

# The Neurobiology of Addiction

Jodi Gilman, Ph.D.

Center for Addiction Medicine  
Massachusetts General Hospital

Associate Professor, Department of Psychiatry  
Harvard Medical School

# Disclosures

Neither I nor my spouse/partner has a relevant financial relationship with a commercial interest to disclose.

# What is Addiction?

- Drug addiction is a chronically relapsing disorder that has been characterized by
  - (1) compulsion to seek and take the drug,
  - (2) loss of control in limiting intake, and
  - (3) emergence of a negative emotional state (e.g., dysphoria, anxiety, irritability) reflecting a motivational withdrawal syndrome when access to the drug is prevented
- commonly associated with a chronic, relapsing course

# How Common is Addiction?

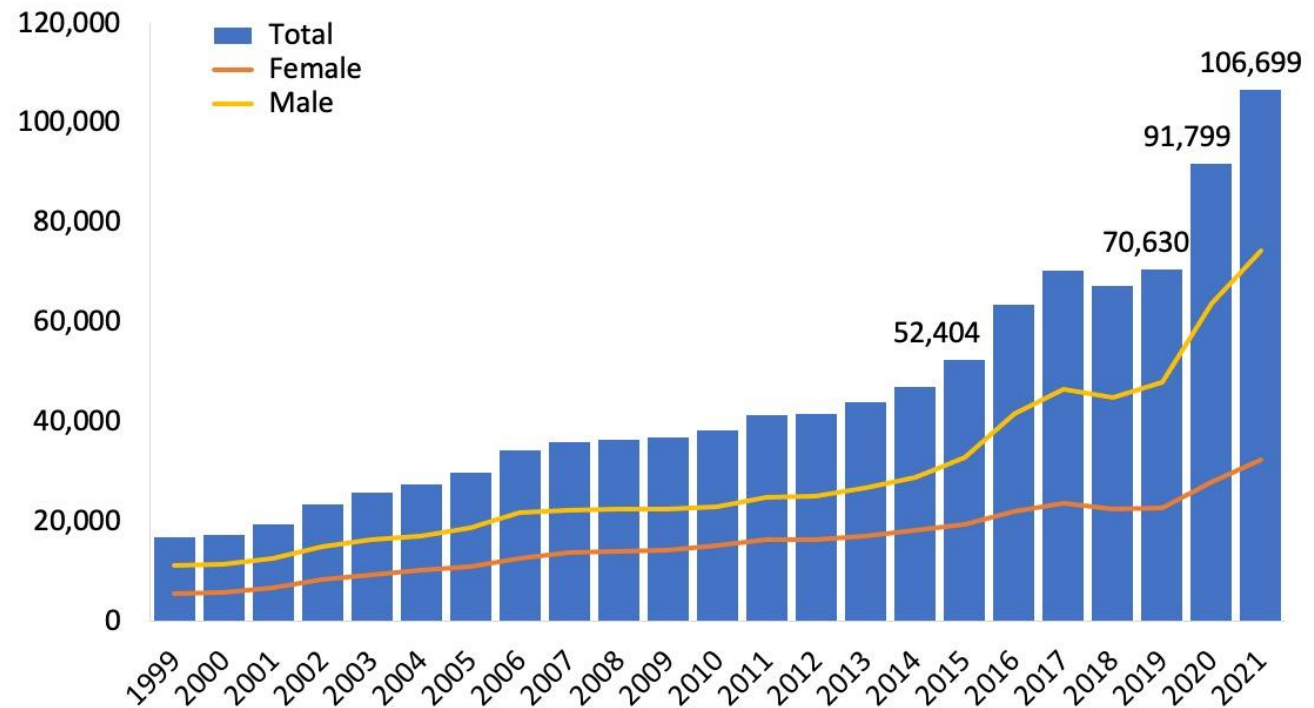
In 2024, 48.4 million Americans aged 12+ had a substance use disorder

- Any substance use disorder: 48.4 million, 16.8%
- Nicotine: 22.9 million Americans, 8% (decreasing for decades, might reverse because of vaping)
- Alcohol use disorder: 27.9 million, 9.7%
- Cannabis use disorder: 20.6 million, 7.1%
- Opioid use disorder: 4.8 million, 1.7%
- Stimulant use disorder: 4.3 million, 1.5%

# Drug overdose is now the leading cause of accidental death in the U.S.

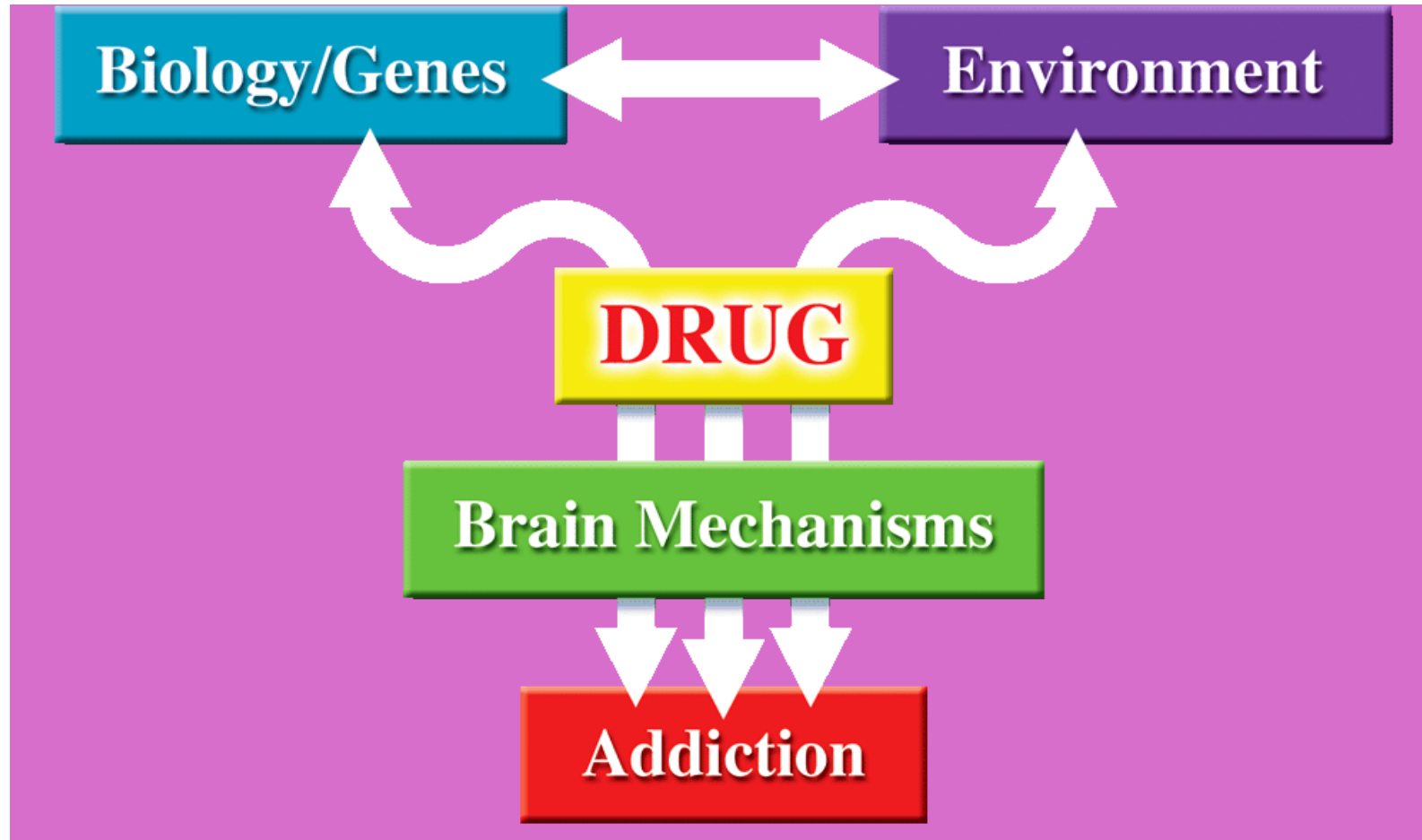
- The death toll has doubled in the last decade, now claiming a life every 14 minutes, making it the number one cause of preventable deaths.

Figure 1. National Drug-Involved Overdose Deaths\*, Number Among All Ages, by Gender, 1999-2021



\*Includes deaths with underlying causes of unintentional drug poisoning (X40–X44), suicide drug poisoning (X60–X64), homicide drug poisoning (X85), or drug poisoning of undetermined intent (Y10–Y14), as coded in the International Classification of Diseases, 10th Revision. Source: Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple Cause of Death 1999-2021 on CDC WONDER Online Database, released 1/2023.

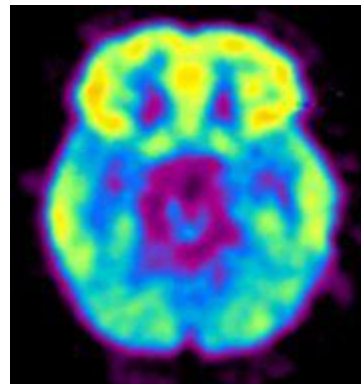
# ***Addiction Involves Multiple Factors***



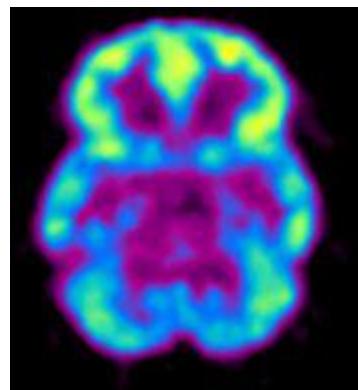
# Addiction is Like Other Diseases...

- It is preventable
- It is treatable
- It changes biology
- If untreated, it can last a lifetime

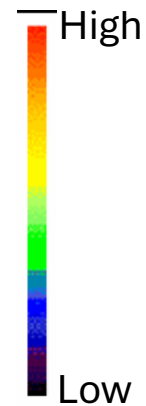
Decreased Brain Metabolism  
in *Cocaine-addiction Patient*



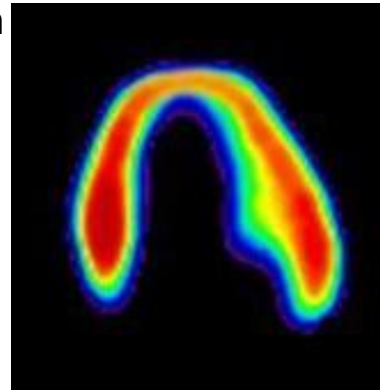
Healthy Brain



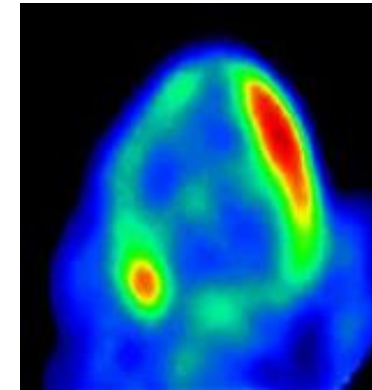
Diseased Brain/  
Cocaine Abuse



Decreased Heart Metabolism  
in *Heart Disease Patient*



Healthy  
Heart

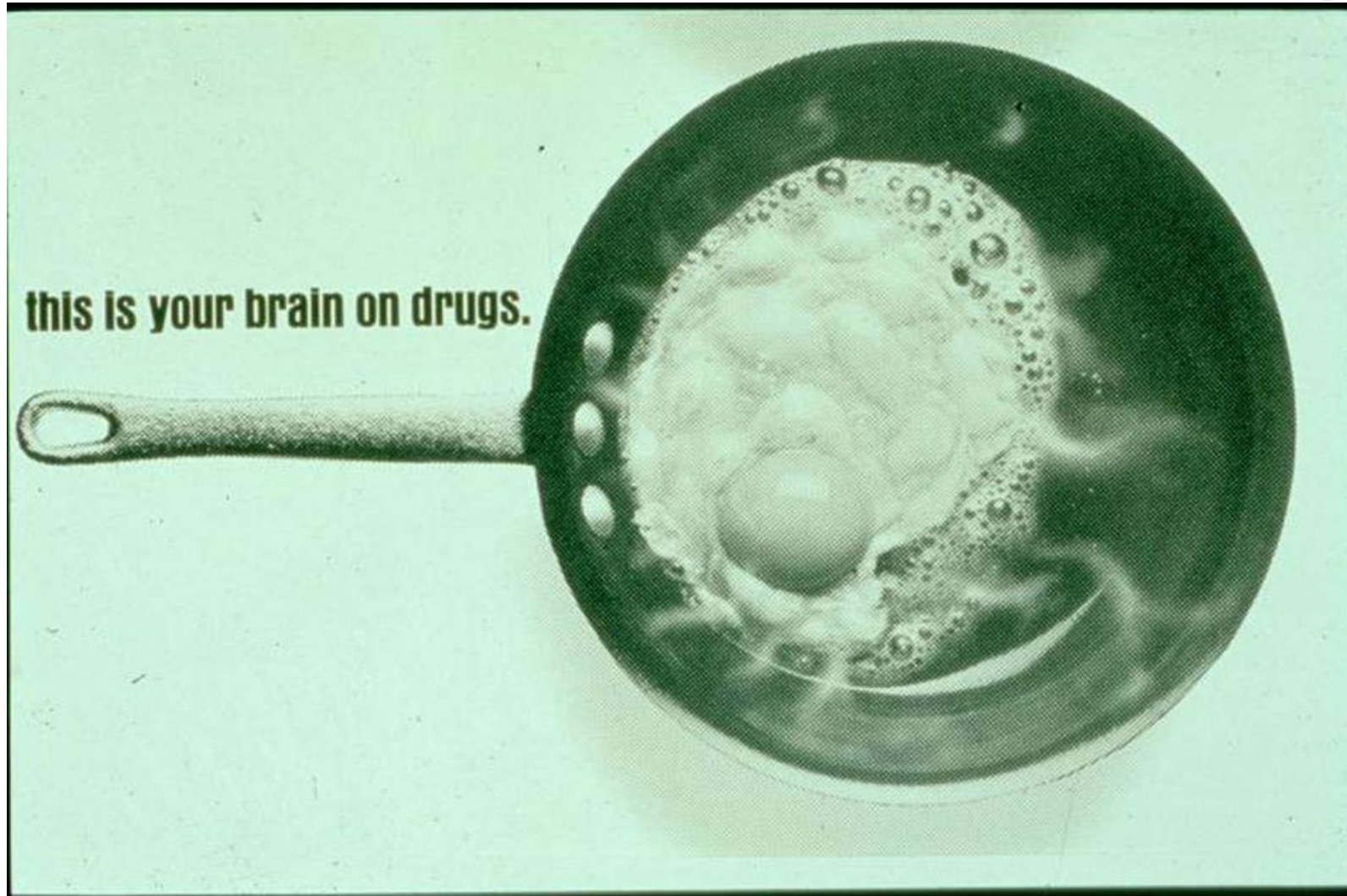


Diseased Heart

Advances in science have revolutionized our fundamental views of drug abuse and addiction.

