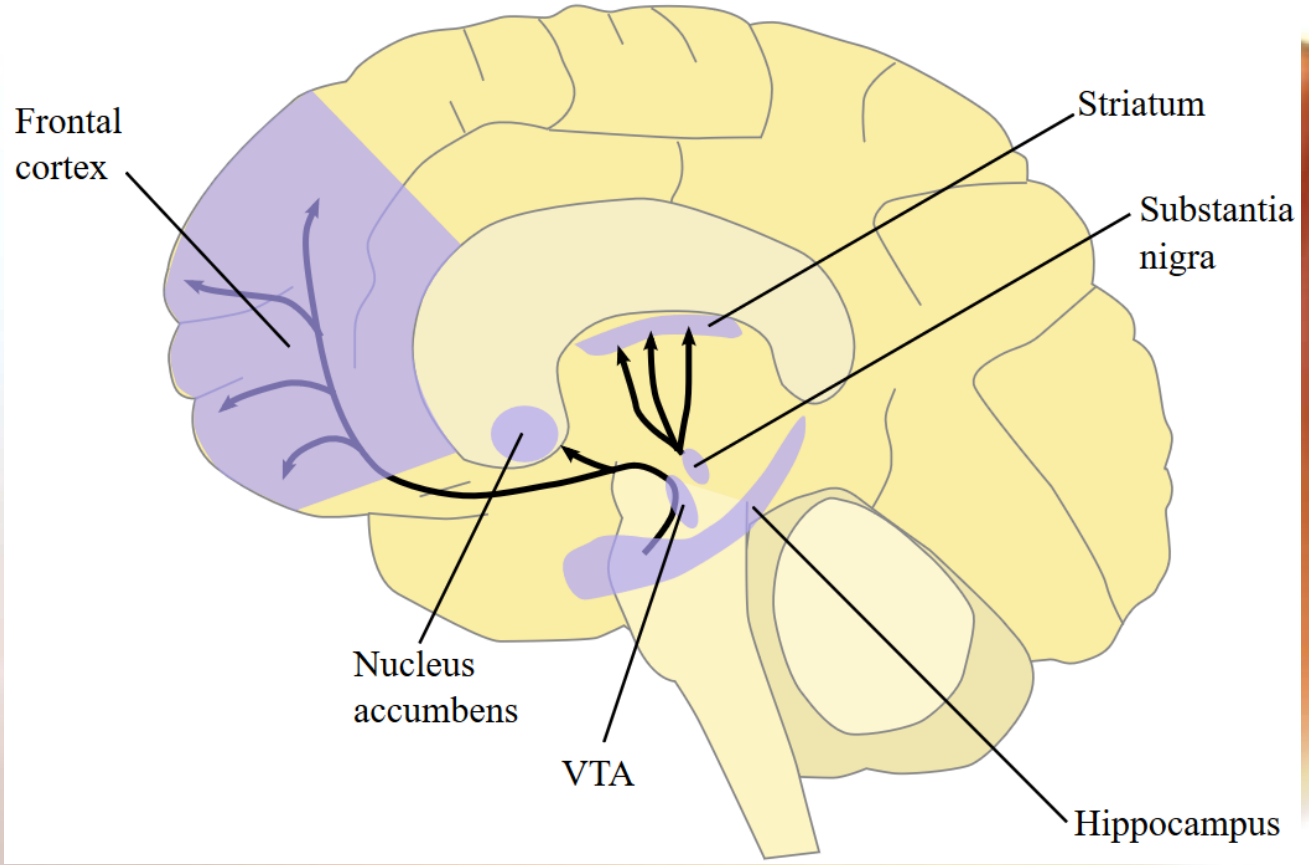
- Cannot understand addiction by looking at only one level
- At a minimum, addiction involves:
  - properties of drugs involved
  - neural circuitry
  - genetic factors
  - developmental experiences
  - psychiatric distress/illness
  - sociocultural context

Reward

- Humans engage in activities that are perceived as rewarding
- Pleasurable experience is a form of reward and results in positive reinforcement
- Natural rewards include food, water, sex, companionship
  - Because these things feel good, we keep doing them, and we survive

