



MASSACHUSETTS
GENERAL HOSPITAL

PSYCHIATRY ACADEMY

The Neurobiology of Addiction

Jodi Gilman, Ph.D.

Center for Addiction Medicine
Massachusetts General Hospital

Associate Professor, Department of Psychiatry
Harvard Medical School

WWW.MGHCME.ORG



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



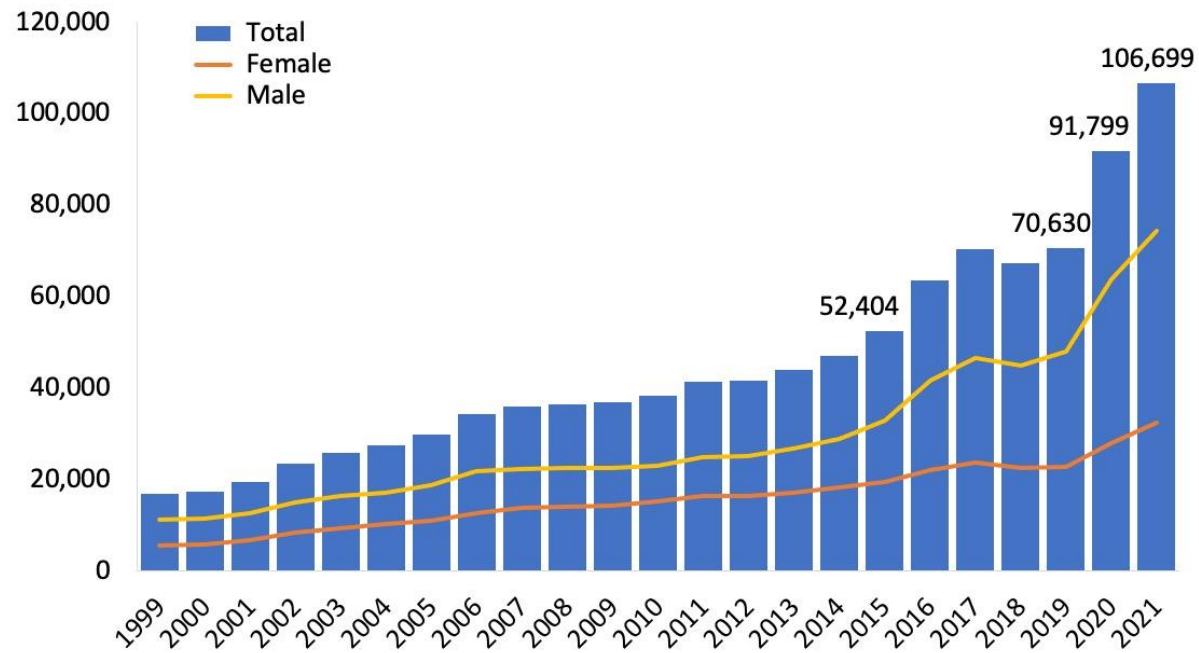
How Common is Addiction?

- **Alcohol:** 17 million Americans (11% of the population) are addicted (steady for the past few decades)
- **Nicotine:** 55 million Americans (21% of the population) are addicted (decreasing... For now... E-cigarettes may change this)
- **CANNABIS:** ~9 million (6% of the population) Americans are addicted (increasing- *increases occurred across gender, region, educational level, and employment status*)
- **VAPING:** nicotine or cannabis or both: 37 percent of 12th graders report vaping (dramatic increase- nearly **doubling**)
- **5.4 million** (3% of the population): addiction to illicit drugs/non-prescribed drugs (increasing due to opioids)

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



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.

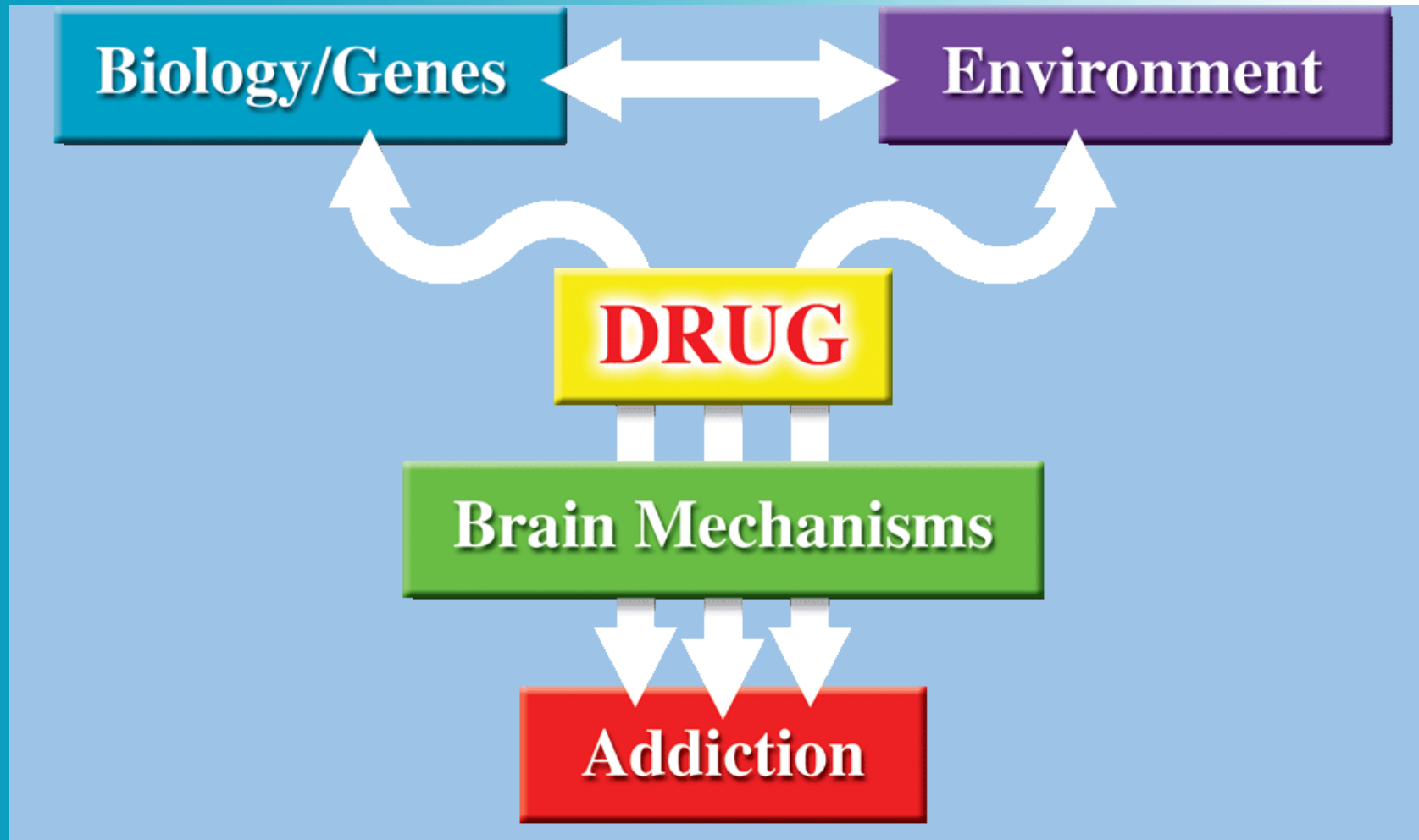
The death toll has doubled in the last decade, now claiming a life every 14 minutes, making it the number one cause of preventable deaths.

Addiction Involves Multiple Factors



MASSACHUSETTS
GENERAL HOSPITAL

PSYCHIATRY ACADEMY



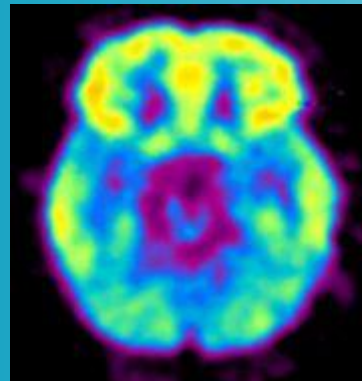
NIDA

Addiction is Like Other Diseases...

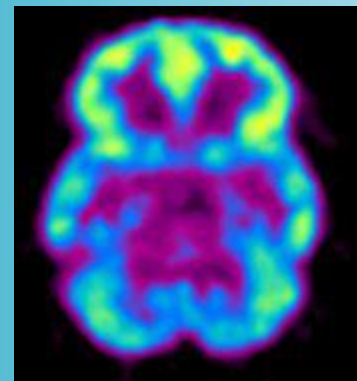


- It is preventable
- It is treatable
- It changes biology
- If untreated, it can last a lifetime

Decreased Brain Metabolism
in *Cocaine-addiction Patient*

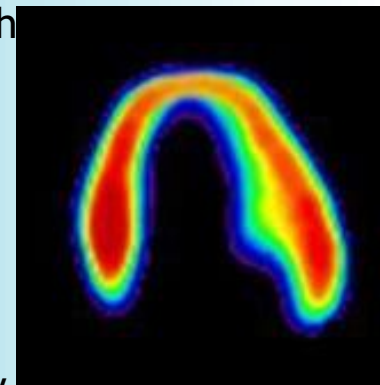
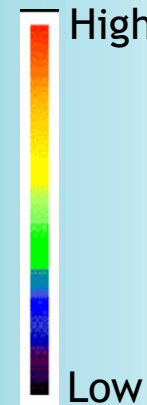