# ***Your Brain on Drugs in the 1980's***

 **Massachusetts General Hospital**  
Founding Member, Mass General Brigham  
Psychiatry Academy



# Today's Talk

- **Who gets Addicted?**
- The Addiction Cycle
  - Role of Dopamine/Reward in Addiction
  - Role of Impaired Inhibition in Addiction
- Changes in the Brain that Occur
- Treatment and Recovery

# Vulnerability

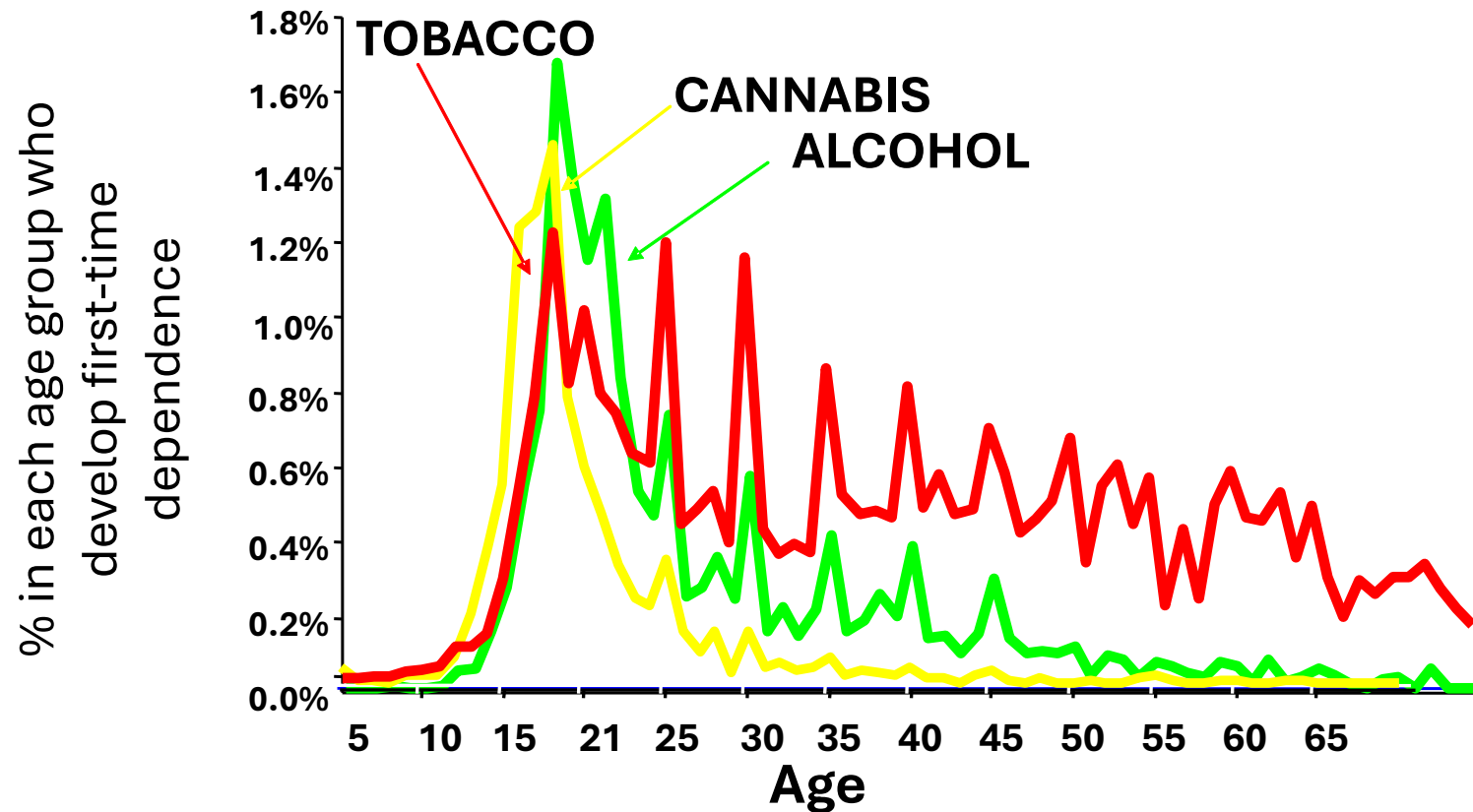
**Why do some people become  
addicted to drugs while others  
do not?**



# Individual Variability

- Mood, anxiety, psychotic disorders are clear risk factors
- 40-60% of the risk for addiction attributed to genetic factors
- Trauma history
- Social determinants of health (poverty, racism, lack of opportunity)

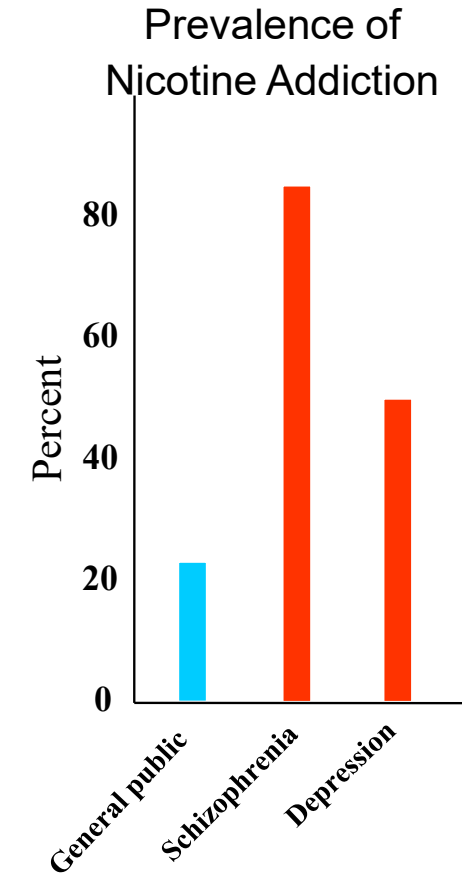
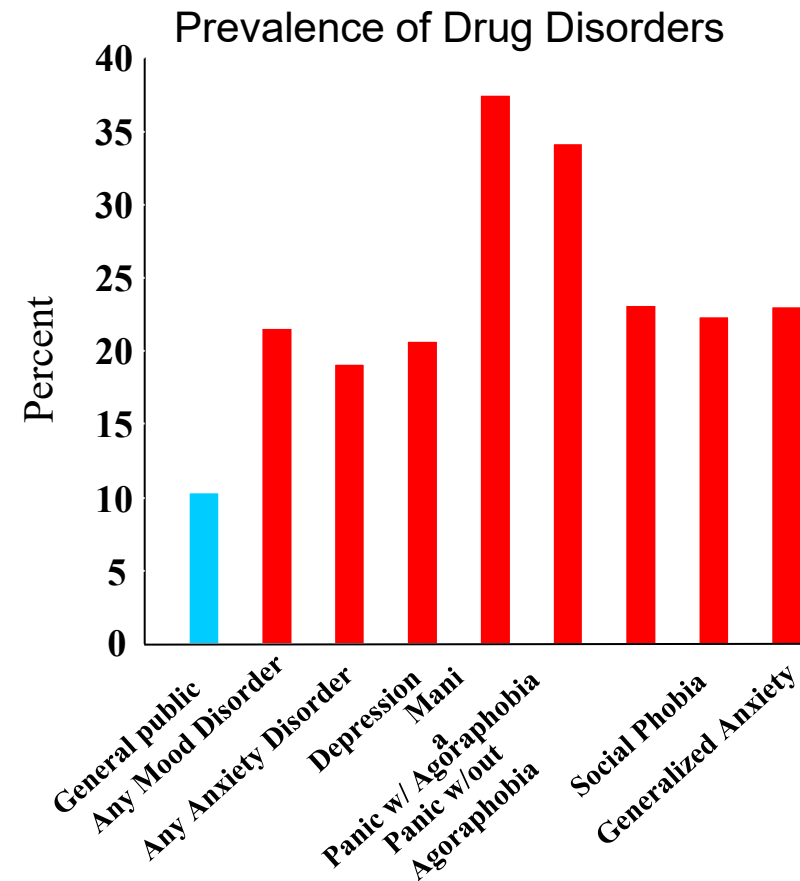
# Addiction often begins during a critical developmental period



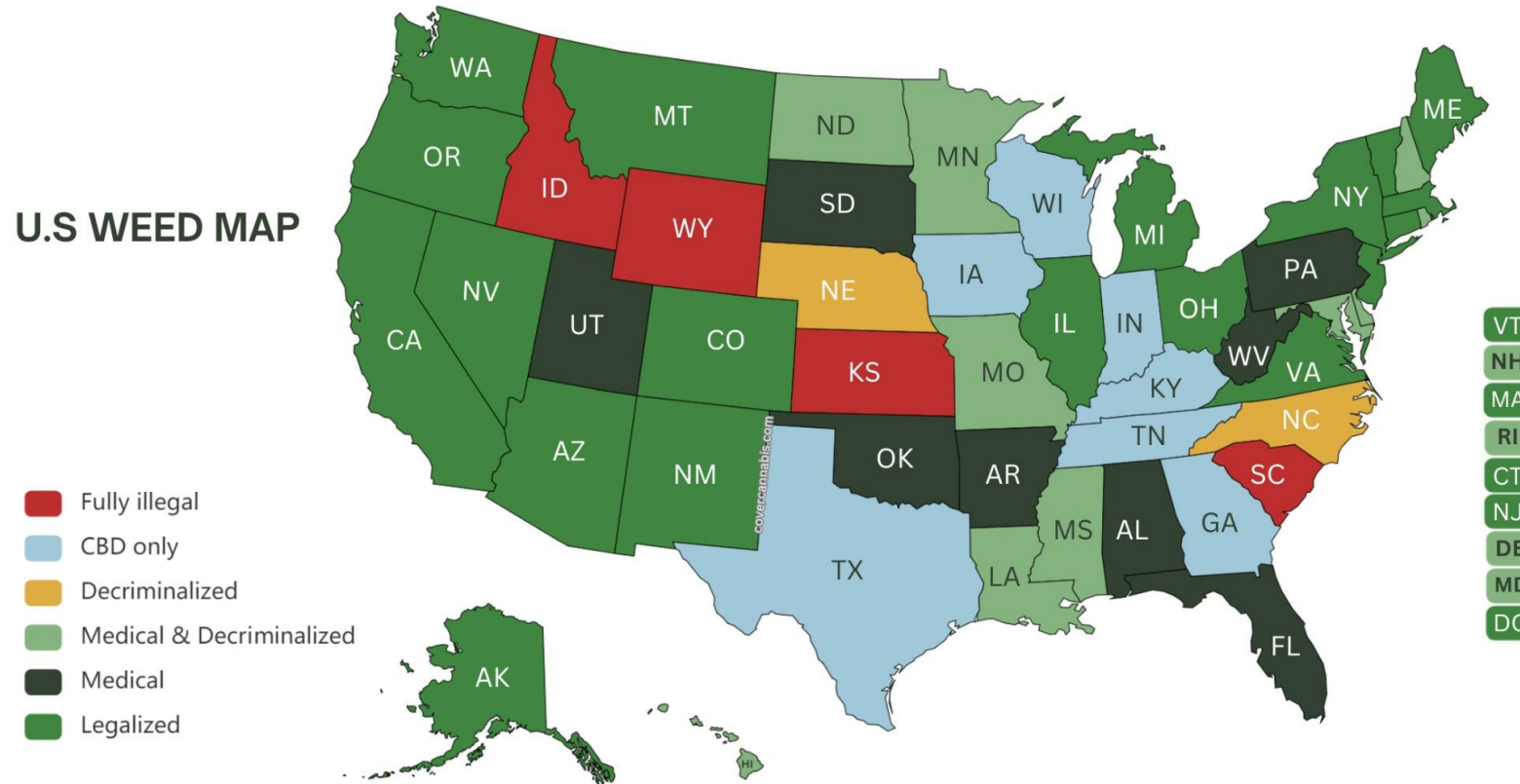
Age at **tobacco**, **alcohol**, and **cannabis** dependence per DSM IV

NIDA

*What Other  
Biological Factors  
Contribute to  
Addiction:  
Comorbidity*



# US STATES, MEDICAL AND RECREATIONAL CANNABIS LAWS



# Cannabis in the 1960's-2000's: THC 1-3%



# Cannabis today

Marijuana is not “just a plant” anymore –  
derivatives contain up to 98% THC



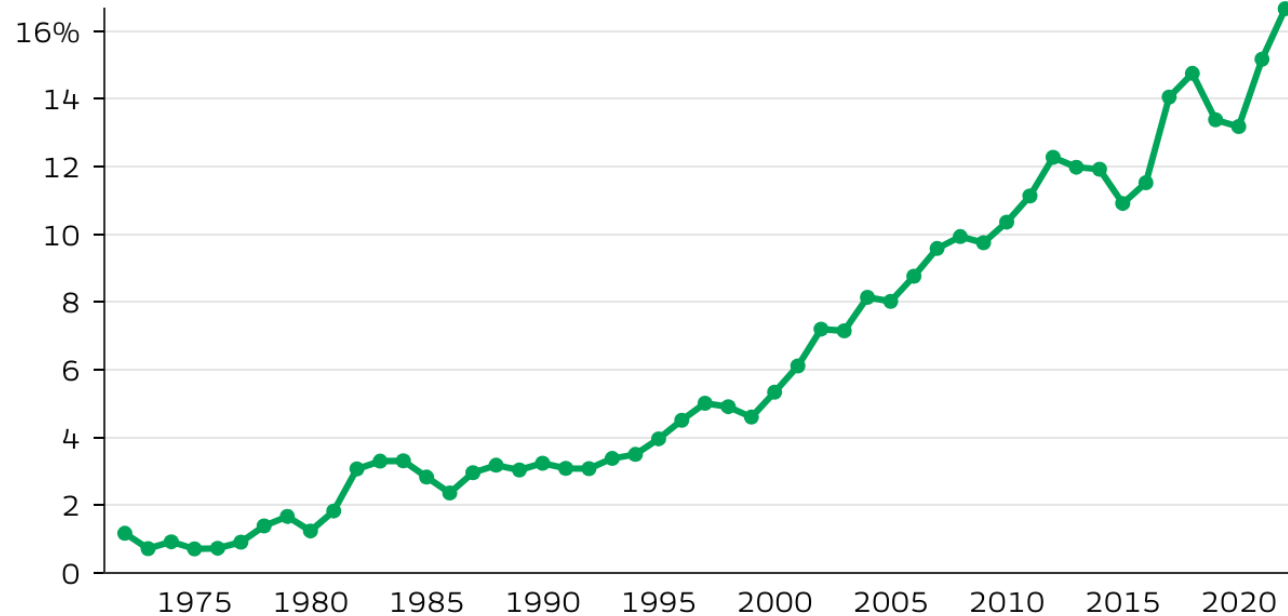


Borodovsky et al., 2016; Schauer, King et al., 2016; Wang et al., 2016; Weiss, 2015

# Cannabis Potency is Increasing

## Today's cannabis is a lot stronger than its predecessors

Cannabis available today contains more than 10 times as much **THC**, on average, than it did in the 1970s



SOURCE: NIDA POTENCY MONITORING PROGRAM, UNIVERSITY OF MISSISSIPPI

- Cannabis growers have worked to make the drug as potent as possible.
- In 1960s-70s average THC concentrations were 1-2%. Today, they are as high as 25%