Reward Circuitry: Mesocorticolimbic Pathway

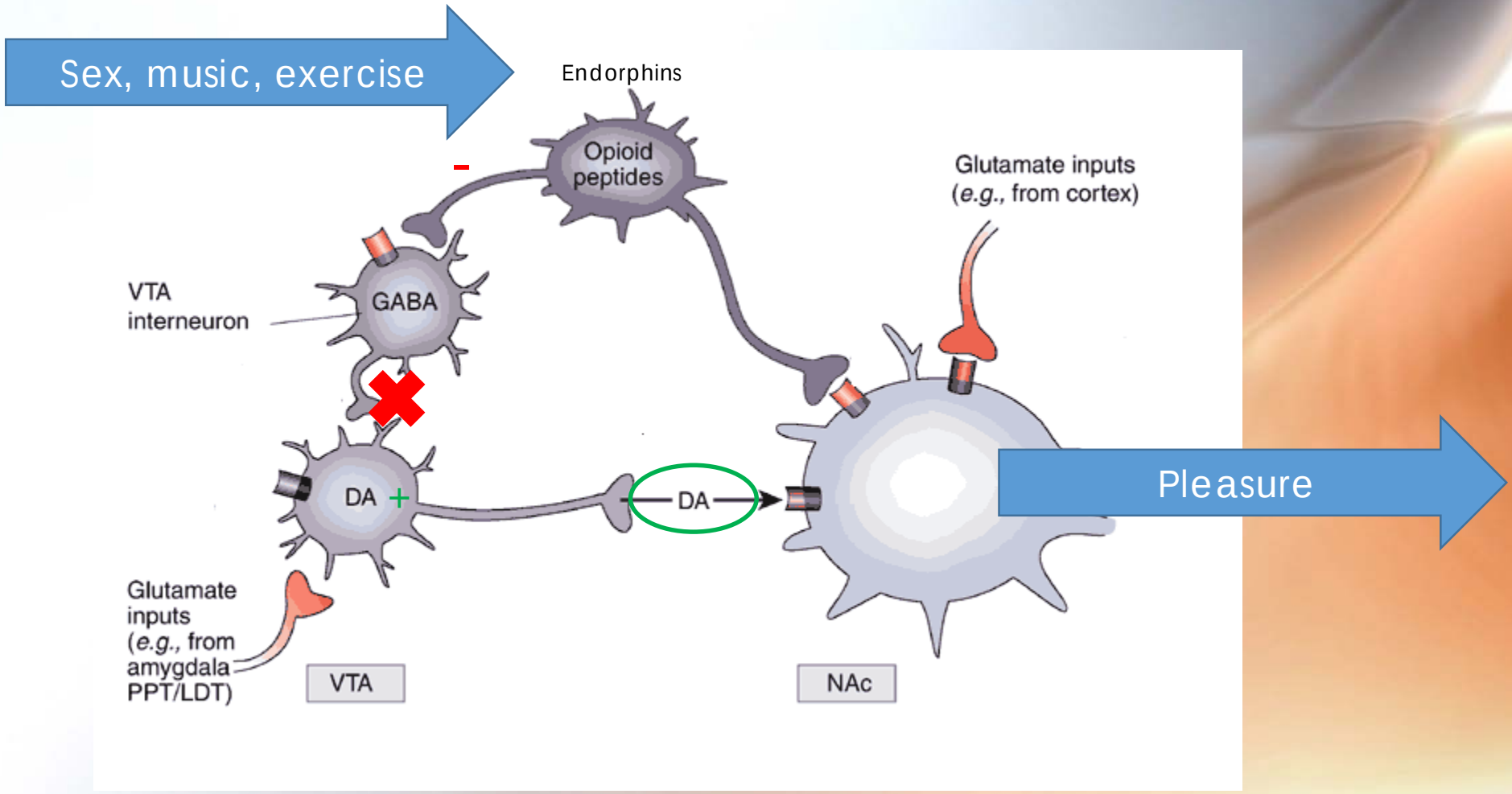
- Behavioral motivation
- Three major structures
  - Prefrontal Cortex (PFC)
  - Nucleus Accumbens (NAc)
  - Ventral Tegmental Area (VTA)
- Common pathway for nicotine, alcohol, stimulants, opioids



Neurotransmitters

- Prefrontal Cortex *"the seat of will"*
  - Releases glutamate which is inhibitory of dopamine release in the nucleus accumbens
  - Acts as a modulator of responses in the nucleus accumbens
- Nucleus Accumbens *"the seat of pleasure"*
  - Receives dopaminergic inputs from VTA, which modulate GABAergic neurons and produce sensation of pleasure
- Ventral Tegmental Area *"the seat of reward"*
  - Stimulates the nucleus accumbens by release of dopamine
- Locus Ceruleus "*the seat of arousal*"
  - Activation releases norepinepherine to produce alertness/wakefulness