Healthy Brain

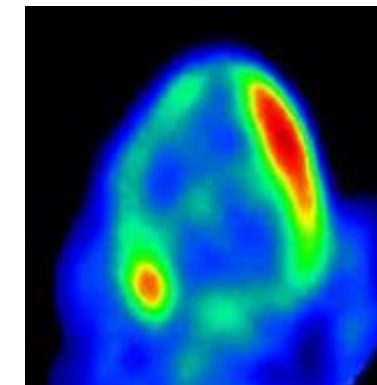


Diseased Brain/
Cocaine Abuse

Decreased Heart Metabolism
in *Heart Disease Patient*



Healthy
Heart



Diseased Heart





MASSACHUSETTS
GENERAL HOSPITAL

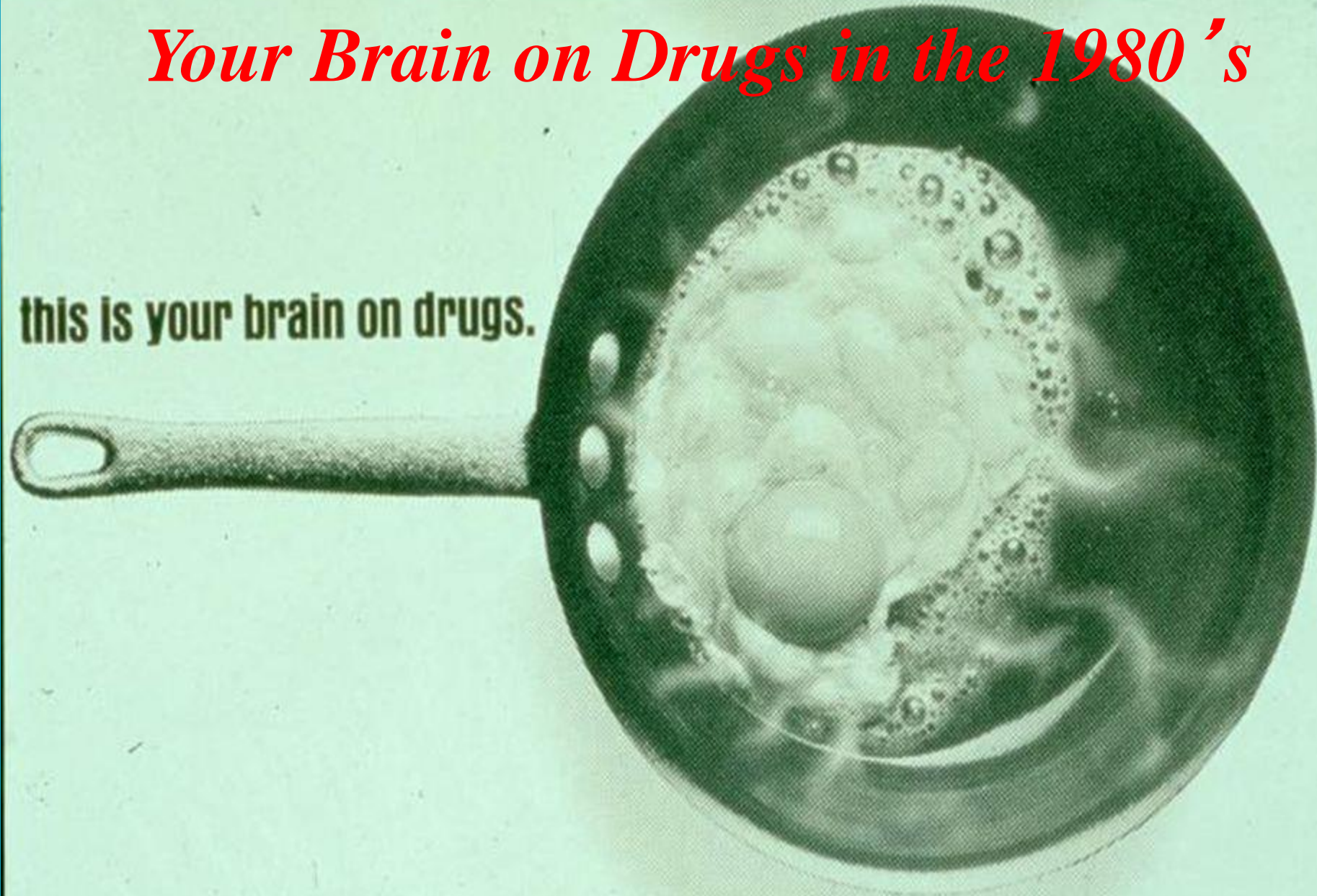
PSYCHIATRY ACADEMY

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



Your Brain on Drugs in the 1980's

this is your brain on drugs.





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



MASSACHUSETTS
GENERAL HOSPITAL

PSYCHIATRY ACADEMY

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

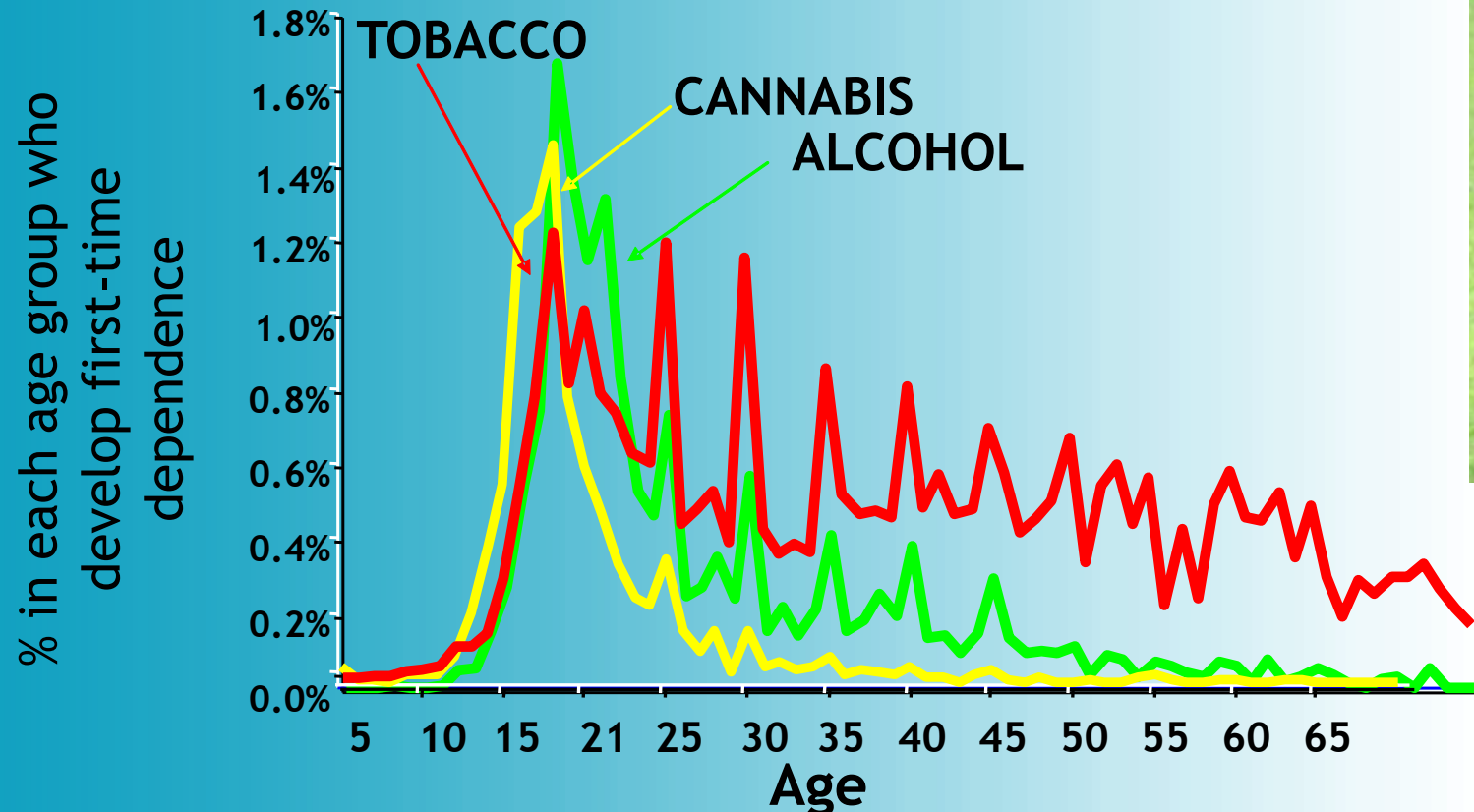




Individual Variability

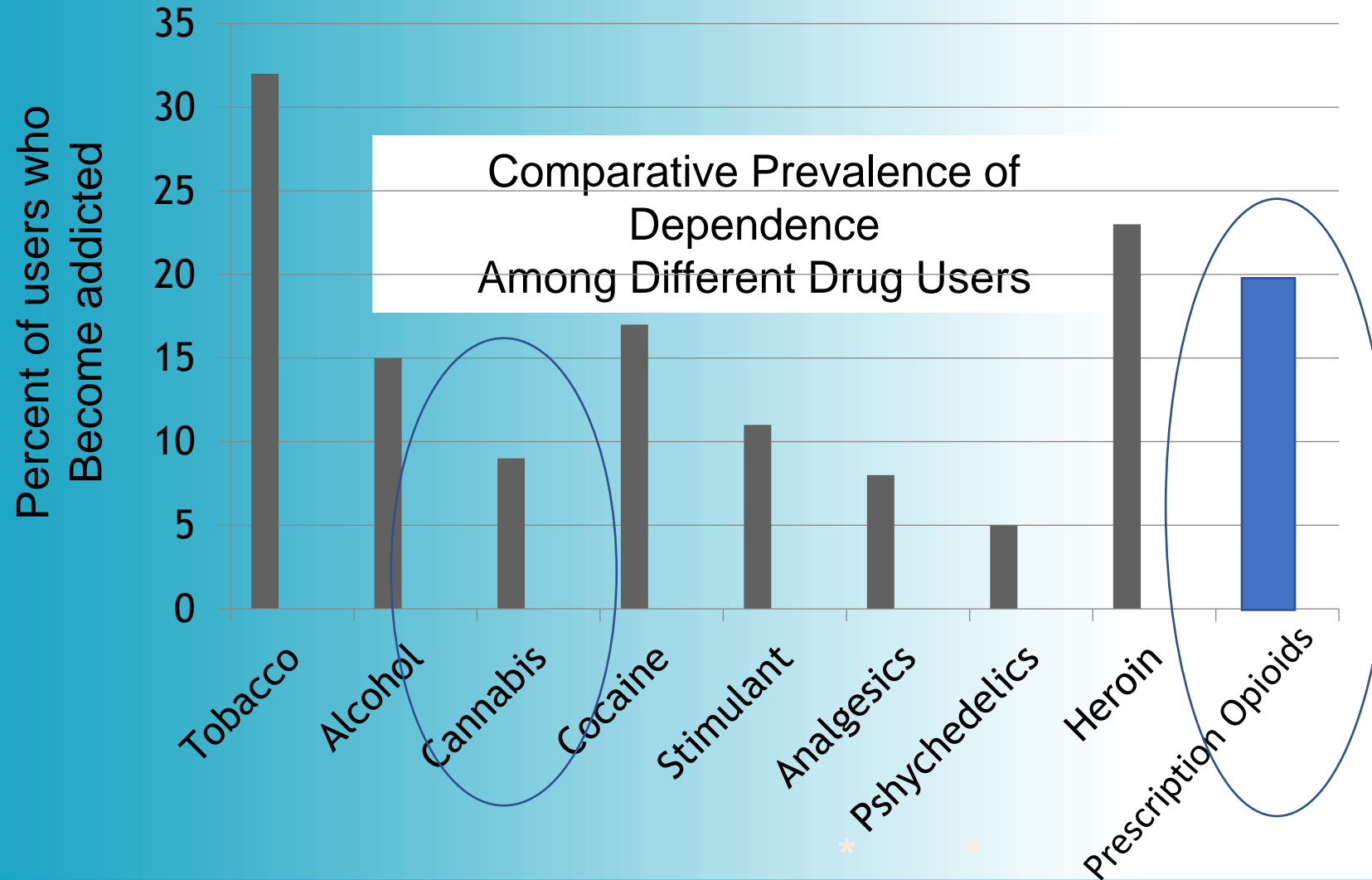
- Mood, anxiety, psychotic disorders are clear risk factors
- 40-60% of the risk for addiction attributed to genetic factors
- Trauma history
- Social determinants of health (poverty, racism, lack of opportunity)