# High Potency Cannabis and Psychosis

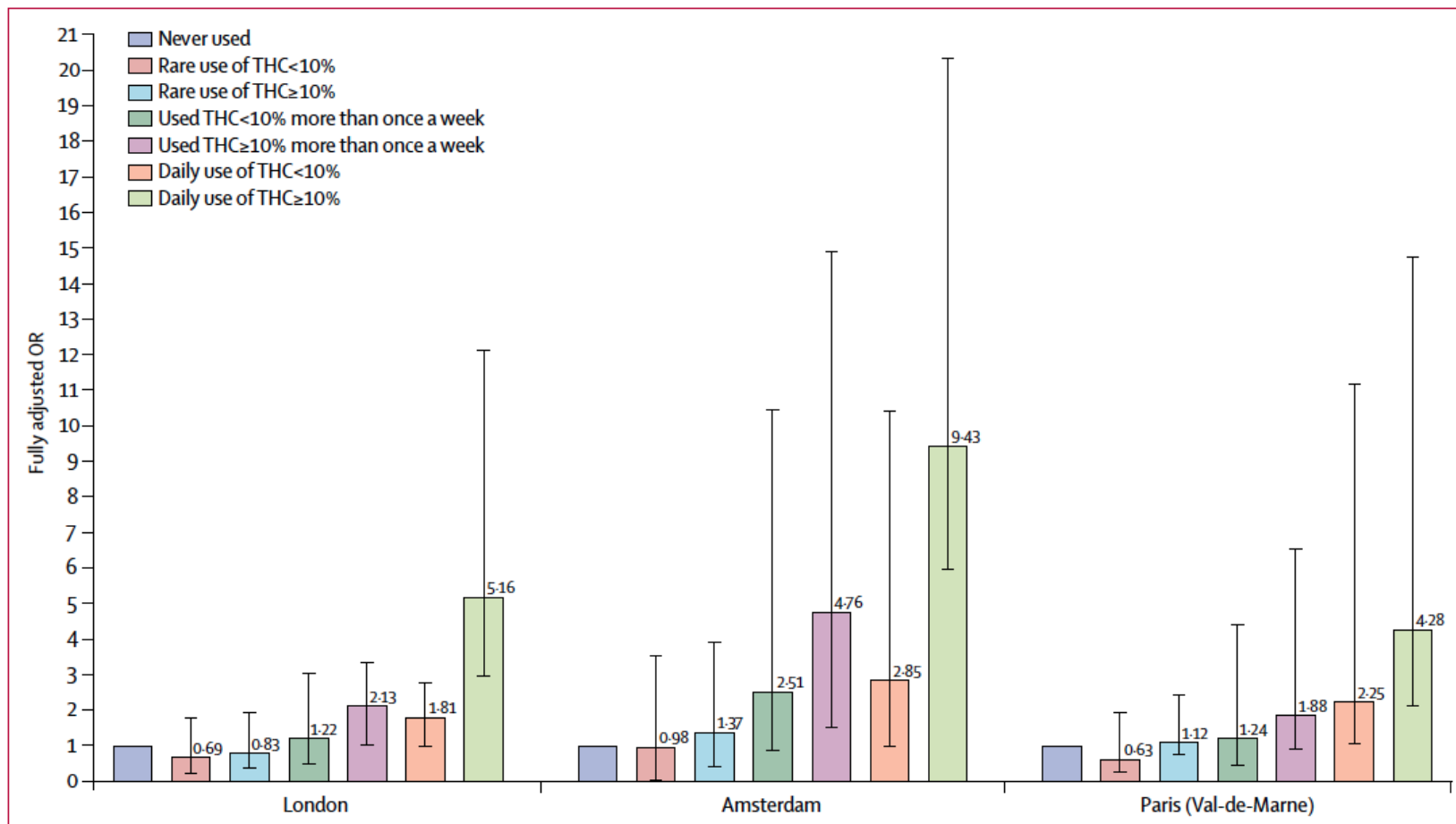
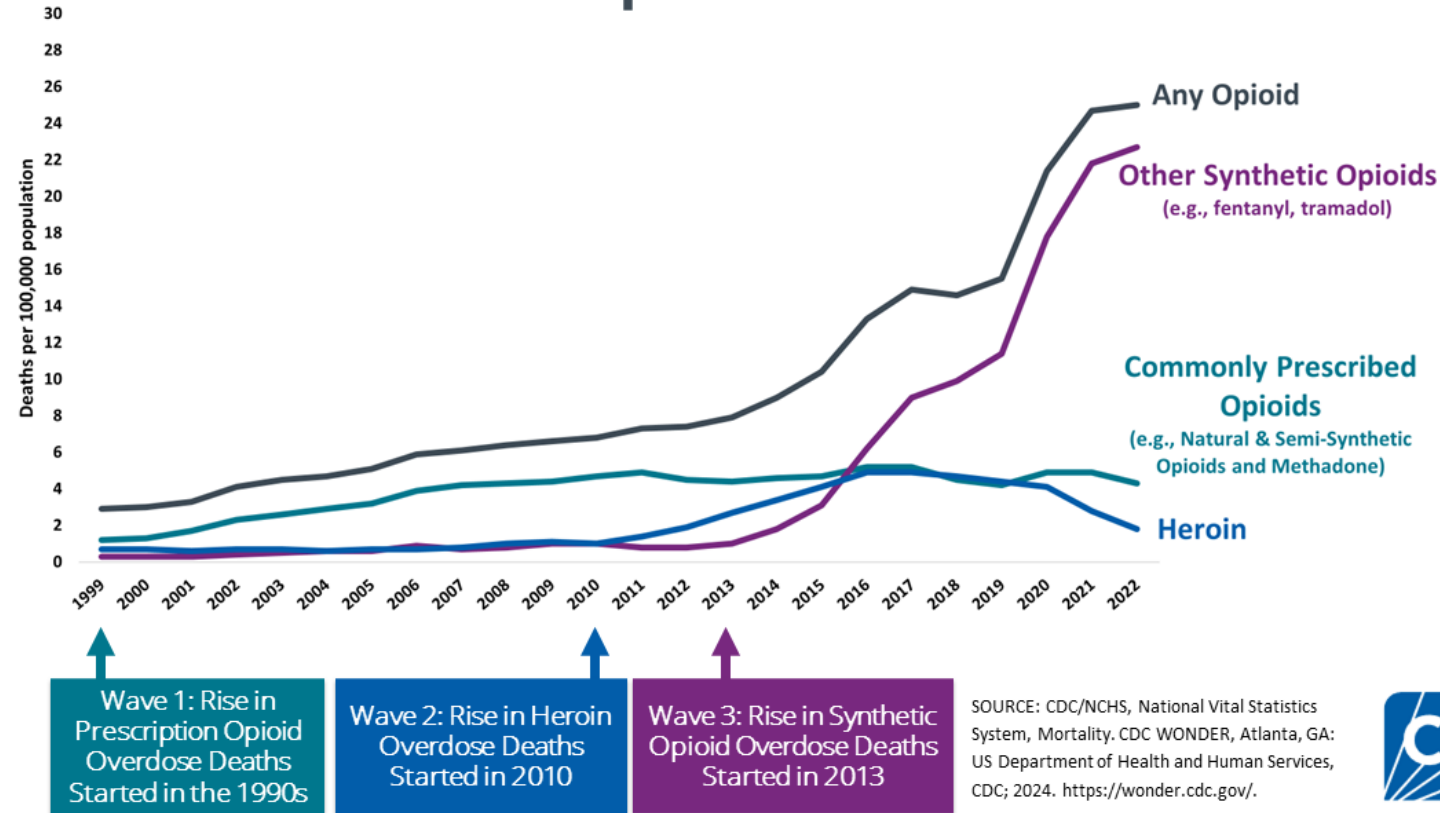


**Figure 2: Fully adjusted ORs of psychotic disorders for the combined measure of frequency plus type of cannabis use in three sites**

Data are shown for the three sites with the greatest consumption of cannabis: London (201 cases, 230 controls), Amsterdam (96 cases, 101 controls), and Paris (54 cases, 100 controls). Error bars represent 95% CIs. OR=odds ratio.

# The Opioid Epidemic

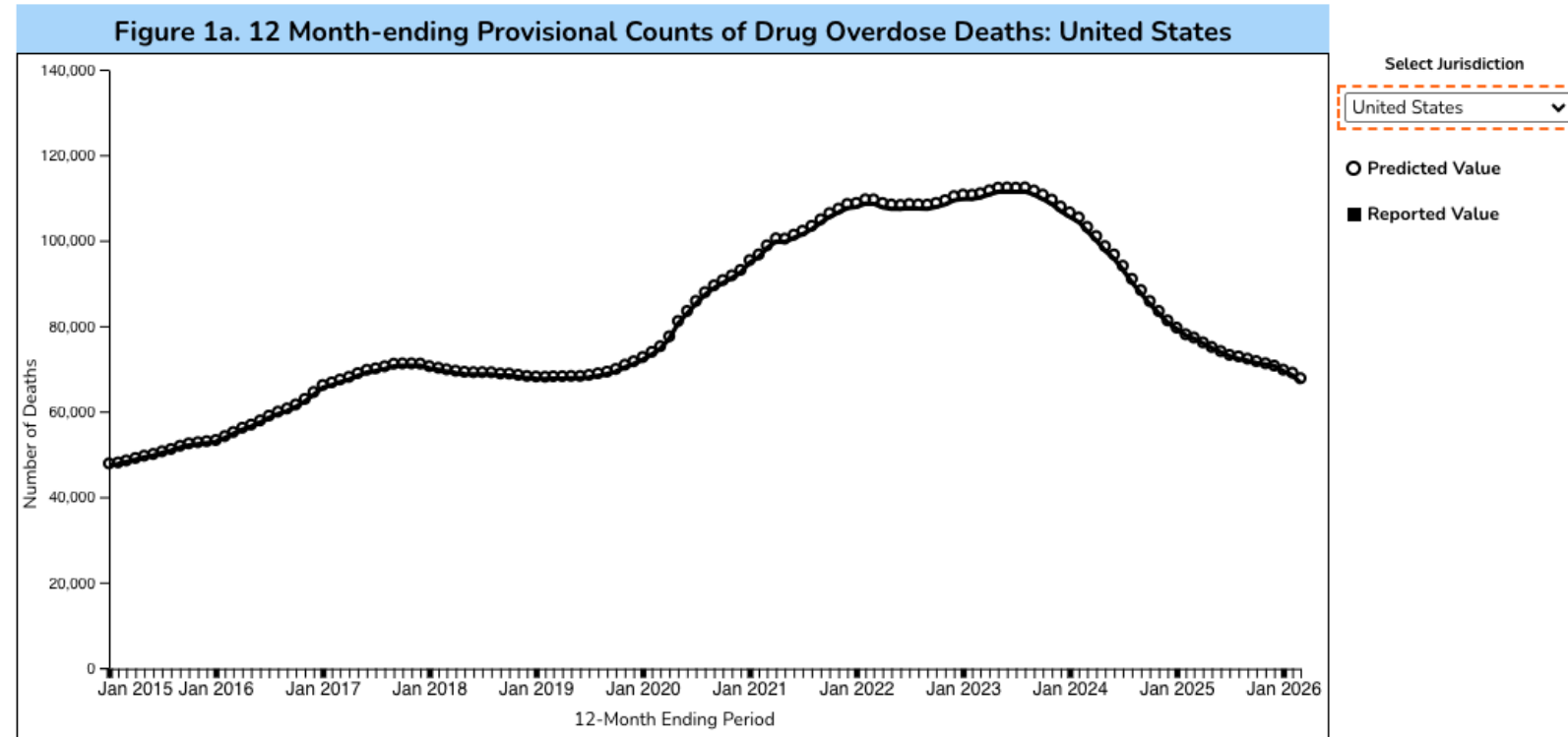
## Three Waves of Opioid Overdose Deaths



# The Opioid Epidemic: Some Good News

## 12 Month-ending Provisional Number and Percent Change of Drug Overdose Deaths

Based on data available for analysis on: August 4, 2026

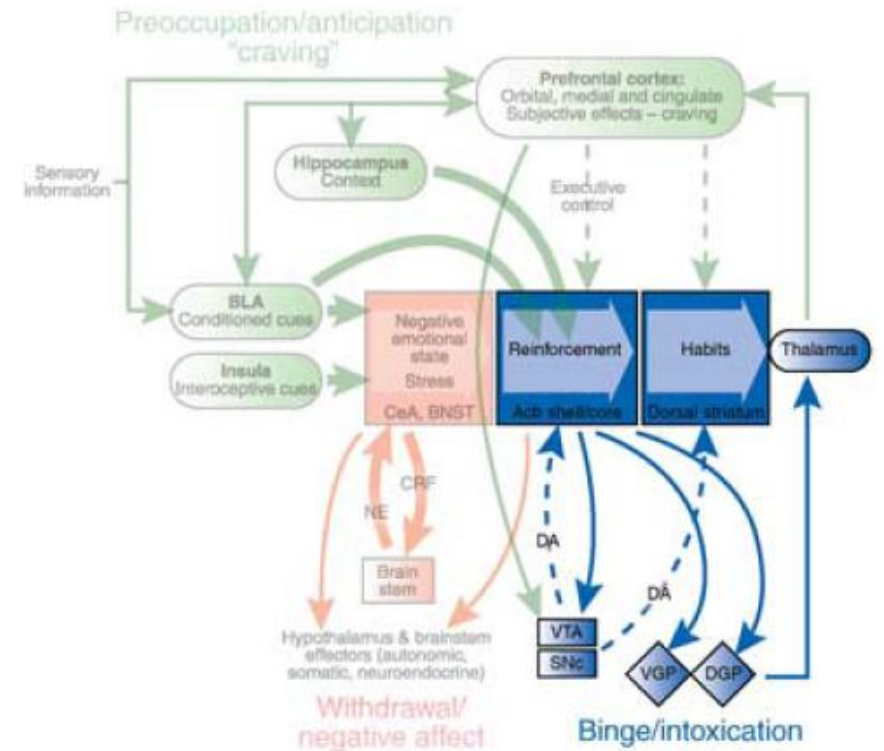
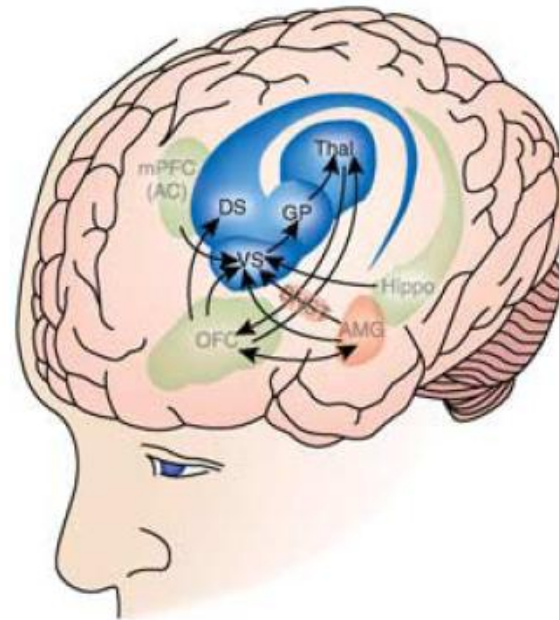


# Today's Talk

- Who gets Addicted?
- The Addiction Cycle
  - Role of Dopamine/Reward in Addiction
  - Role of Impaired Inhibition in Addiction
- Changes in the Brain that Occur
- Treatment and Recovery