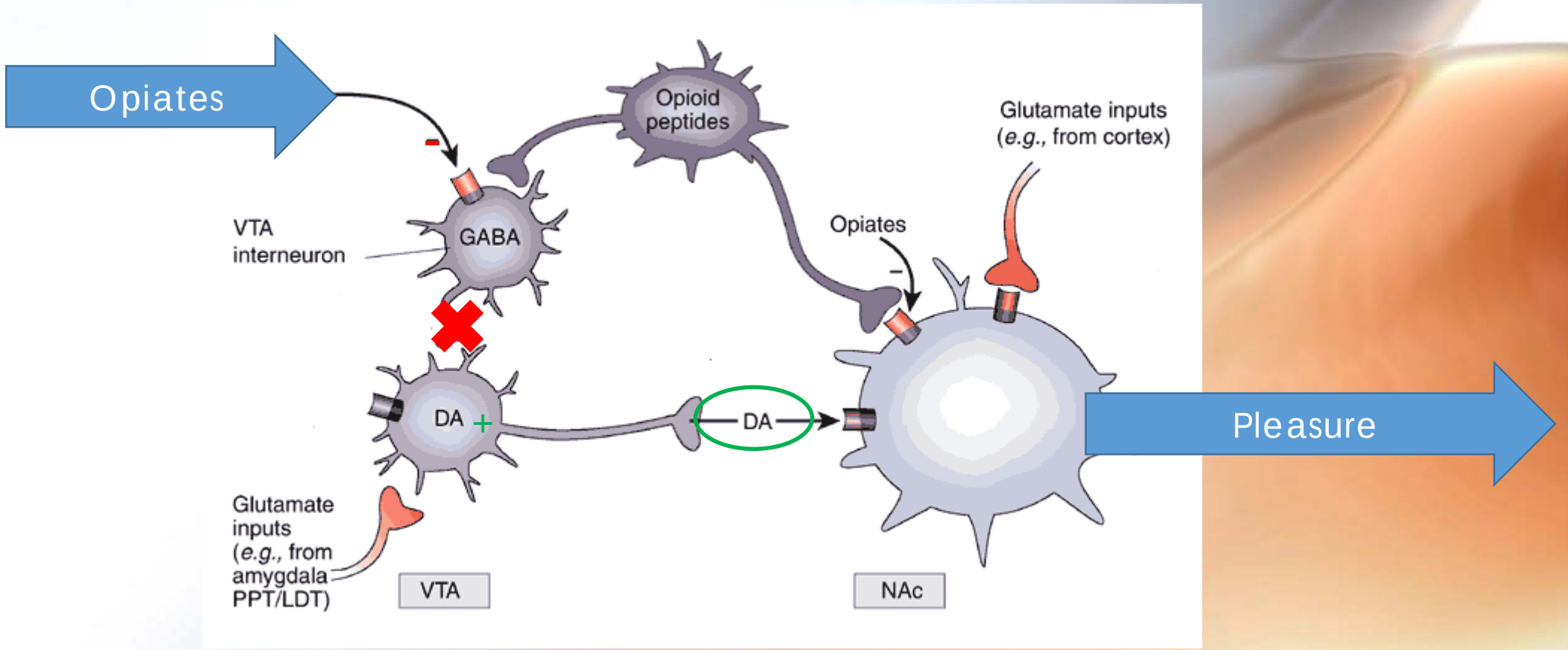
Normal Functioning Pathway



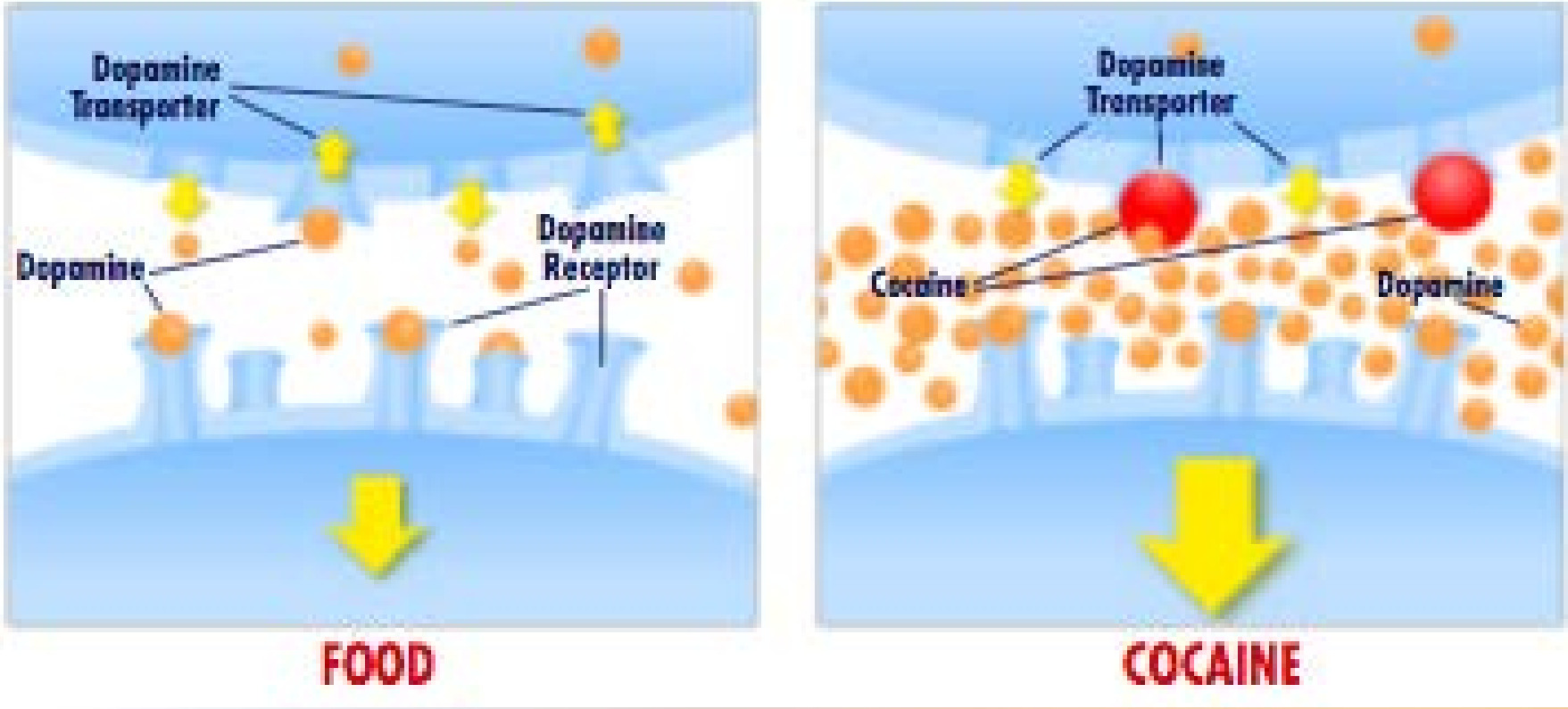
The beginnings of addiction

- Exogenous opioids bind receptors in the VTA
- The VTA sends dopamine to the NAc
- Dopamine in the NAc causes *intense pleasure.*
- Intense pleasure overrules inhibition in the PFC

Opioids & Mesocorticolimbic Pathway



Drugs of abuse increase dopamine



But how is addiction sustained?

- Pleasure is different from craving
- Pleasure is the sensation that is immediately gained after consumption of a rewarding stimulus
- Craving is something different
- In fact, as addiction progresses, someone may want a drug more and more, and like the drug less and less as tolerance develops

Sensitization & Incentive Salience

- Unlike other areas of the brain, in the NAc repeated drug exposure leads to sensitization
  - Amount of dopamine release increases as a result of repeated drug exposure
  - Strengthens stimulus-drug associations (associative learning)
  - Associations less prone to extinction
  - Environmental stimuli become drug cues
  - Exposure to environmental stimulus triggers a desire to use the drug
- Interestingly, other non-drug stimuli result in habituation, with a decrease in dopamine release with future stimuli exposure