Addiction is a Developmental Disease that starts in adolescence and childhood



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

Addictiveness by Drug Type



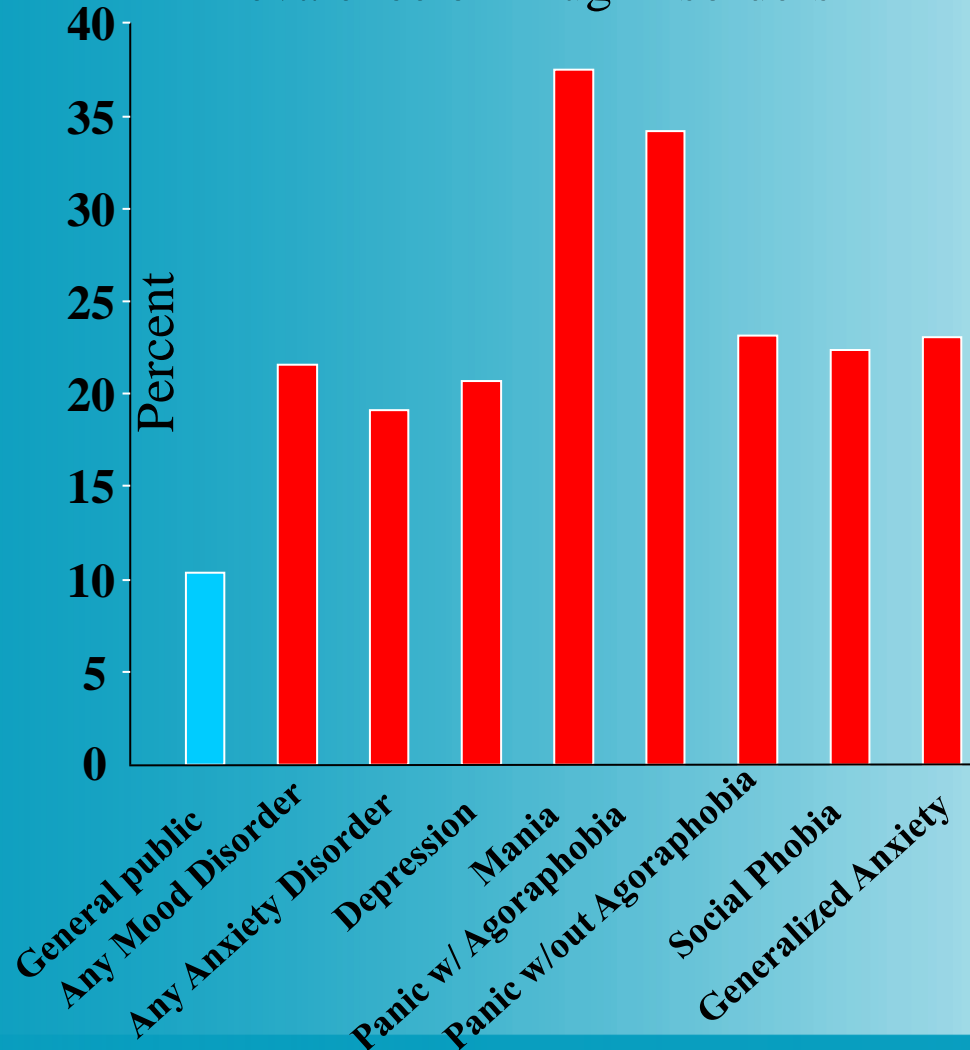
What Other Biological Factors Contribute to Addiction-- Comorbidity