# The addiction cycle

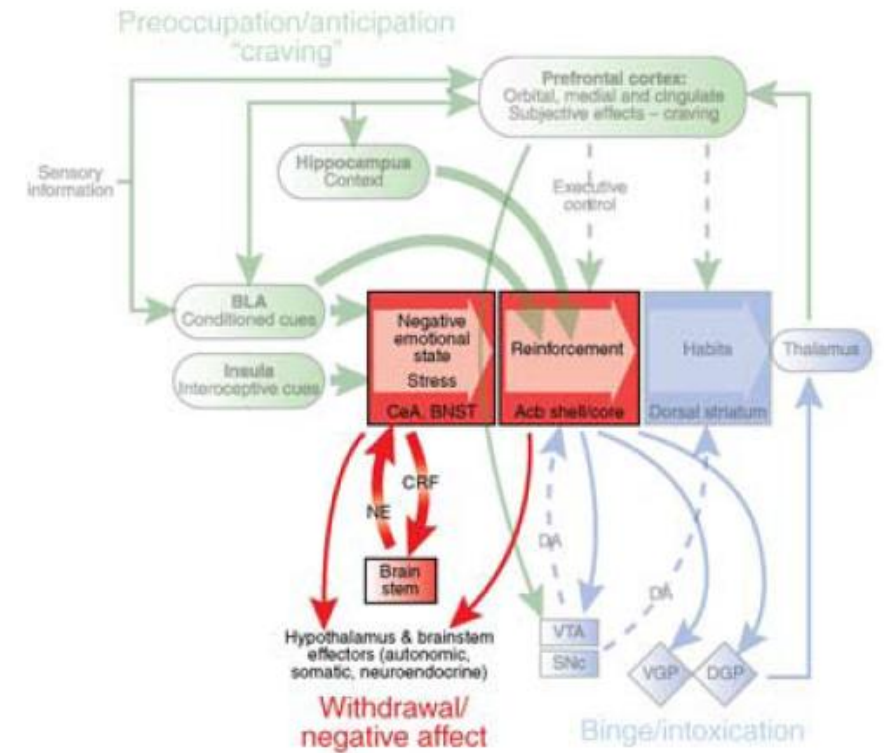
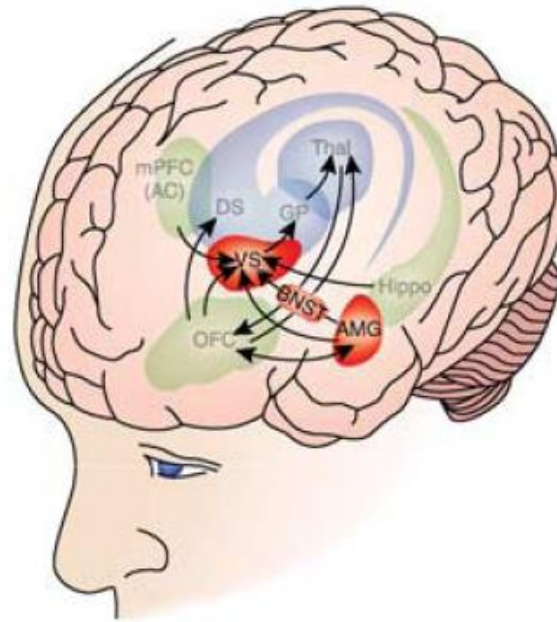
a



*Koob and Volkow 2010*

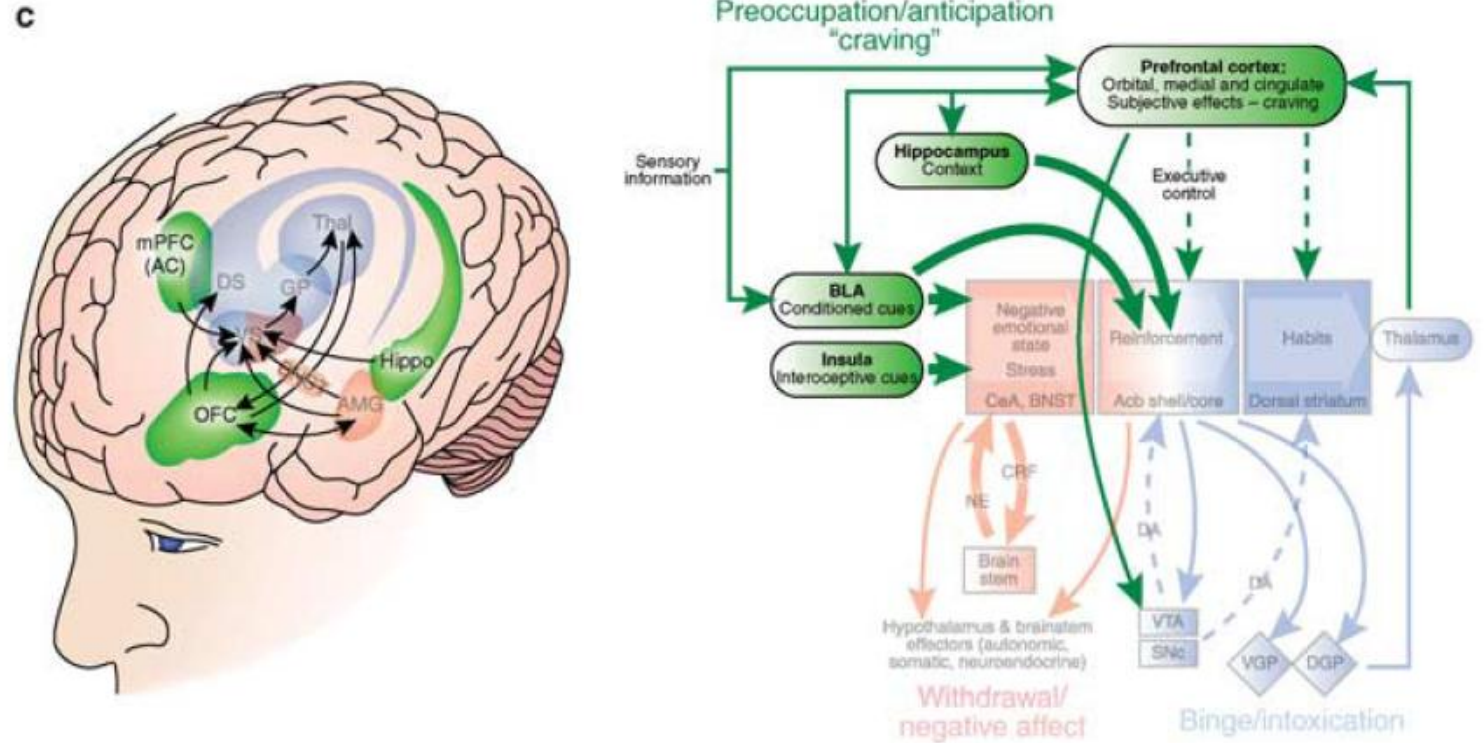
# The addiction cycle

b



*Koob and Volkow 2010*

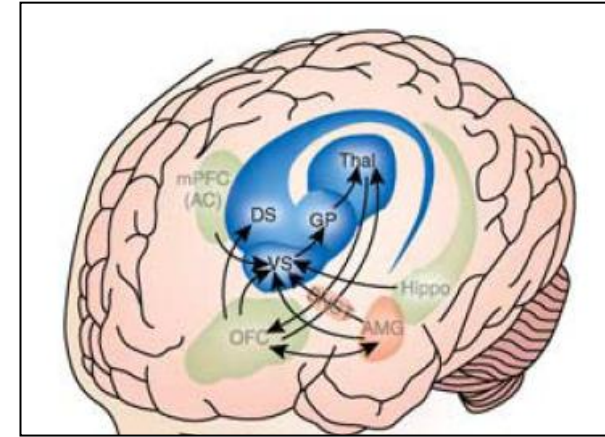
# The addiction cycle



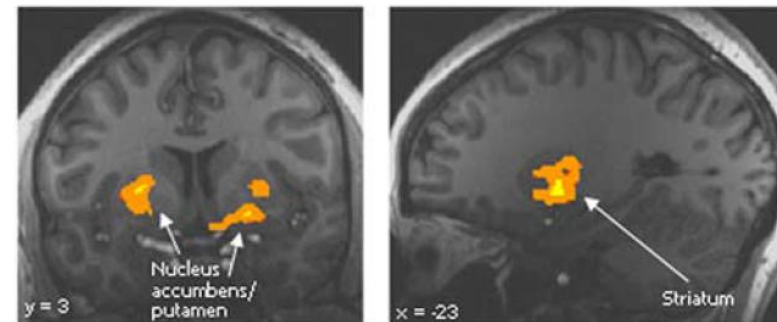
*Koob and Volkow 2010*

# Reward, Dopamine, and the Nucleus Accumbens (NAc)

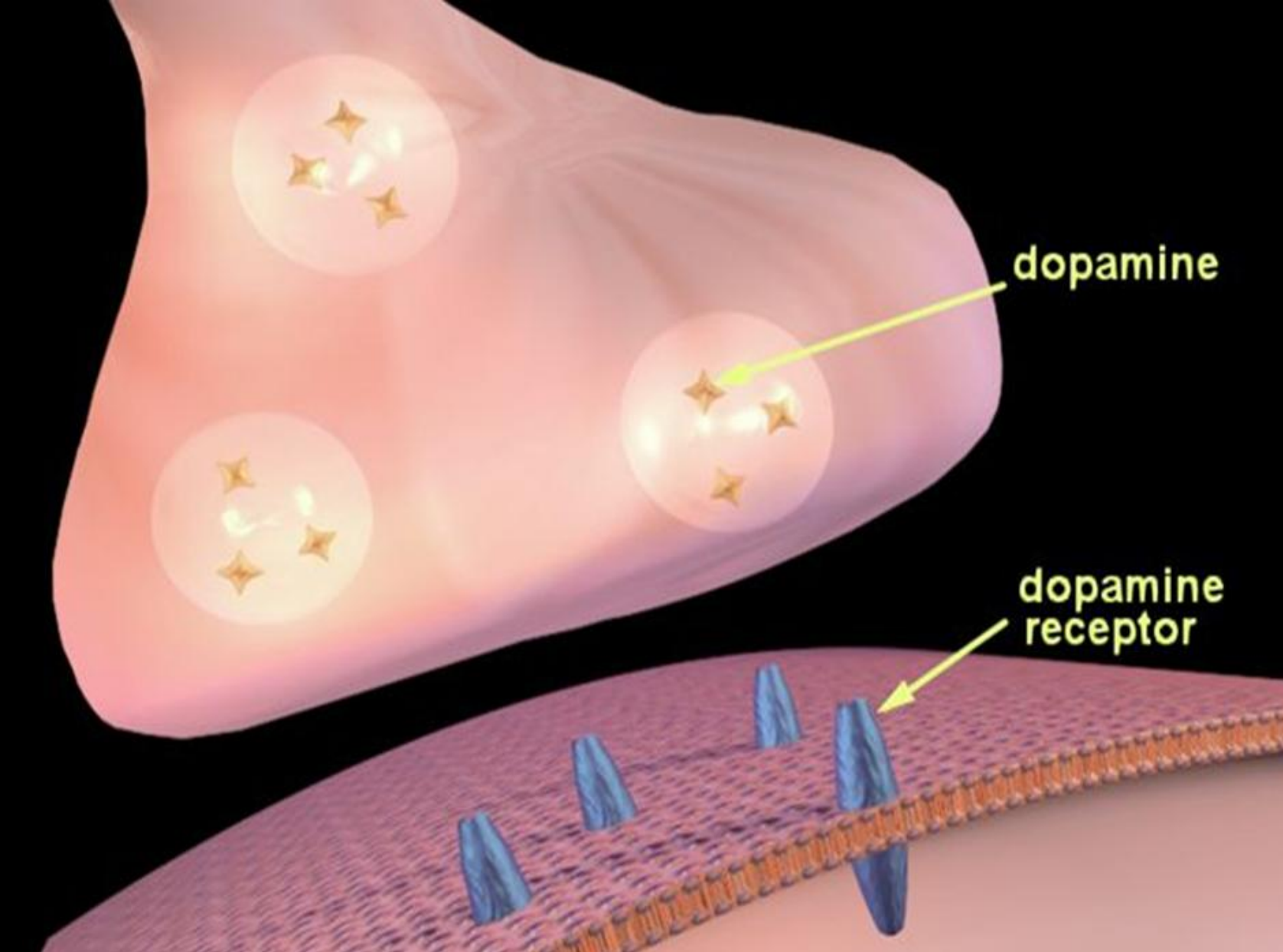
- Reward: stimulus that induces subjective feelings of pleasure.
- Rewarding stimuli activate the mesocorticolimbic reward circuit.
- All drugs of abuse share the ability to activate this circuit.
  - increase extracellular dopamine (DA) levels in the NAc

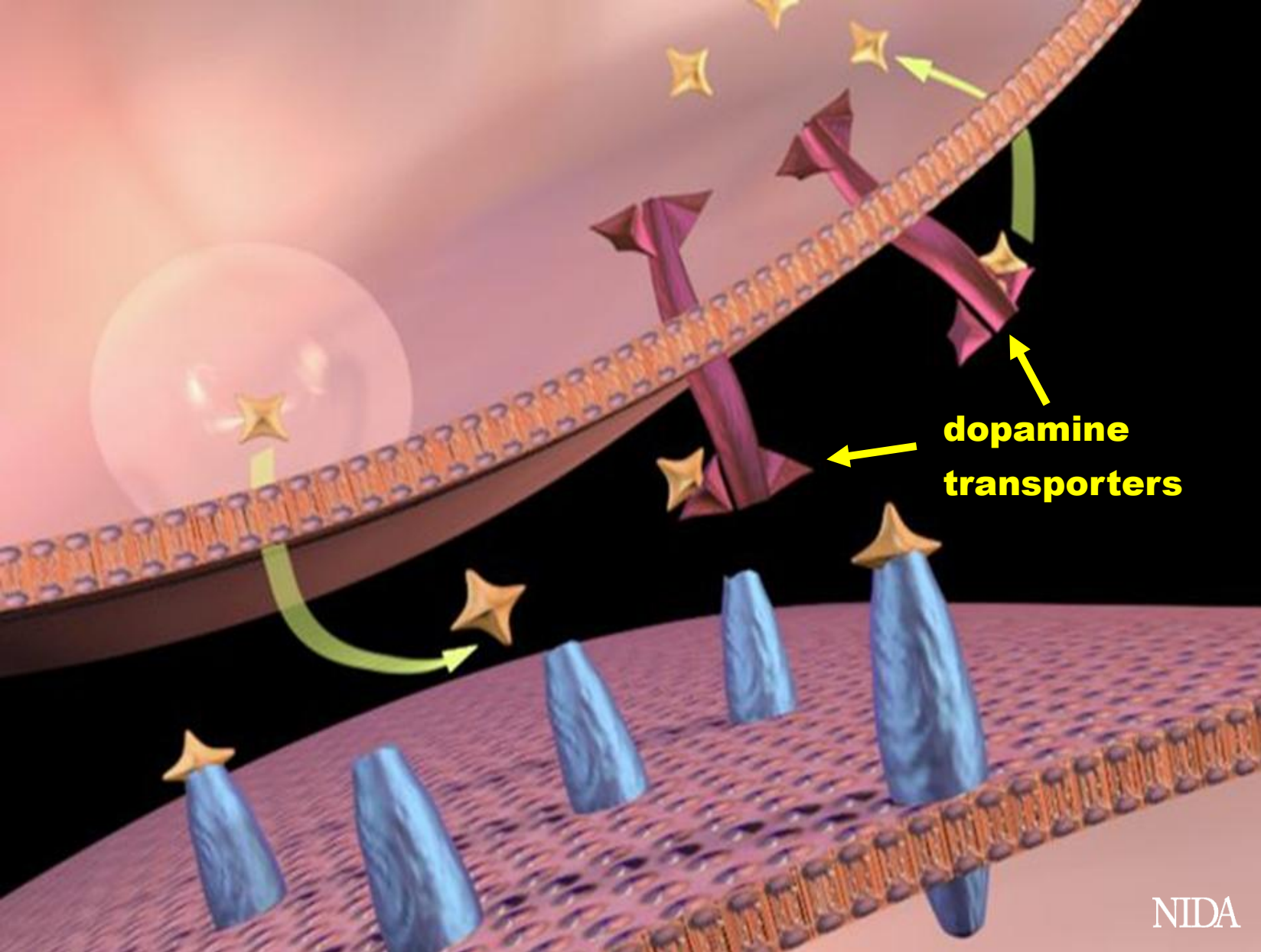


Alcohol:

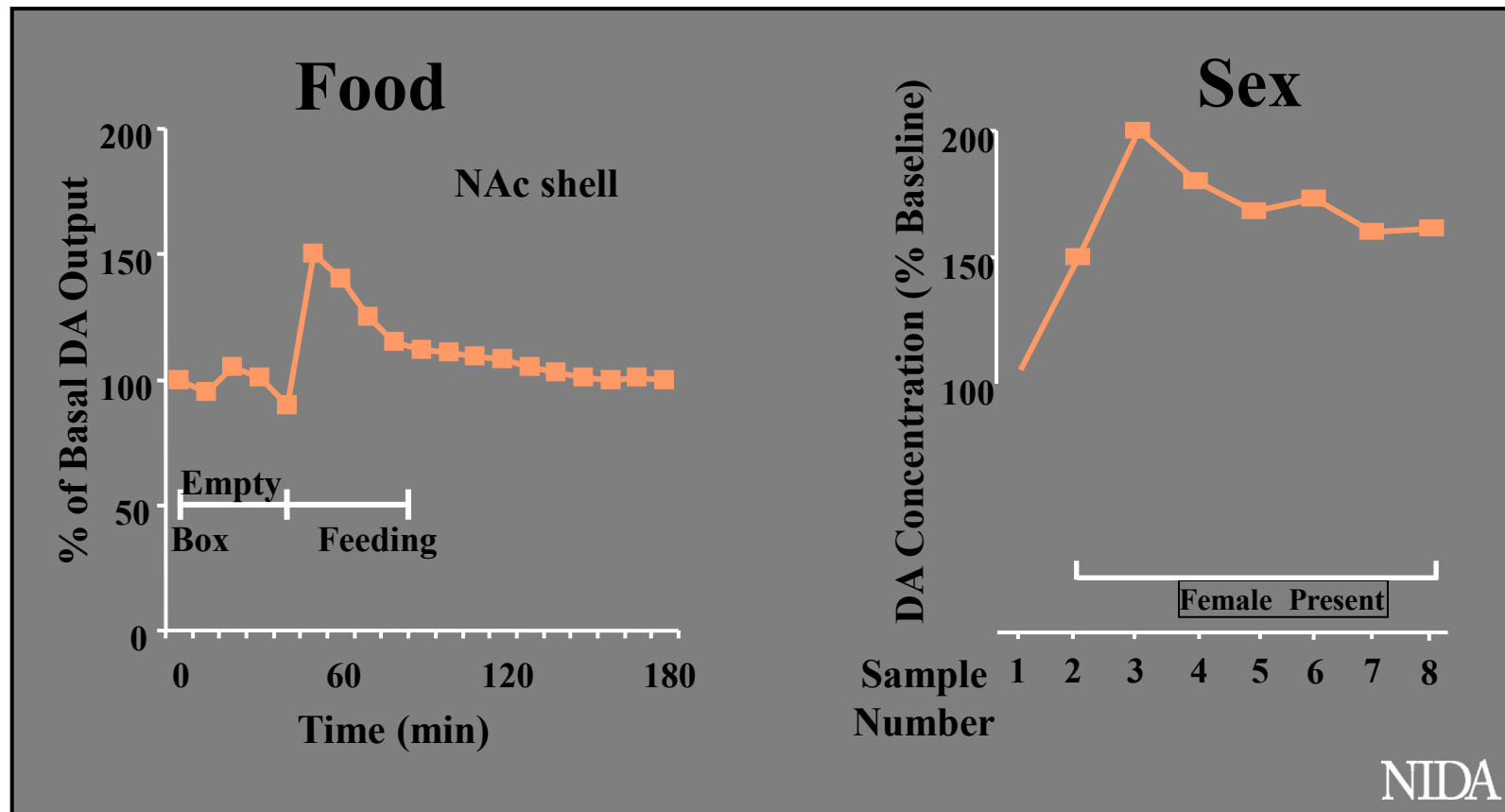


Gilman et al. 2008

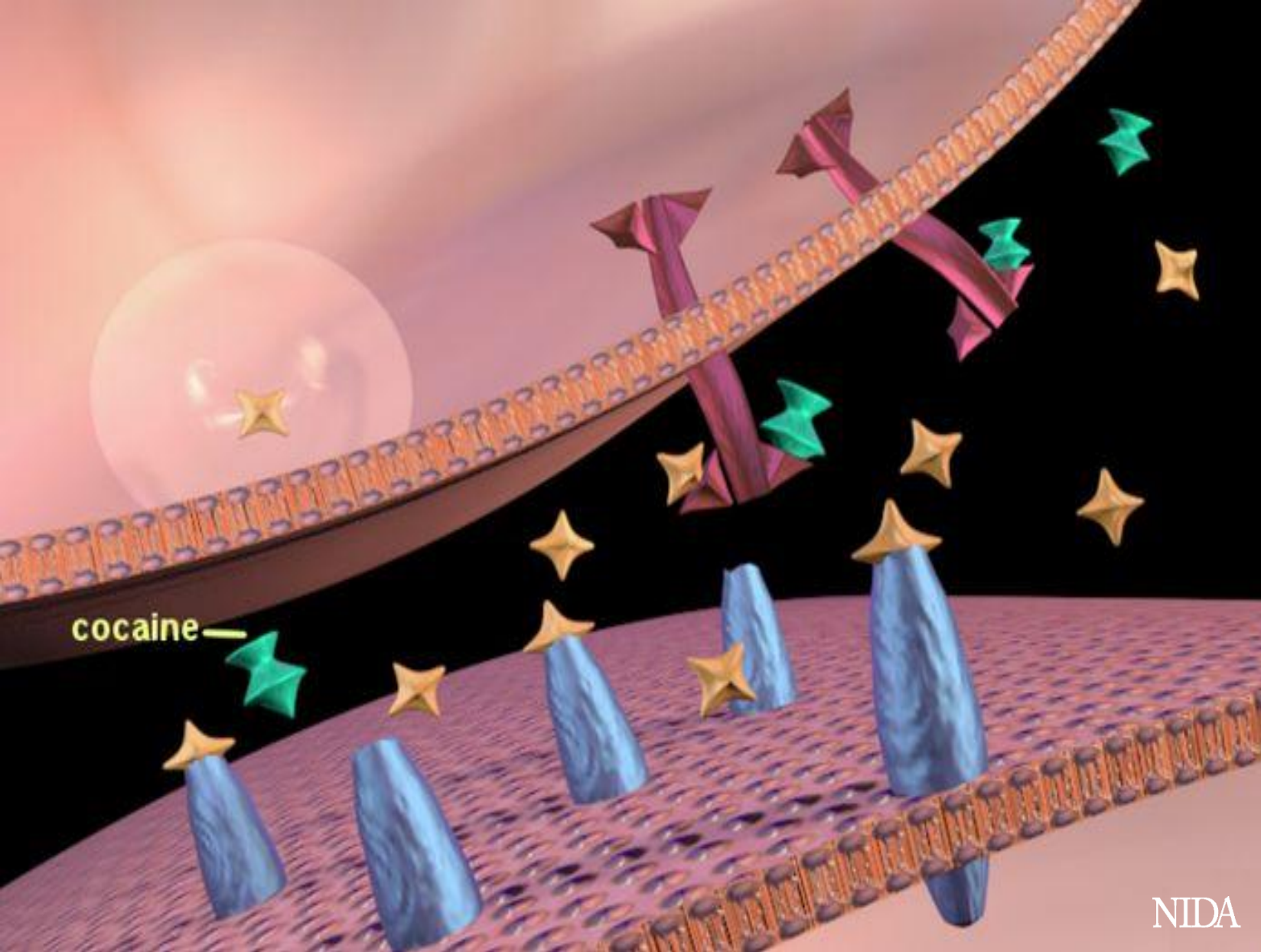




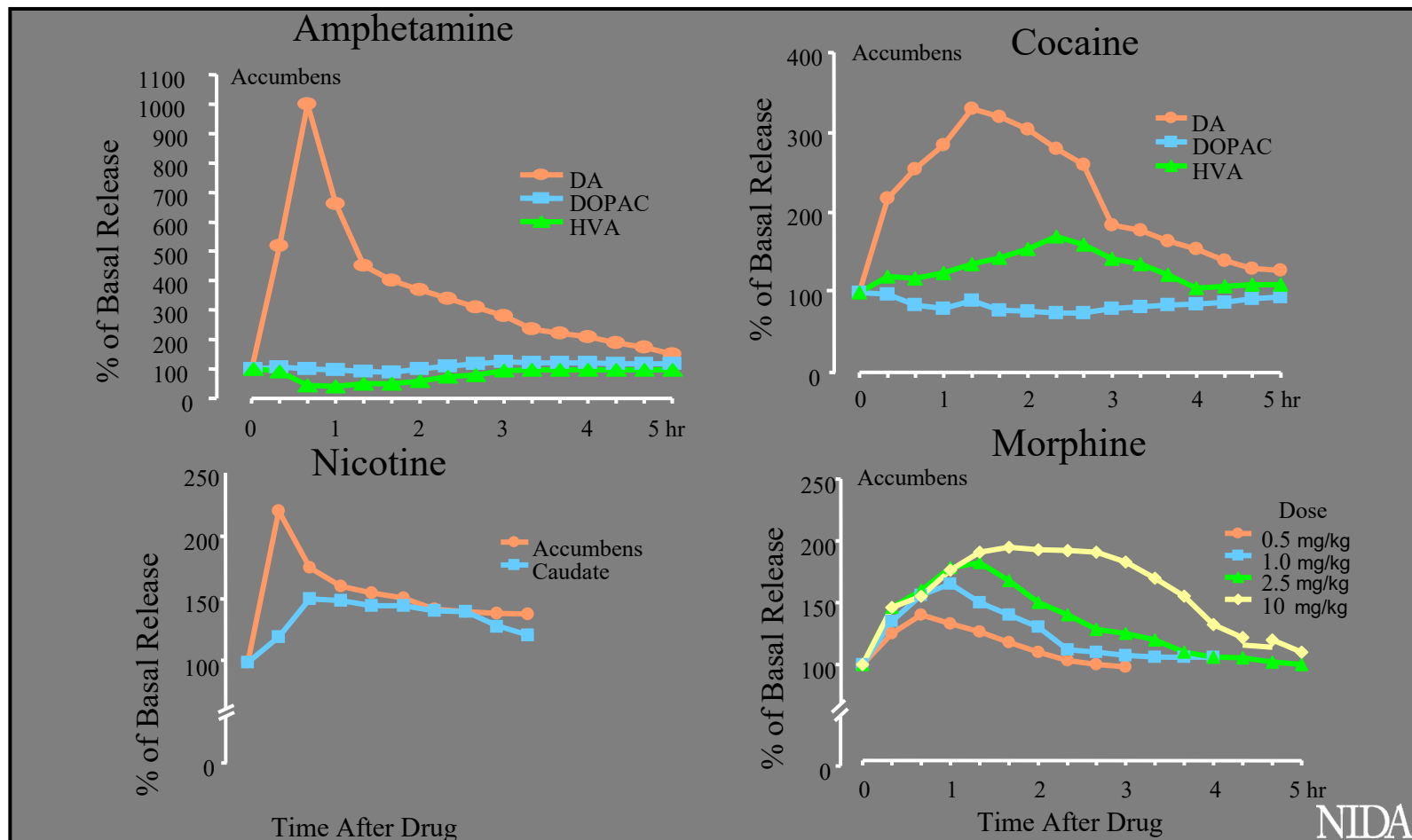
# Natural Rewards Elevate Dopamine Levels



Di Chiara et al., Neuroscience, 1999., Fiorino and Phillips, J. Neuroscience, 1997.



# Effects of Drugs on Dopamine Release



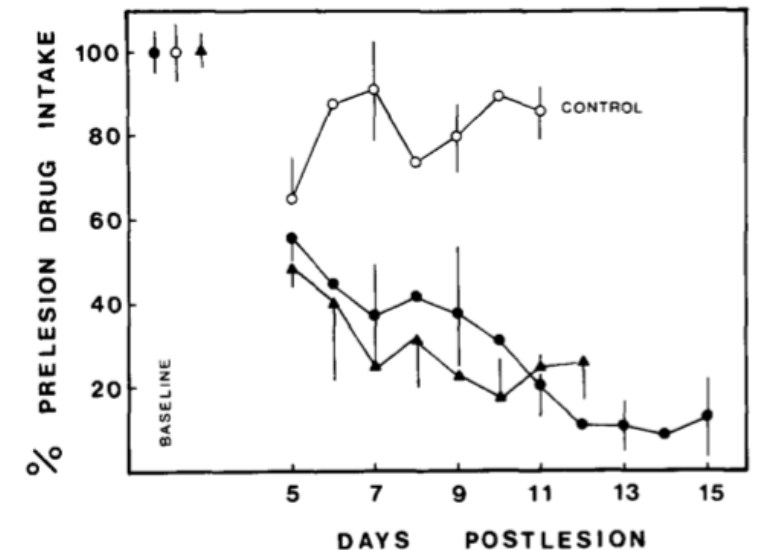
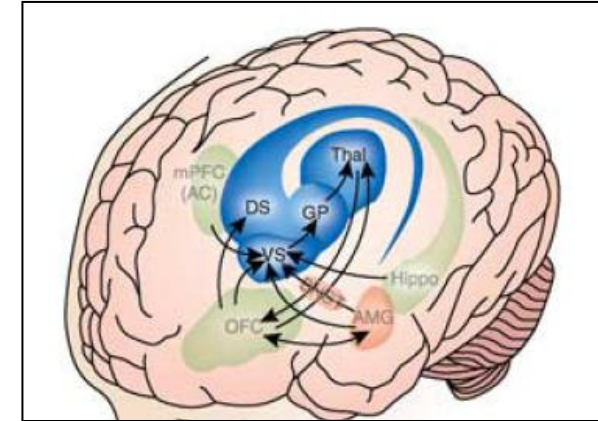
*Di Chiara and Imperato, PNAS, 1988*

# Reward

Enhanced dopamine in the NA is responsible for the acute high or initial reinforcing effects of drugs of abuse.

Drugs of abuse can more rapidly and markedly elevate DA levels to supraphysiological levels for sustained periods of time compared with natural rewards

Drugs outcompete natural reinforcers and end up “hijacking” and corrupting the initial process of reward processing.



Roberts & Koob, 1980

# Is this Responsible for Addiction?

---

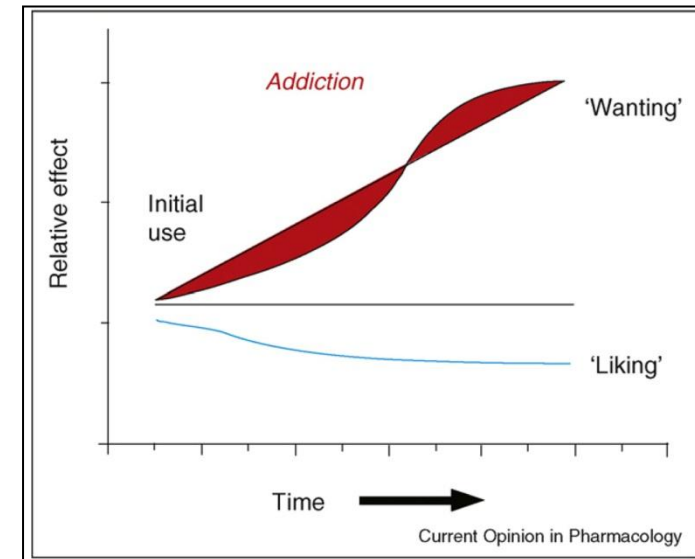
Behaviors persist despite **tolerance** to the positive effects of drugs over time

---

Individuals maintain use of substances through negative reinforcement to **avoid negative states** such as withdrawal states or to attempt to self-medicate for underlying psychic distress.