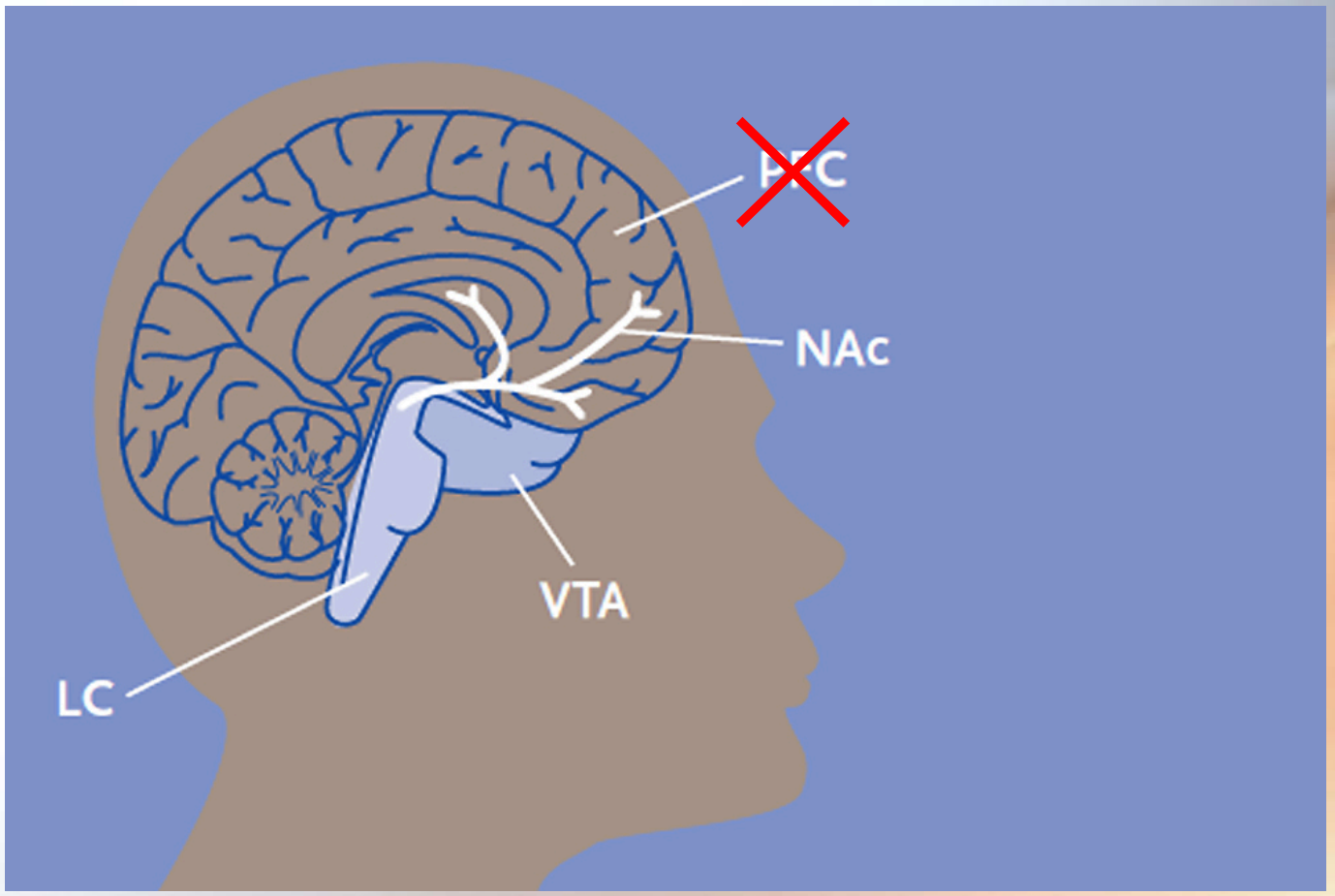
But why certain people?

- Requires adequate dose, frequency, chronicity
- Genetic pre-disposition
- Younger age
- Psychiatric factors/trauma

Biomedical Models of Addiction

- **Changed Set Point:** Drug use causes permanent structural and chemical changes that create a new biological and behavioral baseline for the addict.
- **Cognitive Deficits:** Drug use degrades prefrontal cortical inhibition of the drive to use, undermining the addicted person's will at a neurological level.

Cognitive Deficit Model



Cognitive Deficits

- Impulsiveness
  I'm not going to think twice before I get high.
- Increased risk-taking
  I doubt my probation officer will find out.
- Reward hypersensitivity
  Getting high feels better than anything else.
- Harm hyposensitivity
  I forgot how bad it felt the last time I went to jail.
- Outcome myopia (i.e. temporal discounting)
  My kids might get taken away, but not today.

Clinical Implications

- Those with addiction start with impaired decision-making
- Drug use further impairs decision-making by causing permanent changes in brain structure
- Decision-making deficits generalize beyond the context of drug-taking behavior
- Decision-making deficits may persist even long after periods of abstinence

Questions?

- Recommendations for further reading:

  Kosten TR. *The neurobiology of opioid dependence: implications for treatment*. Sci Pract Perspect. 2002 Jul;1(1):13-20

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