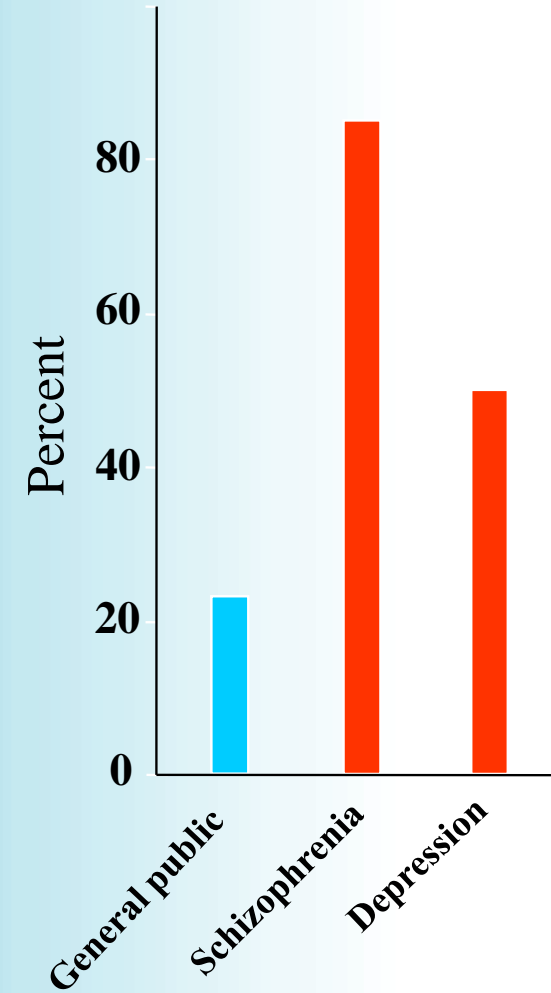
MASSACHUSETTS
GENERAL HOSPITAL

PSYCHIATRY ACADEMY

Prevalence of Drug Disorders

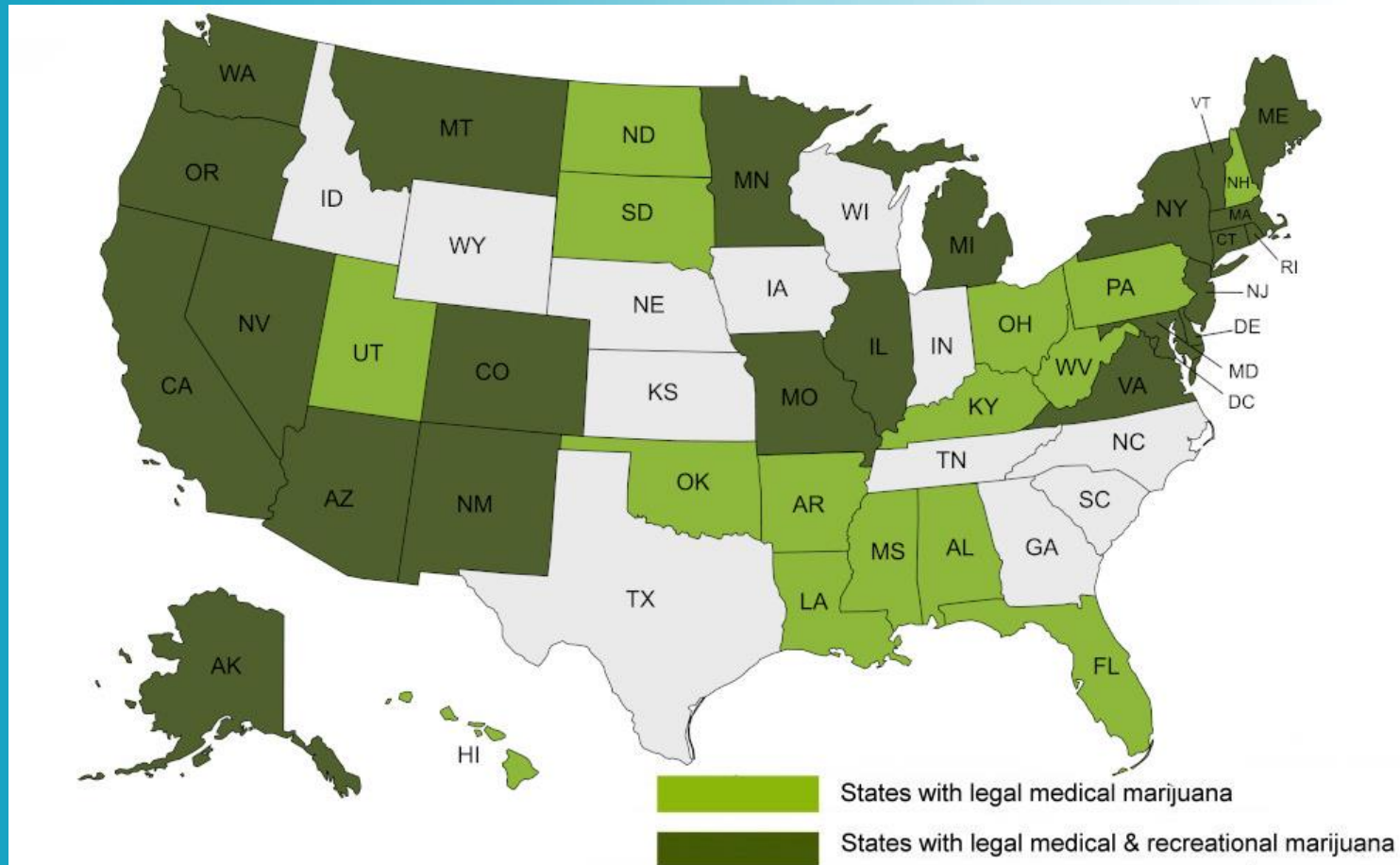


Prevalence of Nicotine Addiction





US STATES, MEDICAL AND RECREATIONAL MARIJUANA LAWS



**38 states as of
2023**



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



Cannabis today



MASSACHUSETTS
GENERAL HOSPITAL

PSYCHIATRY ACADEMY

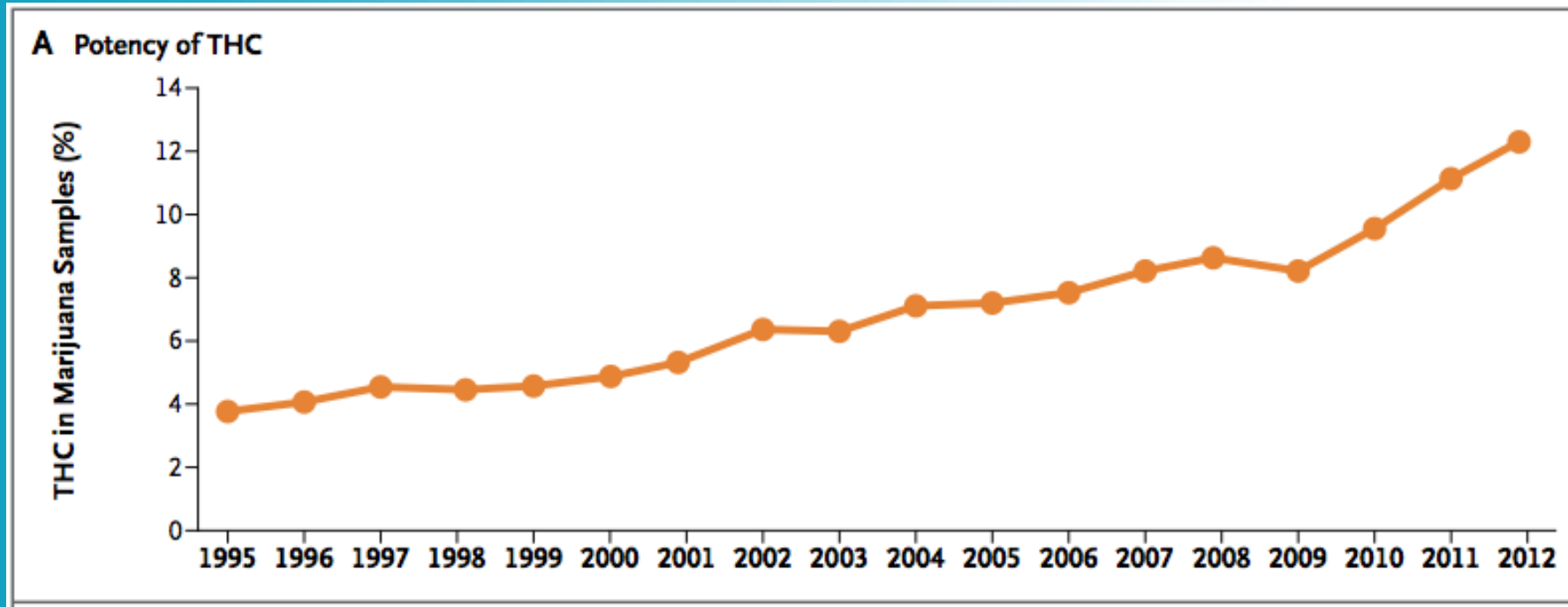
Marijuana is not “just a plant” anymore -
derivatives contain up to 98% THC





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

Cannabis Potency is Increasing



- Marijuana 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

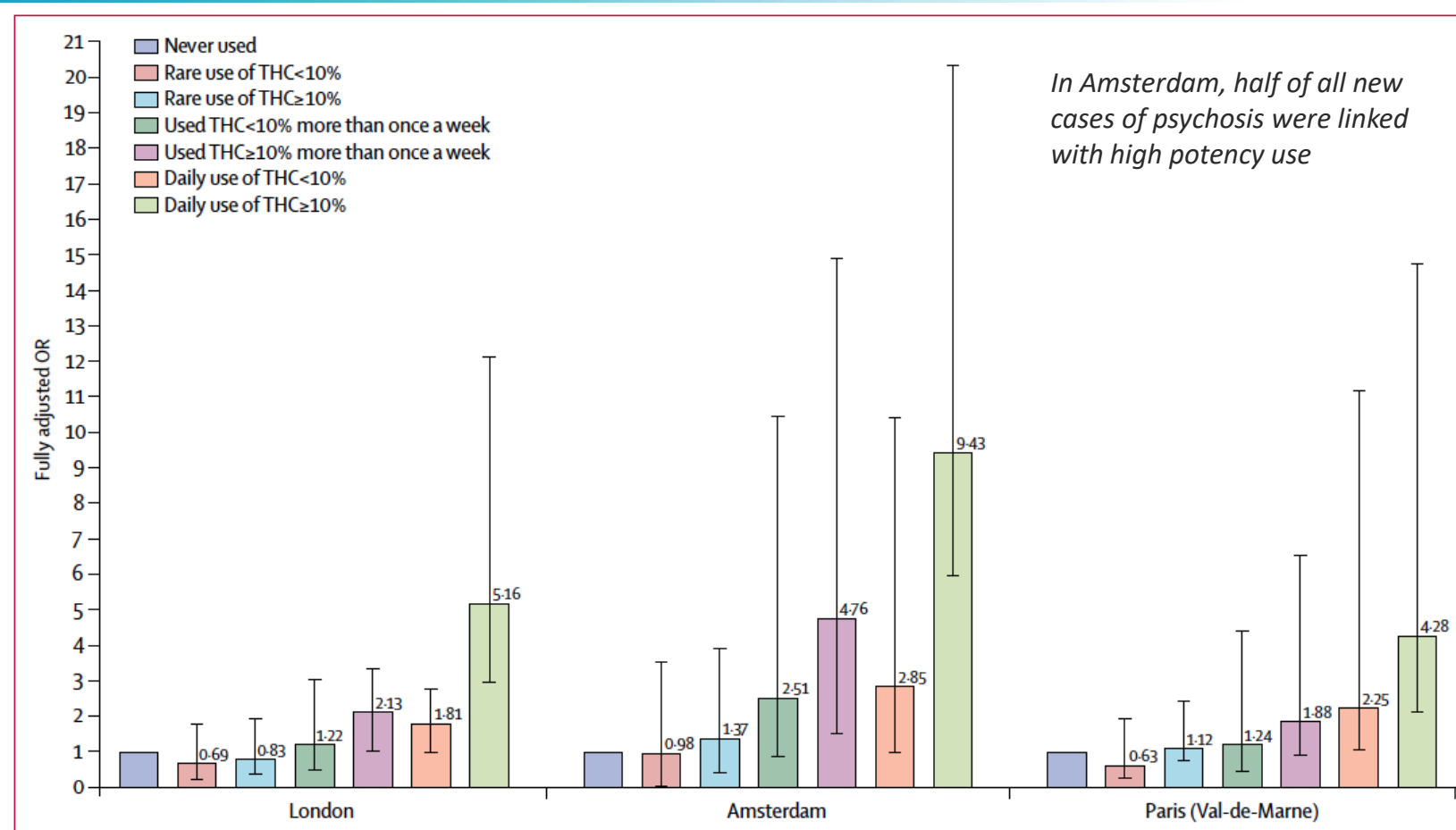


Figure 2: Fully adjusted ORs of psychotic disorders for the combined measure of frequency plus type of cannabis use in three sites
 Data are shown for the three sites with the greatest consumption of cannabis: London (201 cases, 230 controls), Amsterdam (96 cases, 101 controls), and Paris (54 cases, 100 controls). Error bars represent 95% CIs. OR=odds ratio.