---

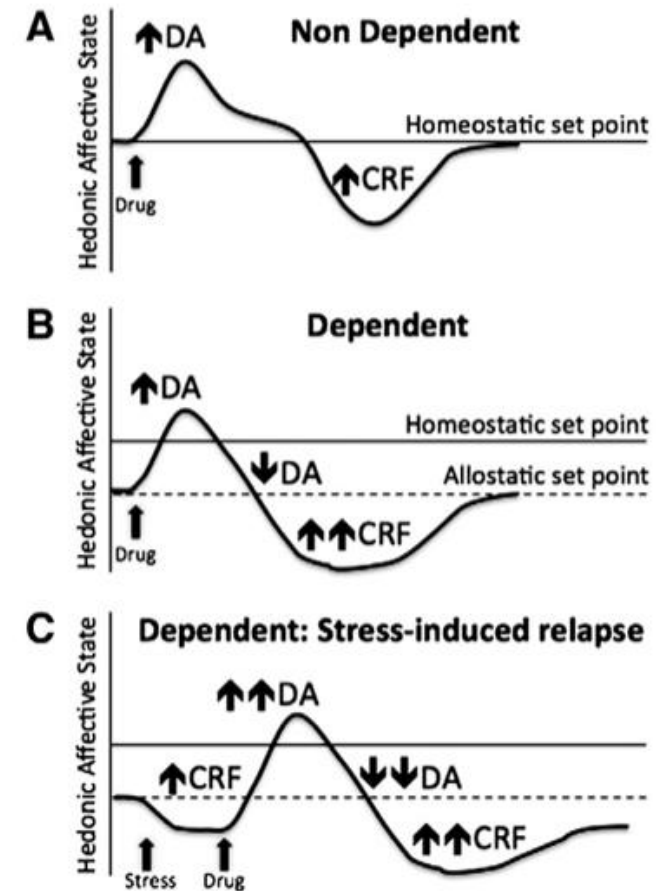
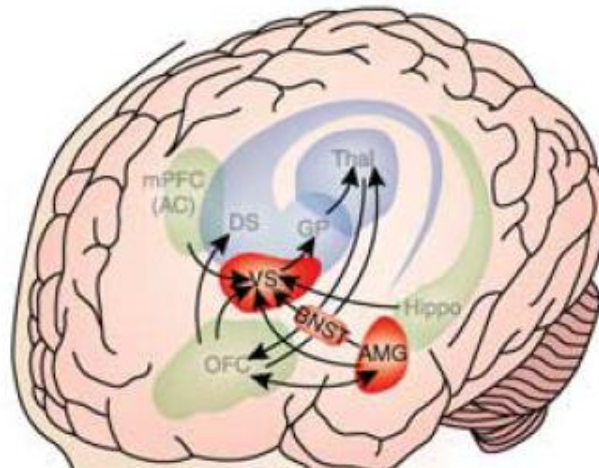
Degree of euphoria of a substance does not necessarily predict its addictiveness (i.e. nicotine)



*Berridge et al., 2009*

# The Switch from Reward to Negative Reinforcement/Withdrawal

- Enhanced dopamine in the NA is responsible for acute high or initial reinforcing effects (i.e., positive reinforcement) of drugs of abuse.
- All major drugs of abuse activate the brain stress systems
  - Elevated corticotropin-releasing factor (CRF) in the amygdala

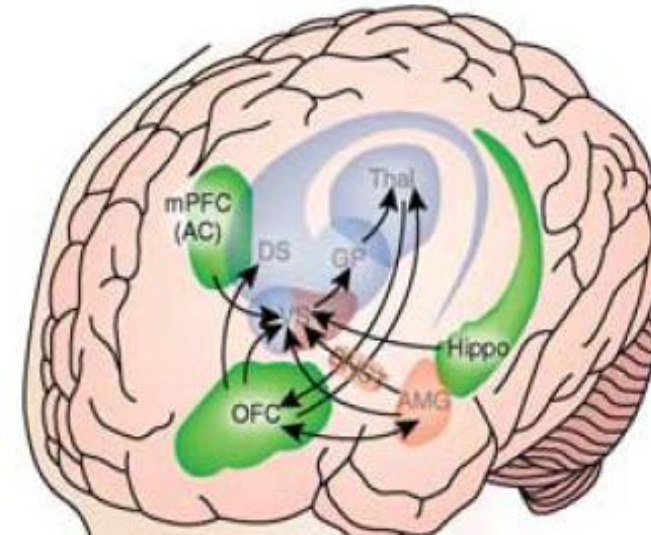


George, Le Moal, and Koob, 2012

# Executive Function Component

Loss of control, impulsivity, and impaired decision-making capacity involves:

- Orbitofrontal cortex (OFC): assigns a motivational value based on a prediction of reward;
- Anterior cingulate (ACC): plays a role in the inhibitory control of behaviors.

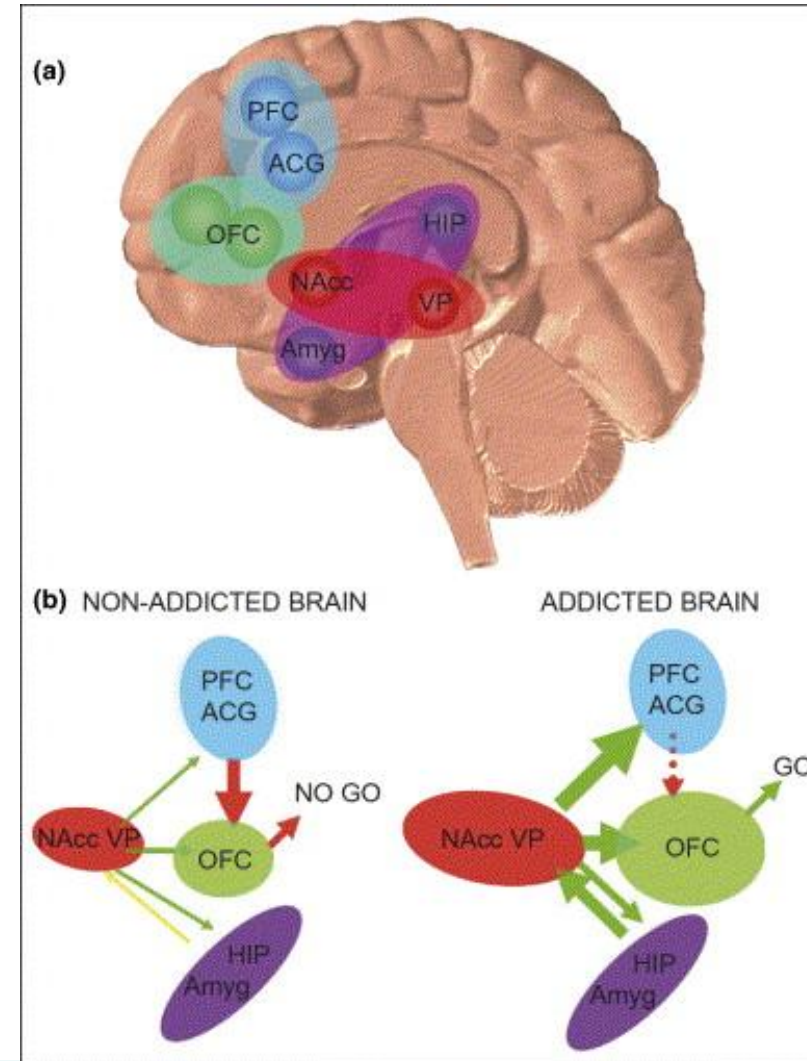


# Abnormal Activity in Two Brain Systems:

- 1) **Reward** (drive to meet goals) – Strong urge to use drugs over natural rewards, associated with impulsivity
- 2) **Inhibition** (control of goal-directed behavior) – Reduced control over behavior despite negative consequences

**~Both abnormalities are worsened by stress**

*Baler & Volkow, 2006; Koob & Volkow 2009*



# Inhibition: Just Say No?

- Addiction: loss of control over intense urges despite adverse consequences.

The model is:

Greater reinforcing (rewarding) properties of drugs/diminished reinforcement from natural rewards = greater drive to use drugs

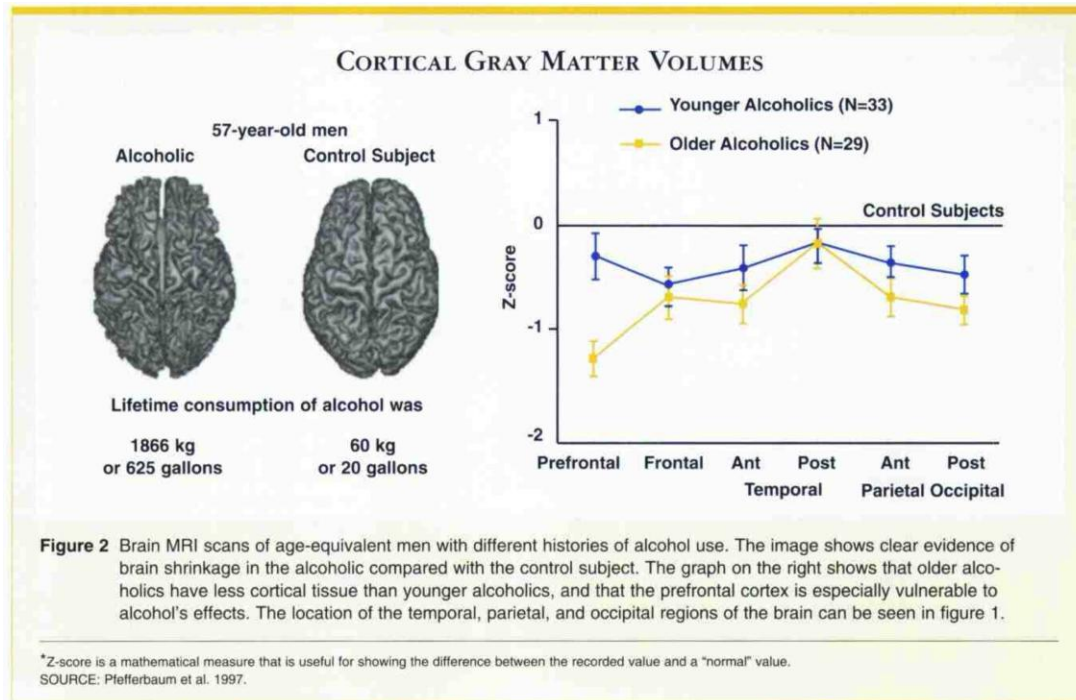
Diminished inhibitory control over behavior as evidenced by reduced prefrontal cortical activity during decision-making tasks = greater use of drugs despite serious negative consequences

# Today's Talk

- Who gets Addicted?
- The Addiction Cycle
  - Role of Dopamine/Reward in Addiction
  - Role of Impaired Inhibition in Addiction
- **Changes in the Brain that Occur**
- Treatment and Recovery

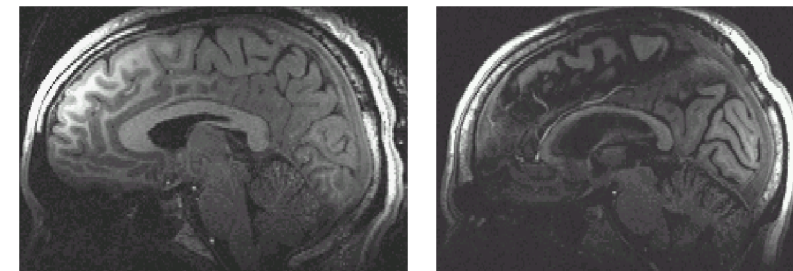
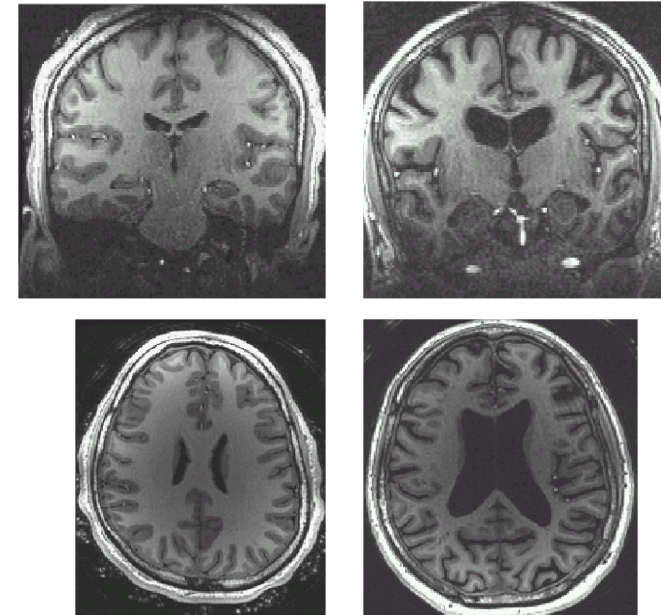
# Prolonged Drug Use Changes the Brain In Fundamental and Long-Lasting Ways

# Structural Effects of Addiction



*Pfefferbaum et al. 1997*

- ventricular enlargement
- Frontal lobe atrophy

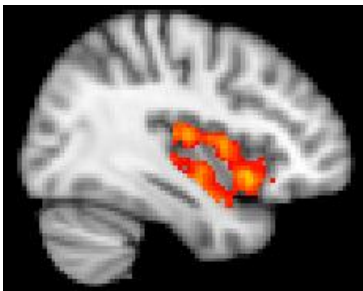


**Control brain**

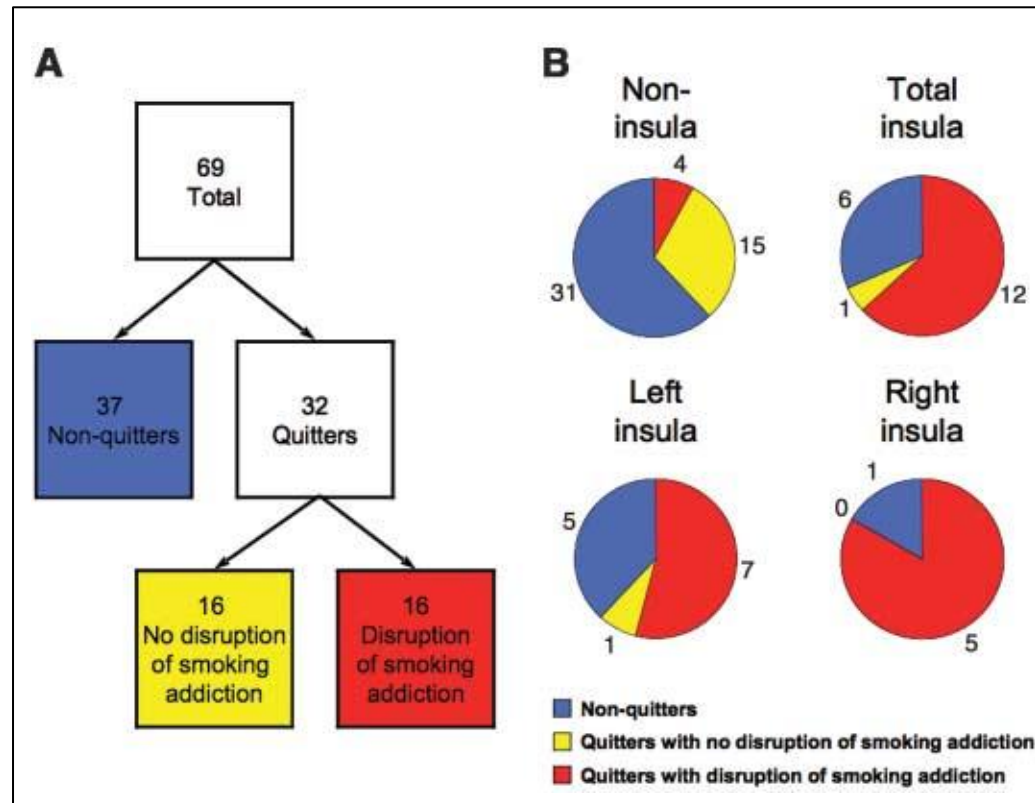
**AUD brain**

# Certain brain regions such as the Insula are especially important in the maintenance of addictive behavior

Patients with damage to the INS were able to quit cigarette smoking “easily, immediately, without relapse, and without persistence of the urge to smoke”



Navqi et al., 2007



# Substance use is particularly damaging to the adolescent brain

- high amounts of alcohol/ cannabis exposure during adolescence:
  - disrupts processes of brain maturation
  - worsens neurocognitive functioning.

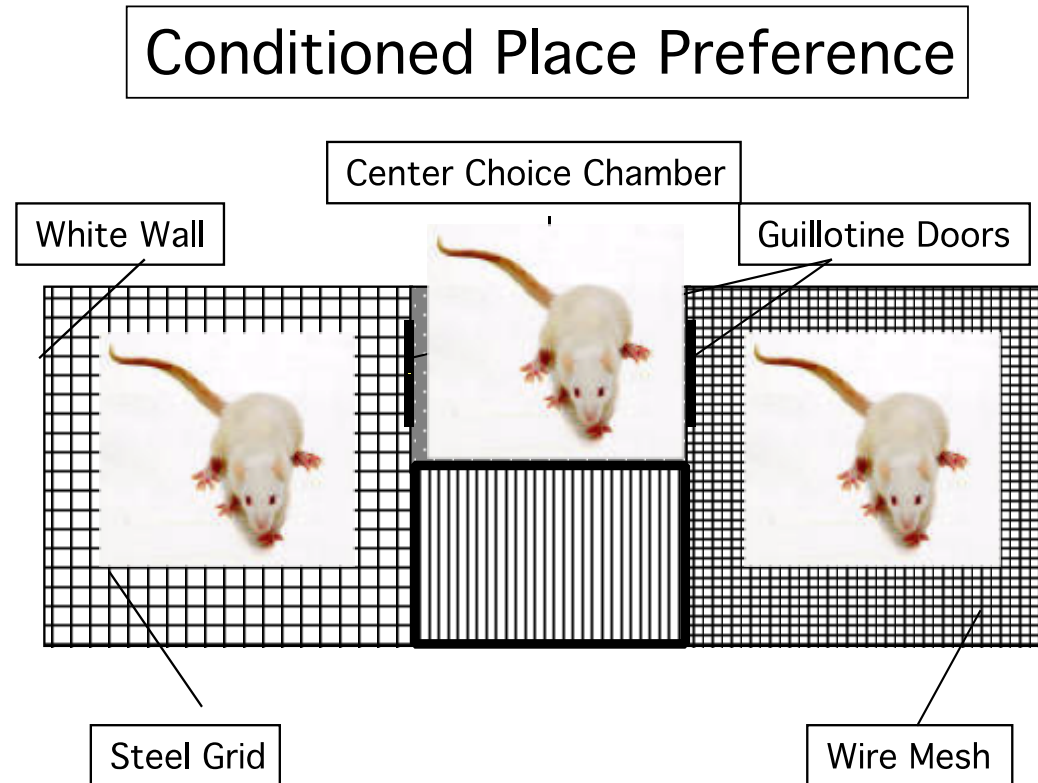
**Table 1**

Overview of consequences of repeated adolescent exposure to ethanol (EtOH), nicotine (NIC), cannabinoids (CBs) and MDMA and methamphetamine stimulants (STIM).

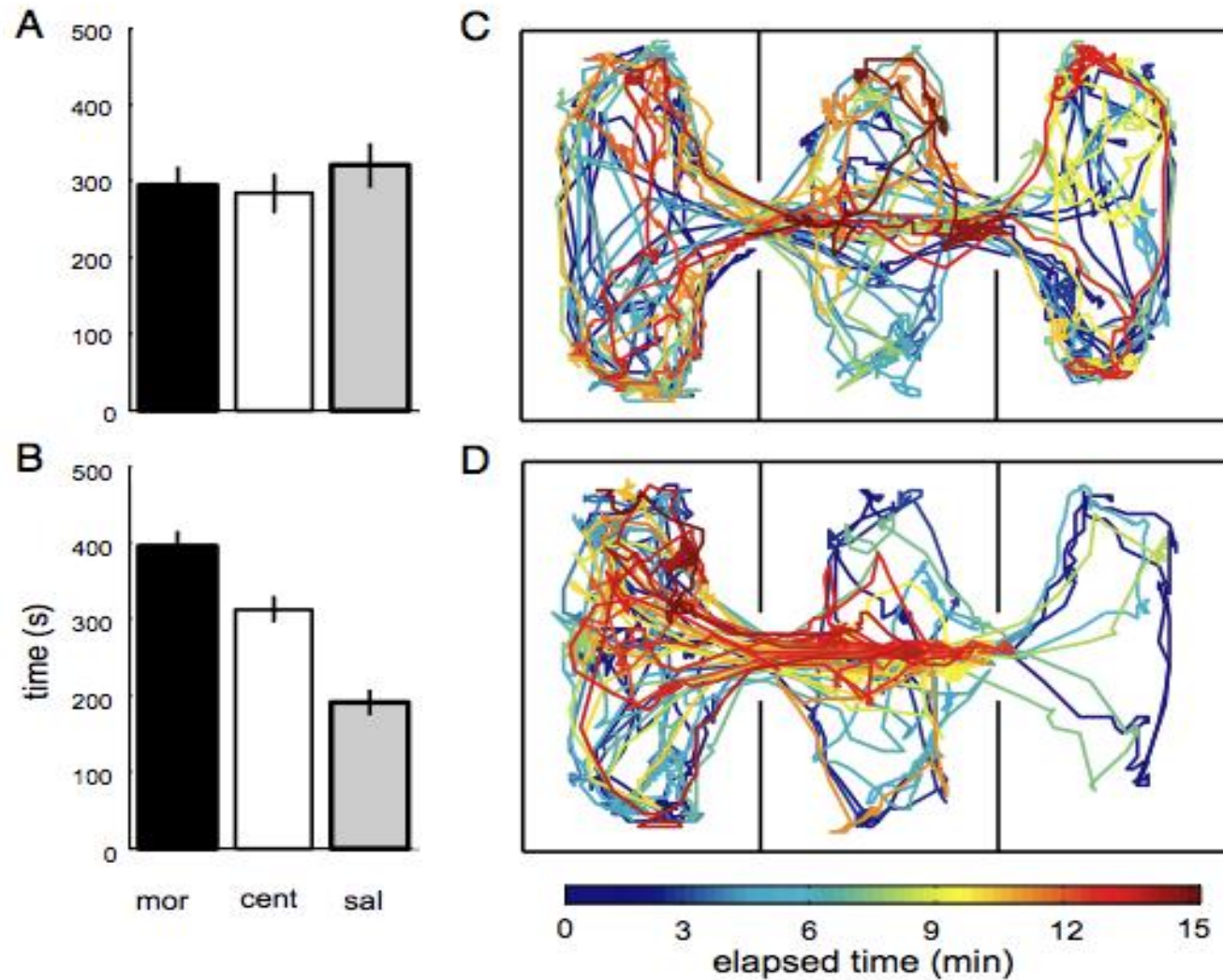
| General Age Vulnerability                   | EtOH<br>Adol > Adult | NIC<br>Adol > Adult | CB<br>Adol > Adult | COC<br>? | STIM<br>Adol < Adult |
|---------------------------------------------|----------------------|---------------------|--------------------|----------|----------------------|
| <b>Cognitive/behav.</b>                     |                      |                     |                    |          |                      |
| Spatial memory                              | ↓=                   |                     | =                  |          |                      |
| Conditional discrimin./pattern learning     | ↓                    | ↓                   |                    |          |                      |
| Attention                                   |                      | ↓                   |                    | (↓)      |                      |
| Obj. recognit./working memory               | ↓                    |                     | ↓                  | =        | ↓                    |
| Pre-pulse inhibition                        |                      |                     | ↓                  |          |                      |
| Cognitive flexibility                       | ↓                    |                     |                    |          |                      |
| Risk preference                             | ↑                    |                     |                    |          |                      |
| Impulsivity/disinhibition                   | ↑                    | ↑                   |                    | ↑*       |                      |
| Retent. of adoles-typical phenotypes        | ↑                    |                     |                    |          |                      |
| <b>Affective/Social behavior</b>            |                      |                     |                    |          |                      |
| Depression-like behaviors                   | ↑                    |                     | ↑                  |          |                      |
| Social interactions                         | ↓                    |                     | ↓                  | =        | ↓                    |
| Social anxiety-like behaviors               | ↑                    |                     | ↑                  |          | ↑                    |
| Other anxiety-like behaviors                | ↑, ↓                 | ↑                   | ↑, ↓, =            | =        | =, ↓                 |
| Later self-administ. (same/different drugs) | ↑, =                 | ↑, =                | ↑, =               |          |                      |
| <b>Neural</b>                               |                      |                     |                    |          |                      |
| Neurogenesis                                | ↓                    |                     |                    |          |                      |
| Cell death                                  | ↑                    | ↑                   |                    |          | ↑                    |
| Spines/dendritic branching                  | ↑ "immature spines"  | ↑                   |                    |          |                      |
| Electrophysiol. Alterations                 | Y                    |                     |                    | Y        |                      |
| Neuroimmune activation                      | Y                    |                     |                    |          |                      |
| Histone acetylation/epigenetic regulat.     | Y                    |                     |                    | Y        |                      |
| <b>Alterations in:</b>                      |                      |                     |                    |          |                      |
| Ach                                         | Y                    | Y                   |                    |          | Y                    |
| Glutamate/GABA                              | Y                    | Y                   | Y                  | Y        | Y                    |
| DA                                          | Y                    | Y                   | Y                  | Y        | Y                    |
| 5HT                                         |                      | Y                   | Y                  |          | Y                    |
| CB                                          |                      |                     | Y                  |          |                      |
| <b>Affected brain regions:</b>              |                      |                     |                    |          |                      |
| PFC                                         | Y                    | Y                   | Y                  | Y        | Y                    |
| HPC                                         | Y                    | Y                   | Y                  | Y        | Y                    |
| nAc                                         | Y                    | Y                   | Y                  | Y        |                      |
| AMYG                                        | Y                    | Y                   | Y                  | Y        | Y                    |

References are provided in text and cited reviews; ↓ impaired/attenuated; ↑ enhanced; = no notable exposure effects; Y alteration(s) reported (often complex). \*data interpreted as decreased cautiousness/attenuated threat evaluation (which are likely similar but may not be the same construct as impulsivity).

# These changes are long-lasting



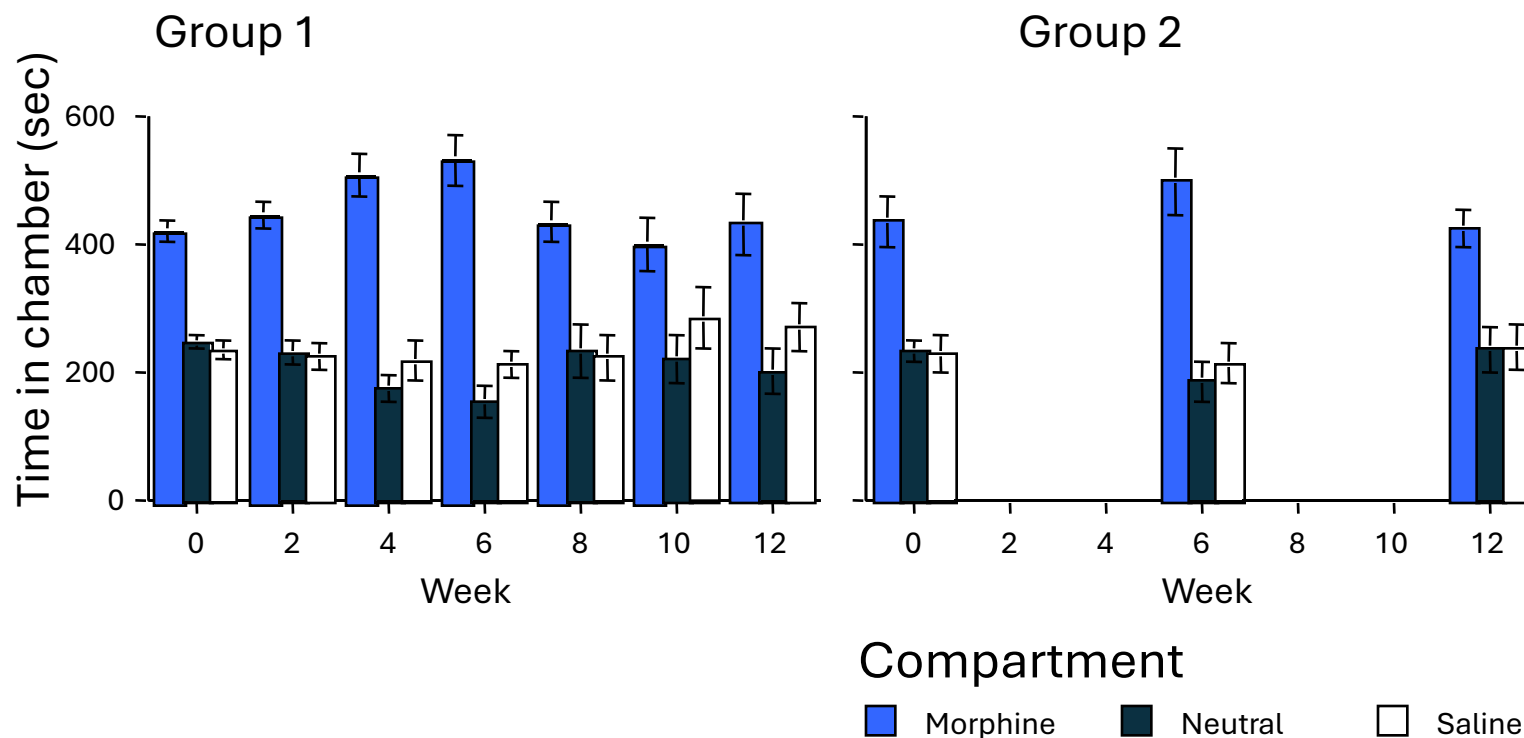
# Morphine-induced Conditioned Place Preference



Movement patterns during a 15-min test before and after four pairings of the left compartment with morphine 10 mg/kg