The Opioid Epidemic



MASSACHUSETTS
GENERAL HOSPITAL

PSYCHIATRY ACADEMY

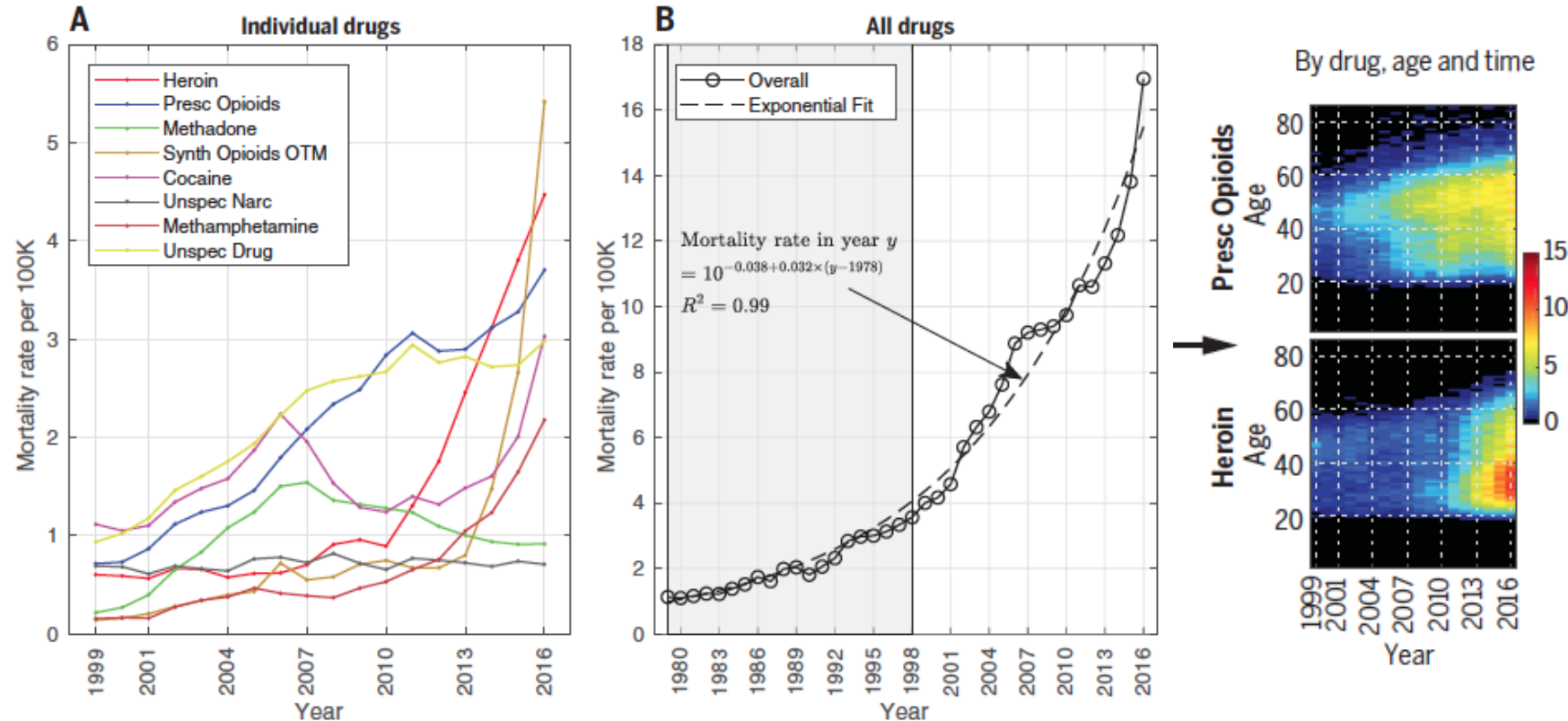


Fig. 1. Mortality rates from unintentional drug overdoses. (A and B) Mortality rates for (A) individual drugs and (B) all drugs. Detailed data for individual drugs are only available from 1999 to 2016, although additional data for all drugs are available since 1979 (this area is grayed out). The exponential equation and fit are shown for all drugs. (Synth Opioids OTM: synthetic opioids other than methadone. This category includes fentanyl and its analogs.)

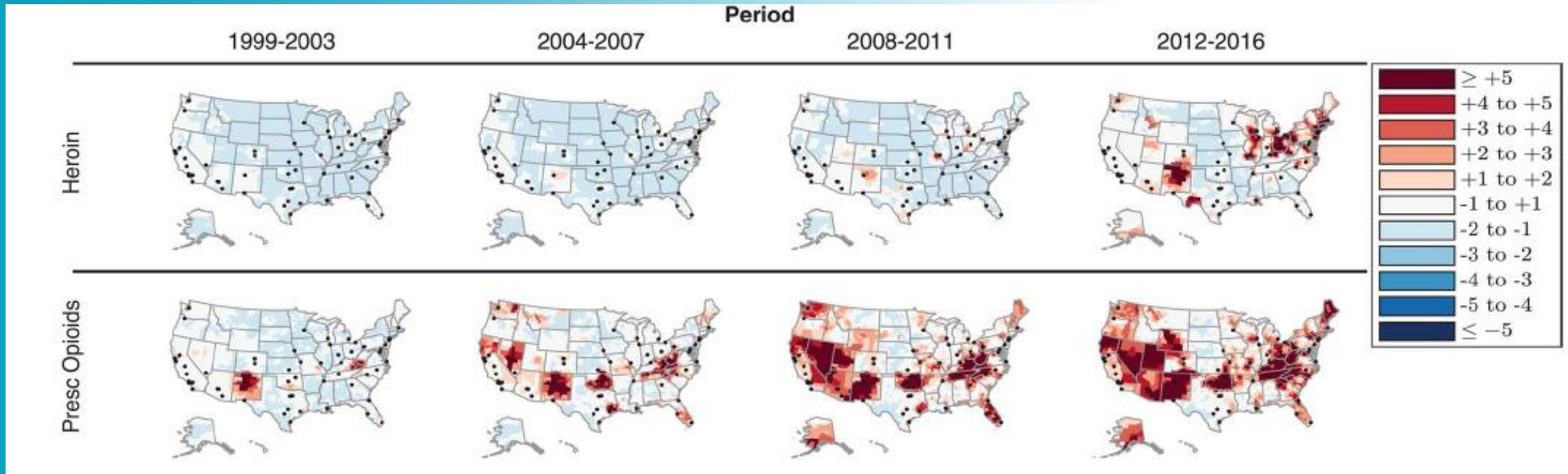
SOURCES: Jalal et al., *Science* 361, 2018

The Opioid Epidemic



MASSACHUSETTS
GENERAL HOSPITAL

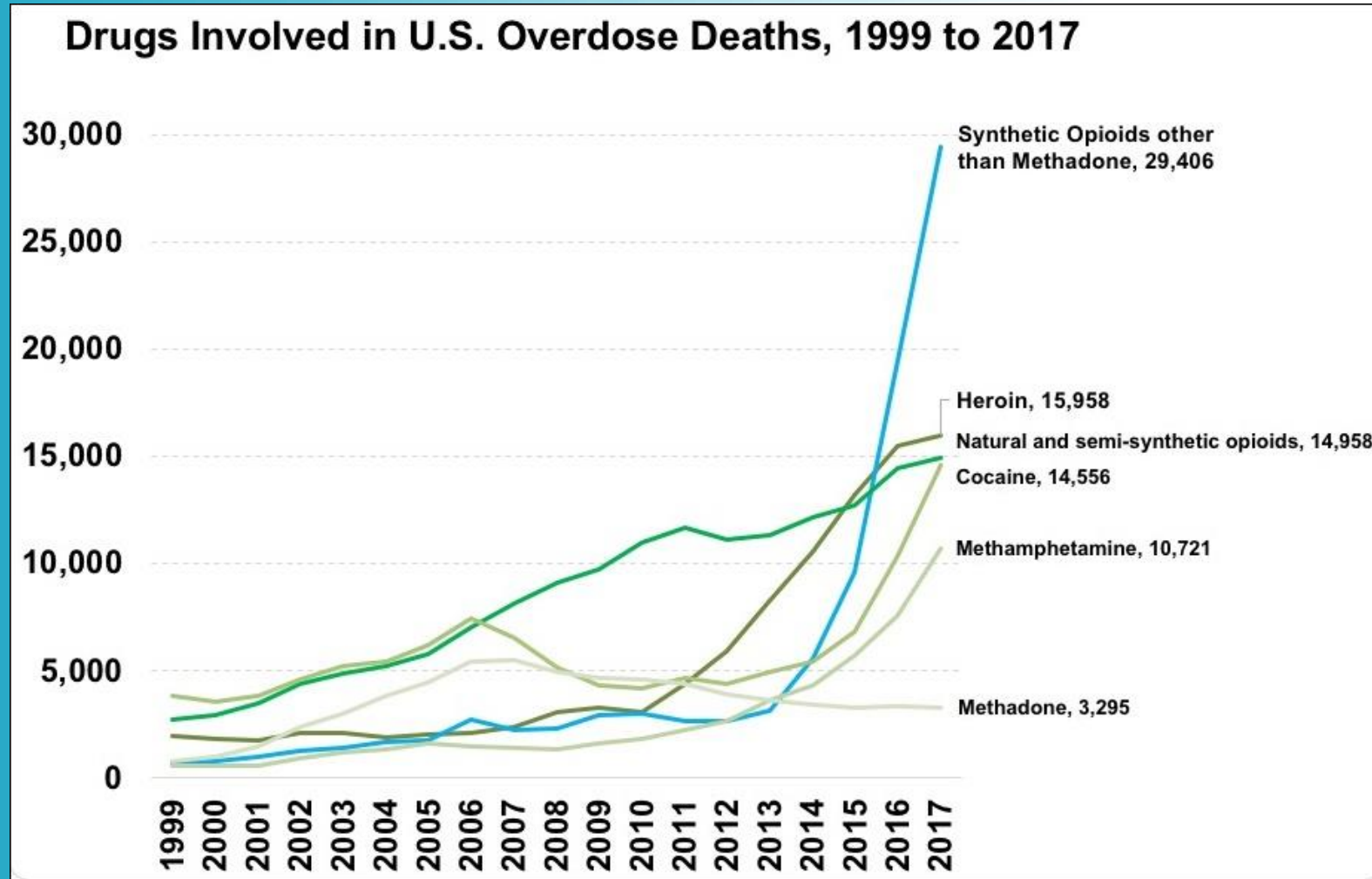
PSYCHIATRY ACADEMY



SOURCES: Jalal et al., Science 361, 2018

WWW.MGH.CME.ORG

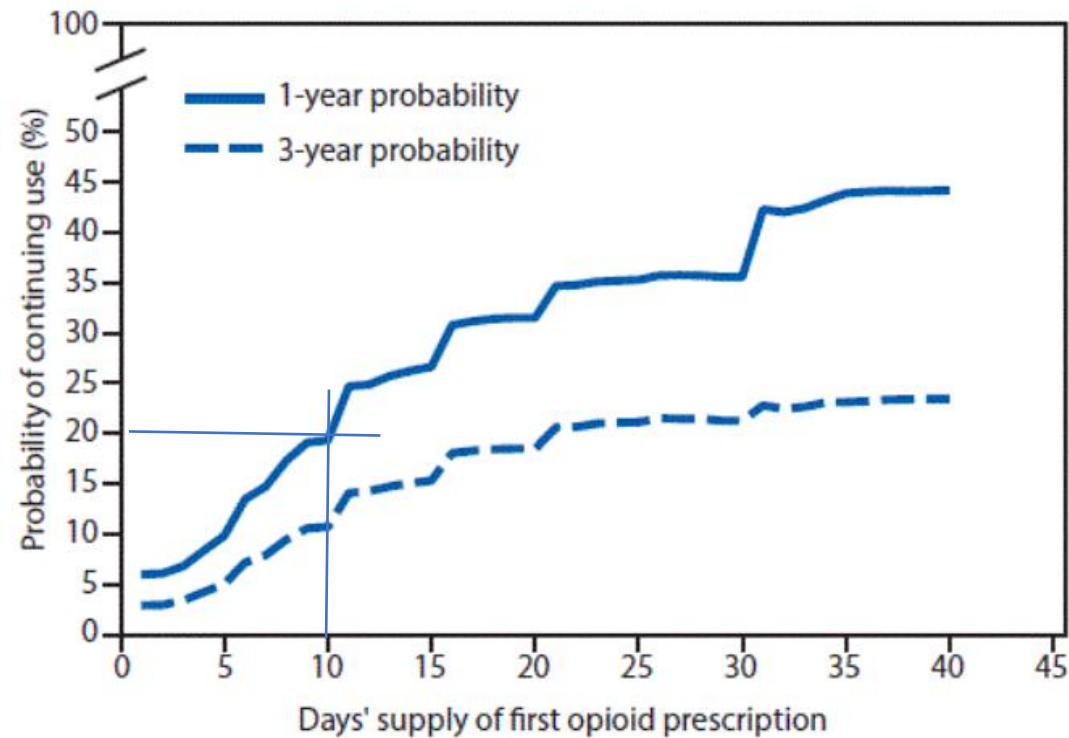
TYPES OF OPIOD OVERDOSES



WHAT ABOUT THOSE WITH 'LEGITIMATE' PRESCRIPTIONS?