*German & Fields, 2006*

# Morphine CPP: Persistence of effect of drug-paired cues infrequent 15-min tests: *no drug since training*



Note the  
lack of  
extinction  
when test  
are widely  
spaced

*Mueller et al., 2000*

# Today's Talk

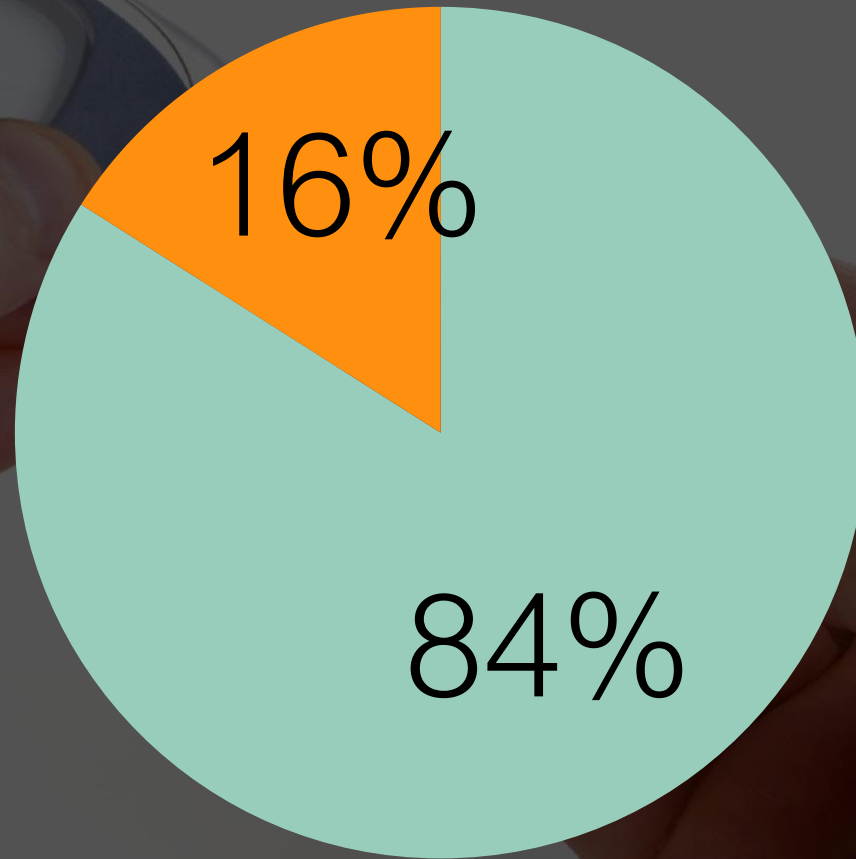
- Who gets Addicted?
- The Addiction Cycle
  - Role of Dopamine/Reward in Addiction
  - Role of Impaired Inhibition in Addiction
- Changes in the Brain that Occur
- Treatment and Recovery

# Who Gets Treatment??

8.3% of Americans have diabetes



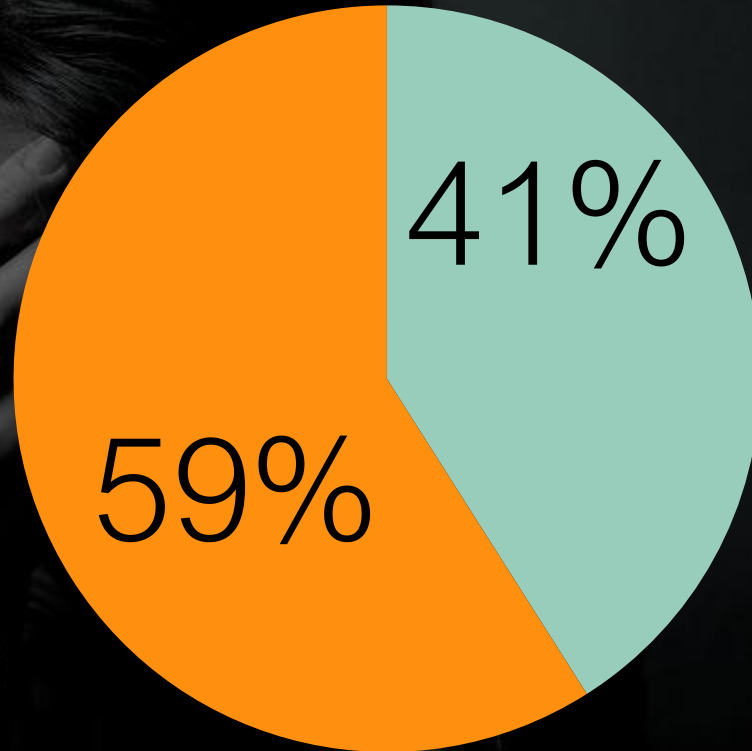
■ Any diabetes treatment ■ No treatment





9.5% of Americans have  
a mood disorder in a  
given year

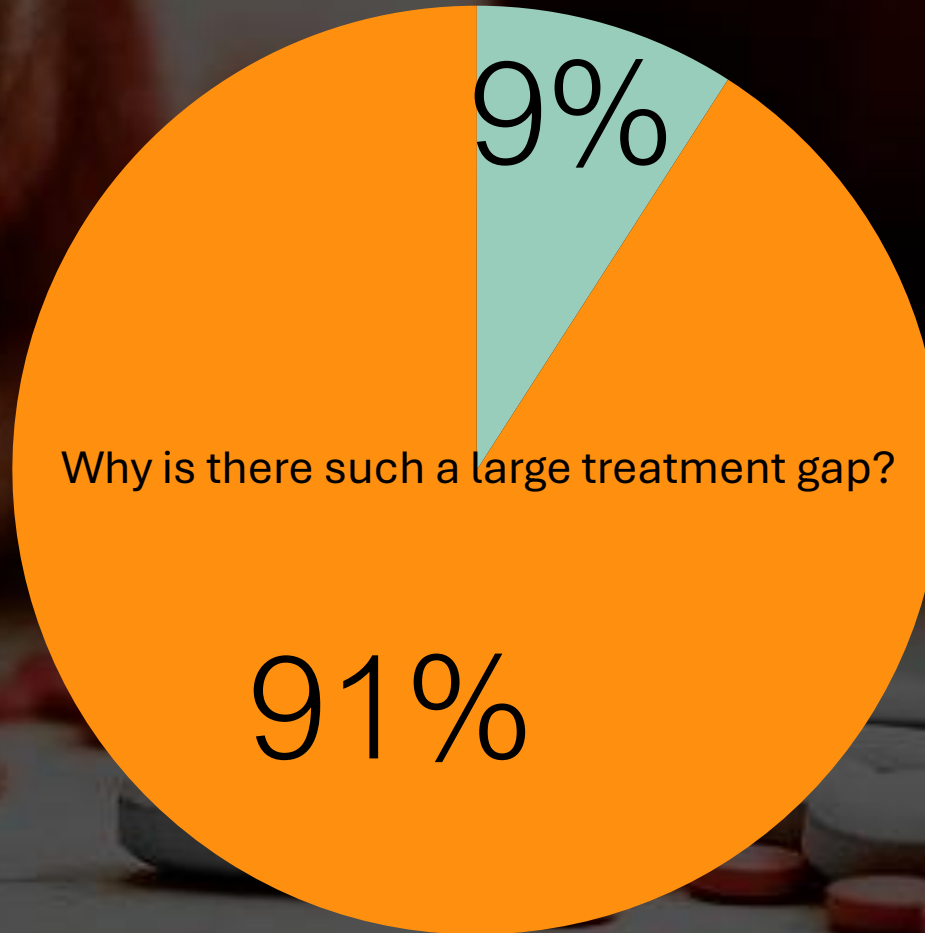
■ Any MH treatment    ■ No treatment





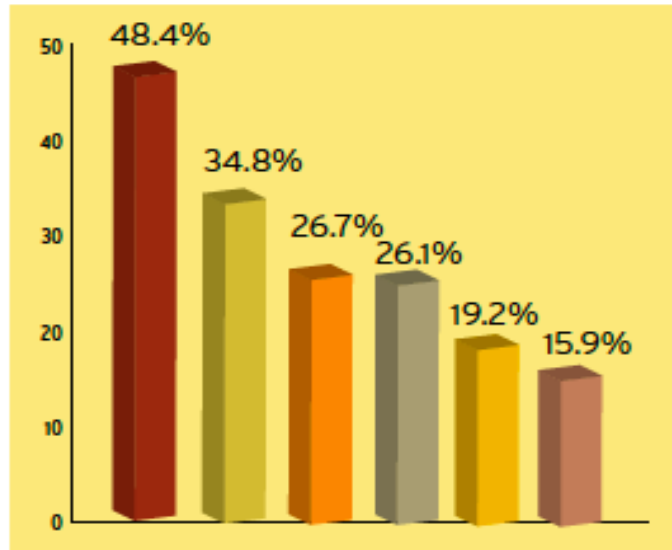
7.4% of Americans have a  
substance use disorder in a  
given year

■ Any addiction treatment    ■ No treatment



# Barriers to receiving SUD treatment

How People Pay for Treatment



- Own savings and earnings
  - Private health insurance
  - Medicaid
  - Public assistance other than Medicaid
  - Medicare
  - Funds from family members
- [note: individuals could report multiple sources of funding for treatment]

# Types of Treatments for SUD

## Behavioral Treatments

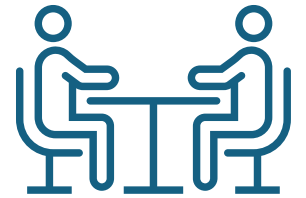
- Motivational interviewing / brief interventions
- Cognitive behavioral therapy
- **Contingency management**
- 12-step facilitation / peer support

## Pharmacological Treatments

- FDA-approved medications for **opioid, alcohol, and nicotine use disorders**
- No FDA-approved medications for **stimulant or cannabis use disorders**

## Emerging Approaches

- **GLP-1 receptor agonists**
- Neuromodulation
- Digital therapeutics / telemedicine



# Medications for Substance Use Disorders

## Nicotine addiction medications<sup>1,2</sup>

- **Nicotine replacement therapy** can aid in abrupt or gradual cessation or in reduction of smoking.
- **Bupropion** is a dopamine/noradrenaline modulator and acts as an antagonist at nicotinic ACh receptors to help reduce smoking.
- **Varenicline** is a partial agonist at the  $\alpha_4\beta_2$  nicotinic ACh receptors, which can help reduce the rewarding and reinforcing effects of nicotine

## Alcohol addiction medications<sup>2,3</sup>

- **Disulfiram** was the first medication approved for alcohol dependence; it inhibits acetaldehyde dehydrogenase, causing a toxic build-up of acetaldehyde in an individual upon drinking alcohol
- **Naltrexone** is an opioid antagonist, which can be useful in reducing the urge to use alcohol
- **Acamprosate** interacts with glutamate and GABA signaling in the brain, and is thought to decrease alcohol withdrawal by modulation of glutamatergic neurons
- Other medications used for, or investigated in, the treatment of alcohol-use disorder include, baclofen, ketamine,<sup>4</sup> the anti-seizure topiramate, as well as certain SSRIs

## Opioid addiction medications<sup>2</sup>

- **Methadone** binds to opiate receptors as an agonist, but does not produce the same short-term cycle of euphoria and withdrawal as opiate substances of abuse (e.g., heroin); this can help to suppress cravings and withdrawal symptoms, although it can be addictive itself.
- **Buprenorphine** works in a similar way to methadone, but is a partial agonist at opiate receptors; it is less closely regulated than methadone because the addiction potential is lower, and is safer if overdosed because of ceiling effects on respiratory depression
- **Naltrexone** is an opioid antagonist that blocks the effects of opioid agonists such as heroin, thereby helping to stop the urge to use the substance

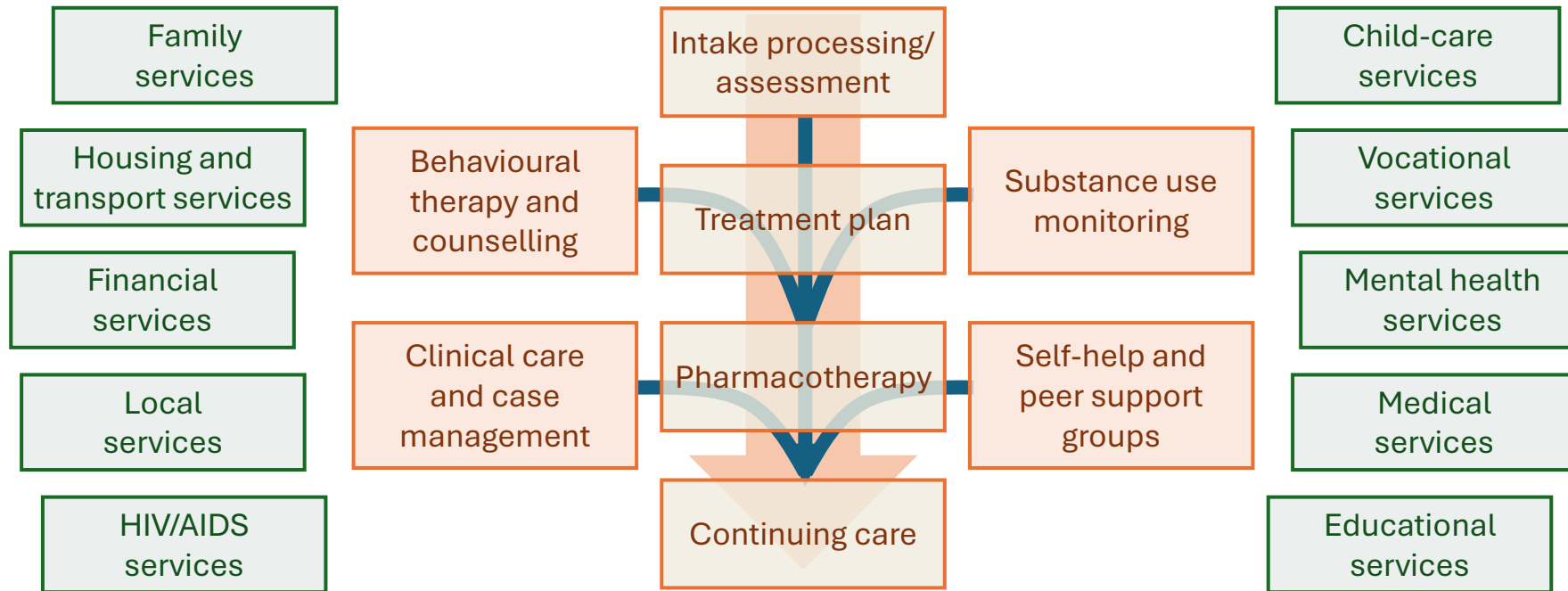
ACh=acetylcholine; GABA=gamma-aminobutyric acid; SSRI=selective serotonin reuptake inhibitor

1. Fagerström & Jiménez-Ruiz. Eur Respir Rev 2008;17(110):192–198; 2. Douaihy et al. Soc Work Public Health 2013;28(3–4):264–278; 3. Stokłosa et al. Int J Environ Res Public Health 2023;20(3):1870; 4. Ivan Ezquerro-Romano et al. Neuropharmacology 2018;142:72–82

# Addiction is Similar to Other Chronic Illnesses Because:

- It has biological and behavioral components, both of which must be addressed during treatment.
- Recovery from it--protracted abstinence and restored functioning--is often a long-term process requiring repeated episodes of treatment.
- Relapses can occur during or after treatment and signal a need for treatment adjustment or reinstatement.
- Participation in support programs during and following treatment can be helpful in sustaining long-term recovery

# Components of comprehensive substance use treatment



- There are a variety of evidence-based approaches to treating addiction
- Therapy can be a pharmacological therapy, psychotherapy, or a combination of both
- The specific treatment approach for a single patient will vary, based on the individual's needs

# Conclusions

- Addiction reflects interactions among biology, development, environment, and drug exposure
- Repeated drug use alters reward, stress, learning, and executive-control systems
- Motivation can shift from reward → craving/negative reinforcement → compulsive use
- These changes can persist, but the brain remains plastic
- Effective treatments exist, and recovery is possible
- Thank you for your attention!!!