FIGURE 1. One- and 3-year probabilities of continued opioid use among opioid-naïve patients, by number of days' supply* of the first opioid prescription – United States, 2006–2015



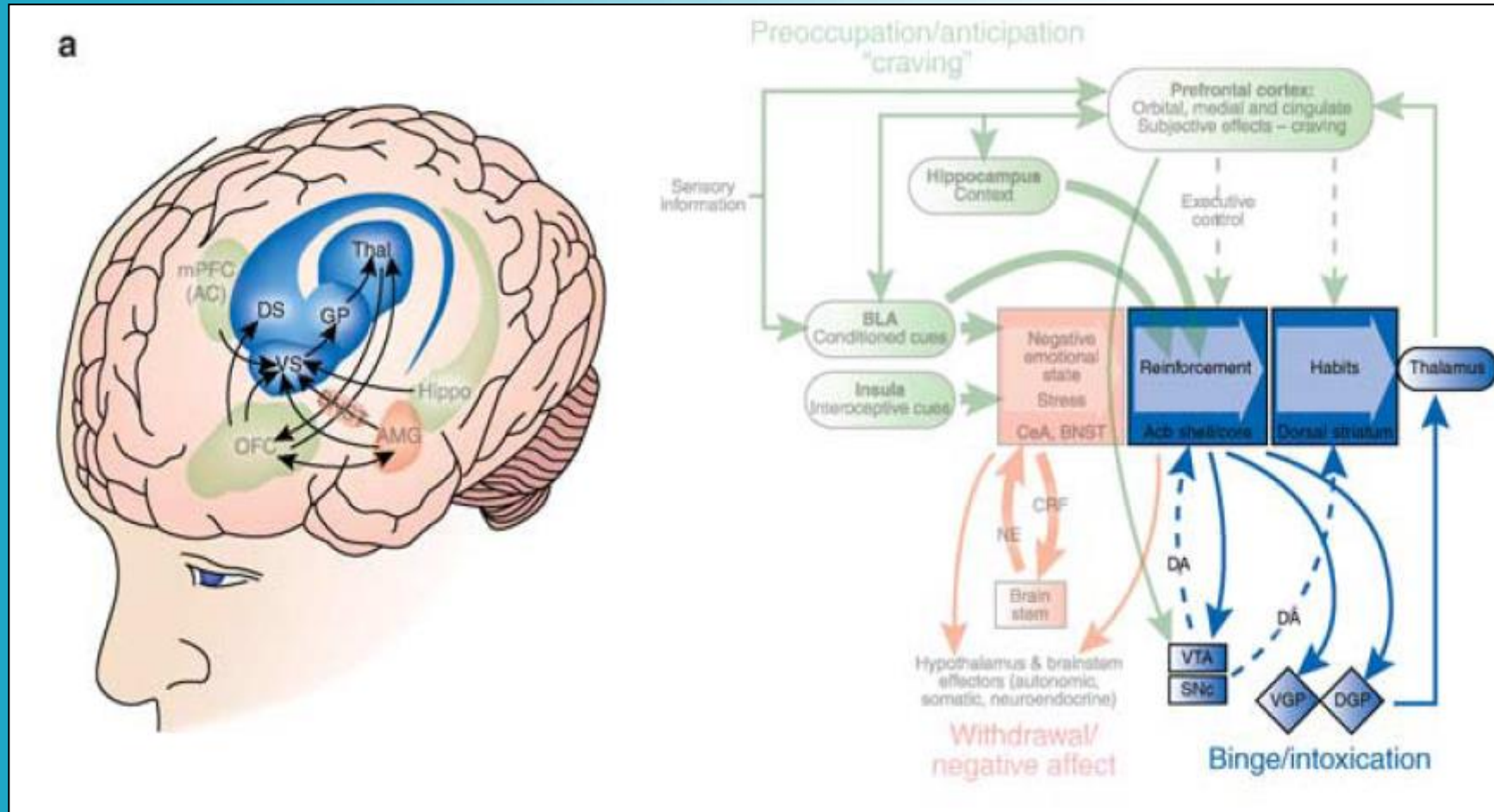
* Days' supply of the first prescription is expressed in days (1–40) in 1-day increments. If a patient had multiple prescriptions on the first day, the prescription with the longest days' supply was considered the first prescription.



Today's Talk

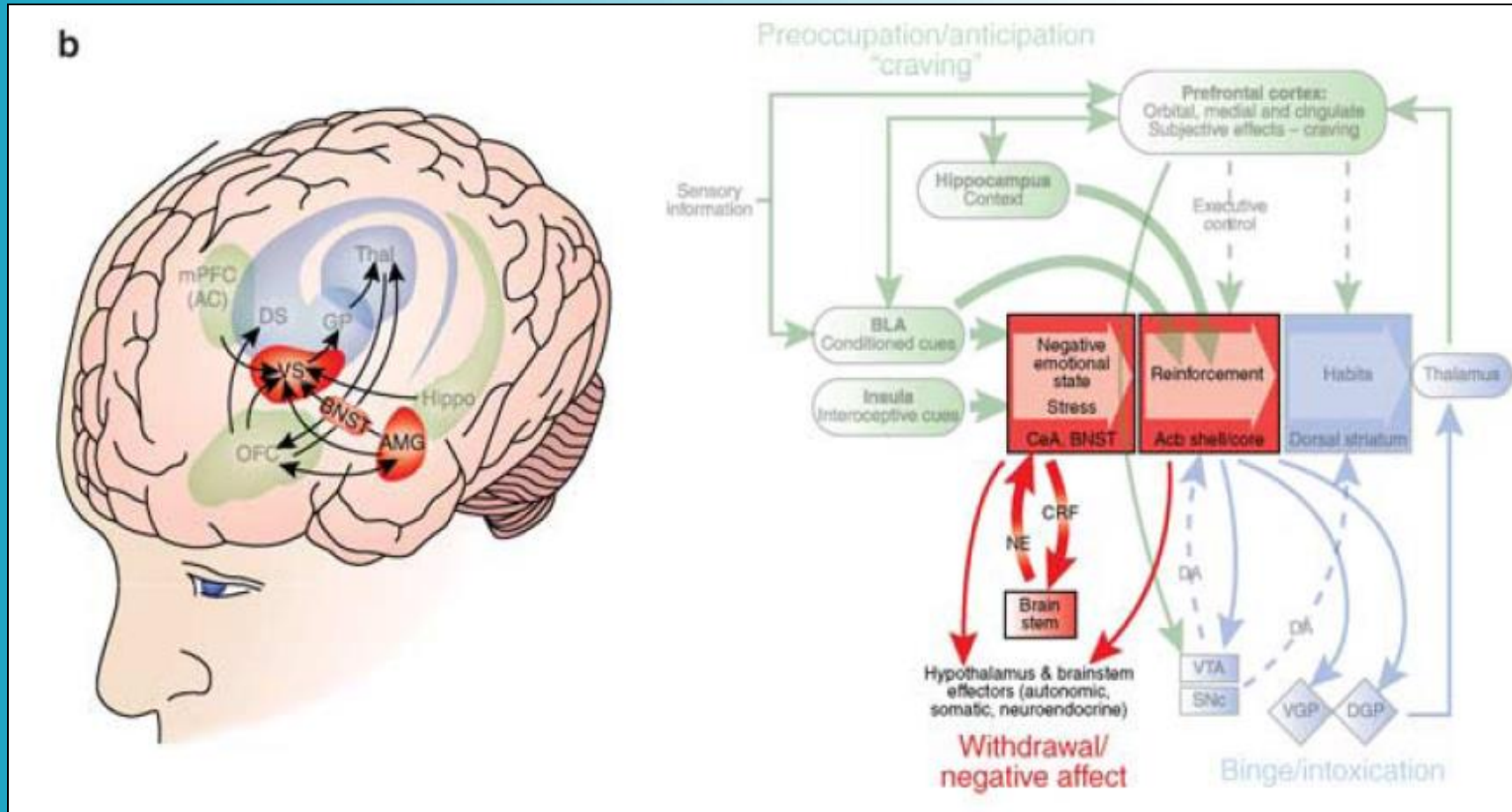
- Who gets Addicted?
- The Addiction Cycle
 - Role of Dopamine/Reward in Addiction
 - Role of Impaired Inhibition in Addiction
- Changes in the Brain that Occur
- Treatment and Recovery

The addiction cycle



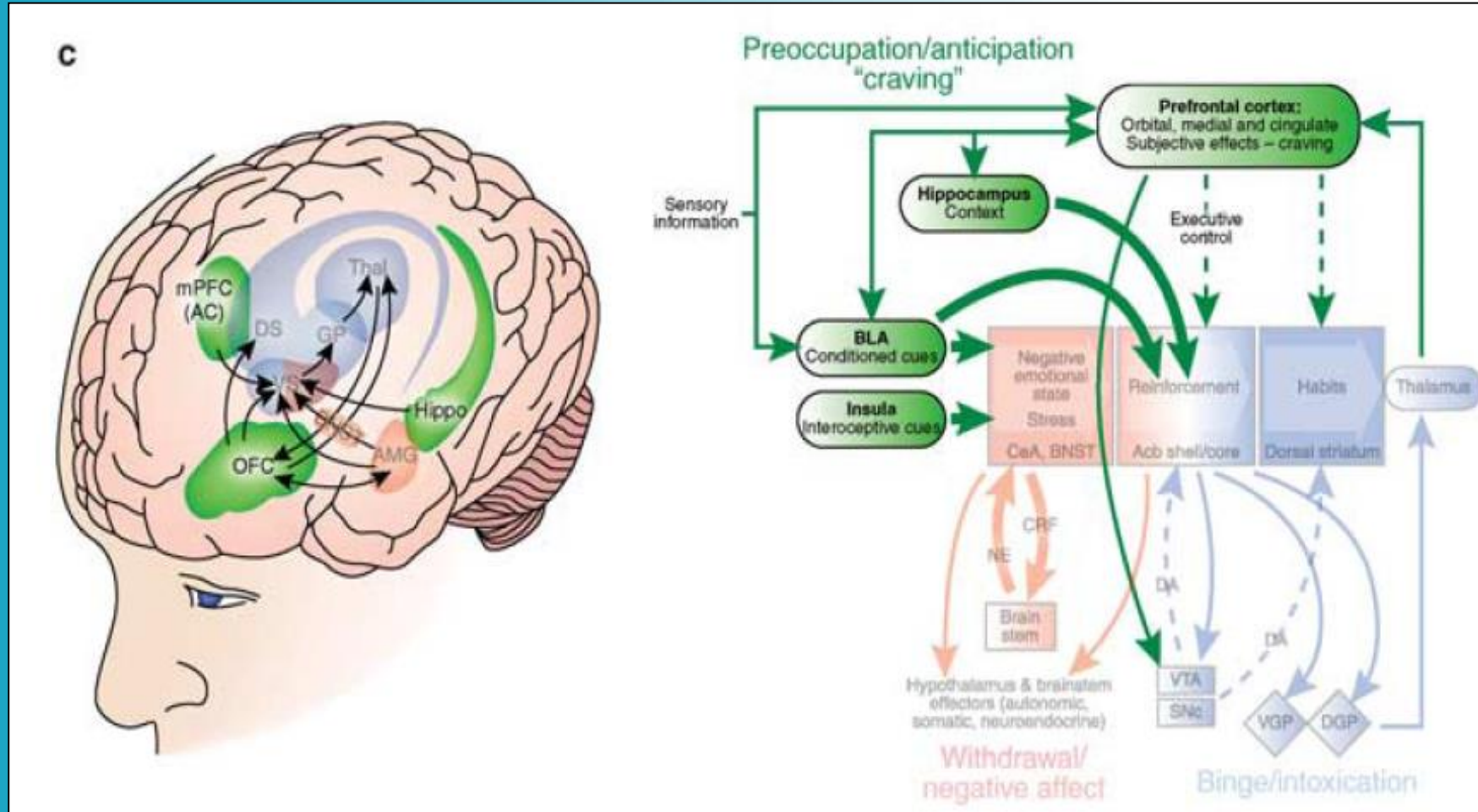
Koob and Volkow 2010

The addiction cycle



Koob and Volkow 2010

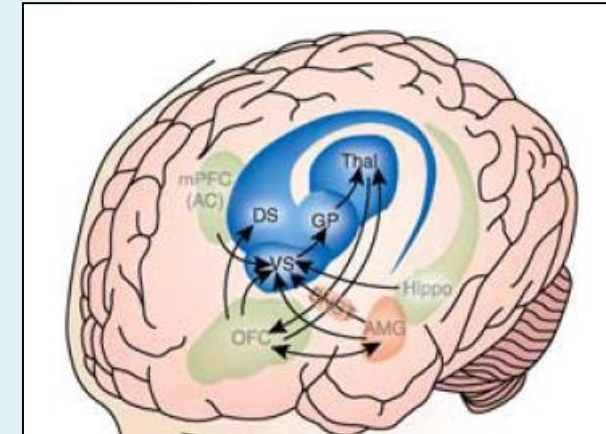
The addiction cycle



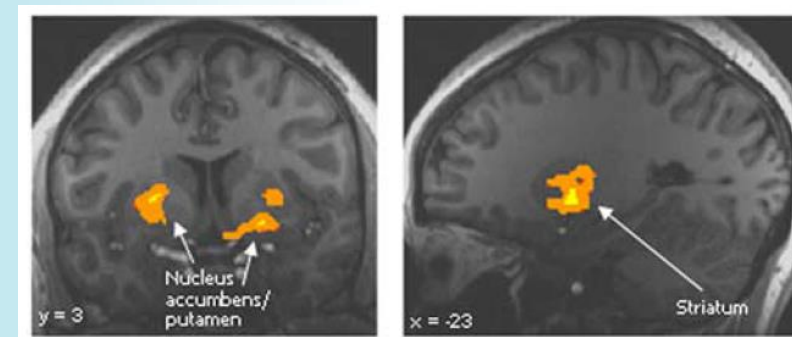
Koob and Volkow 2010

Reward, Dopamine, and the Nucleus Accumbens (NAc)

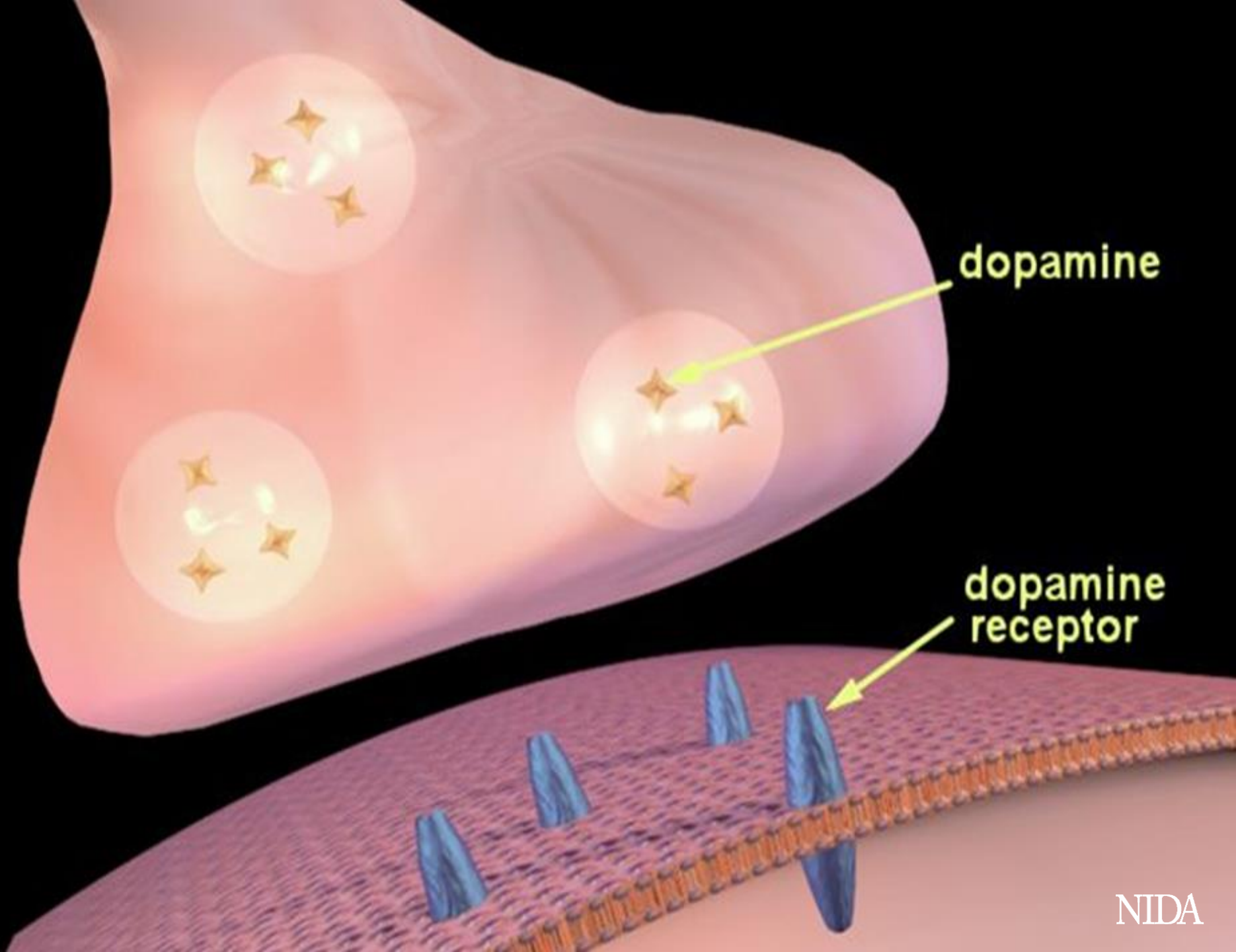
- Reward: stimulus that induces subjective feelings of pleasure.
- Rewarding stimuli activate the mesocorticolimbic reward circuit.
- All drugs of abuse share the ability to activate the this circuit.
 - increase extracellular dopamine (DA) levels in the NAc

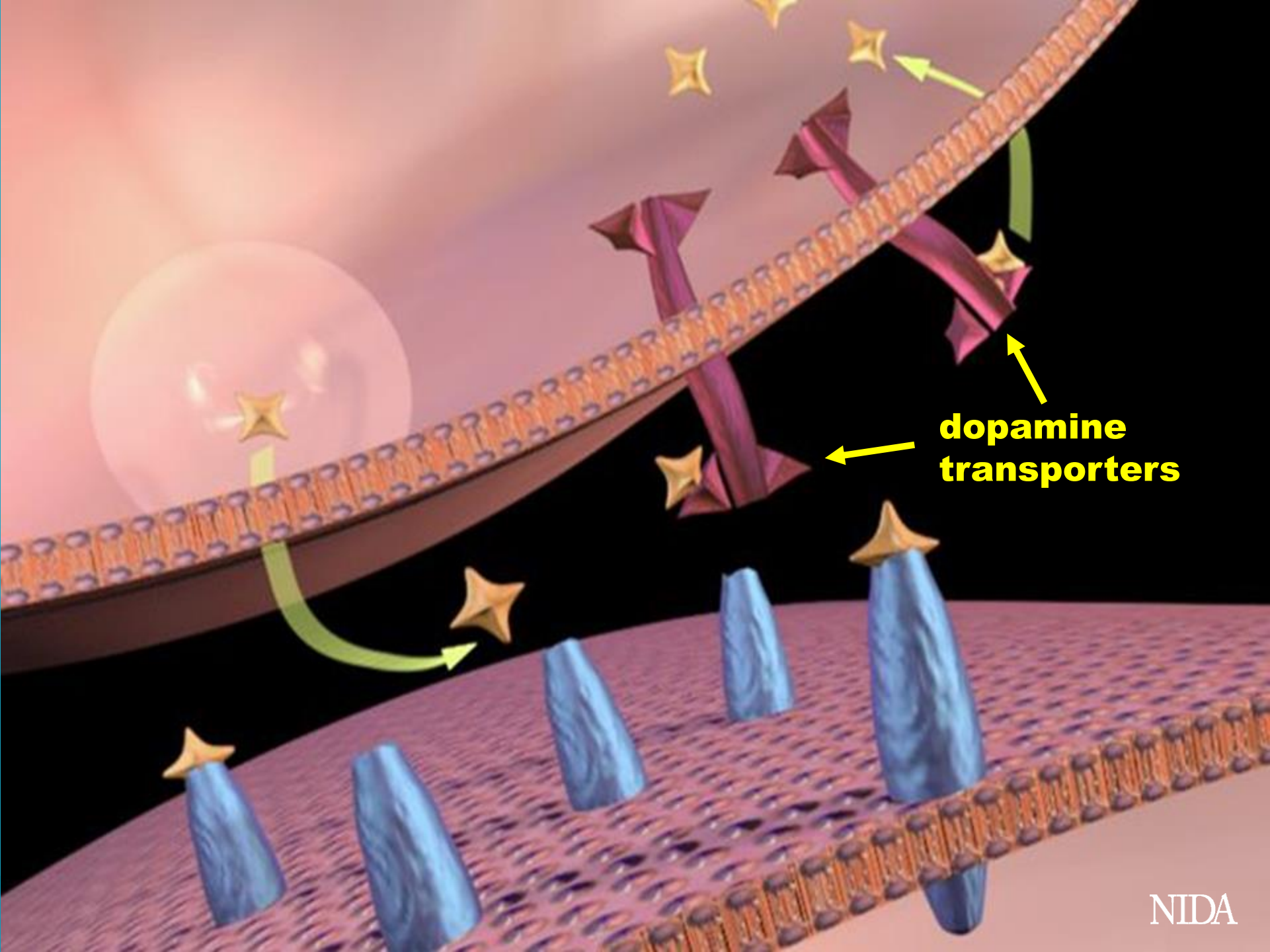


Alcohol:



Gilman et al. 2008





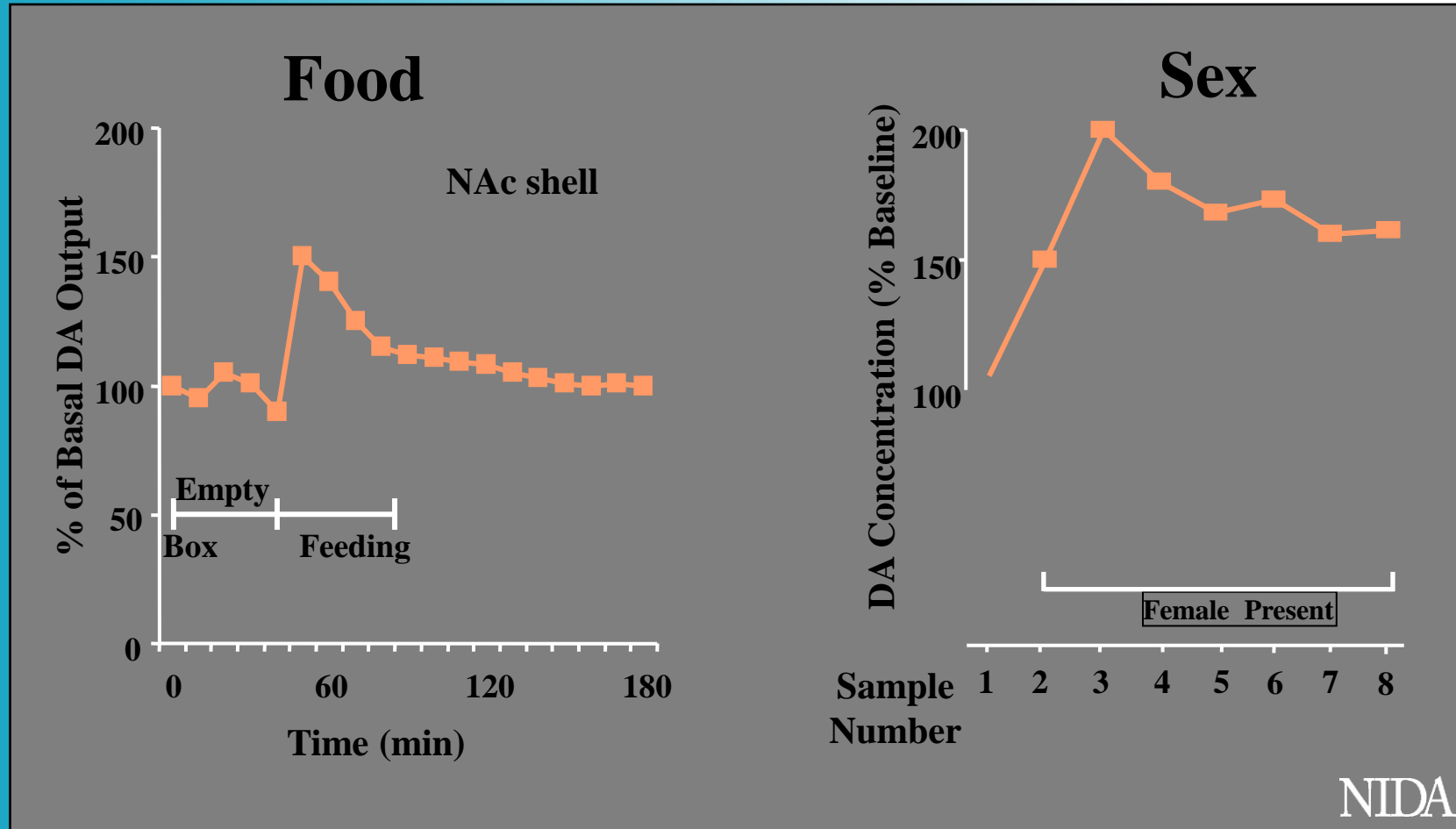
**dopamine
transporters**

Natural Rewards Elevate Dopamine Levels

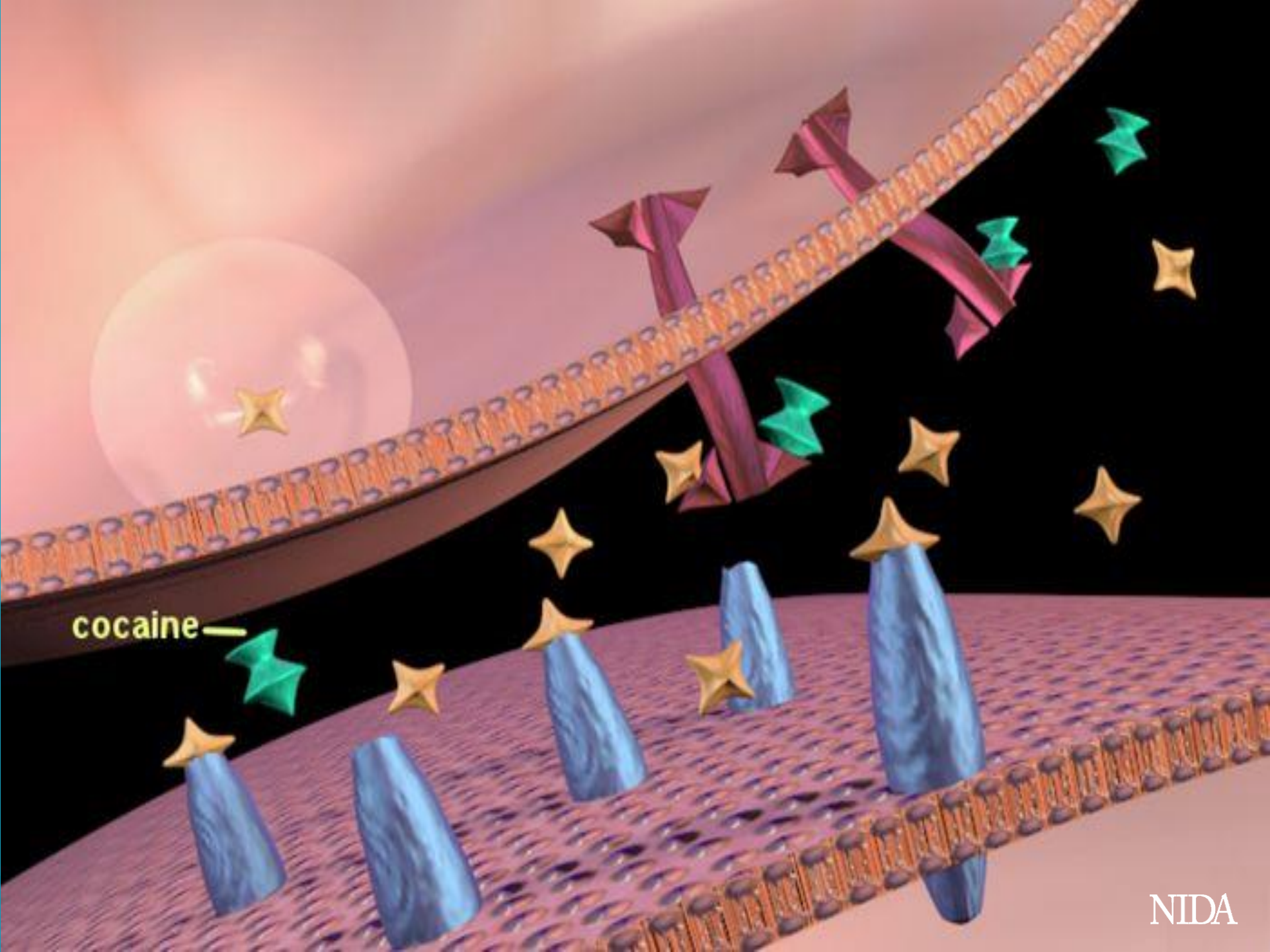


MASSACHUSETTS
GENERAL HOSPITAL

PSYCHIATRY ACADEMY



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



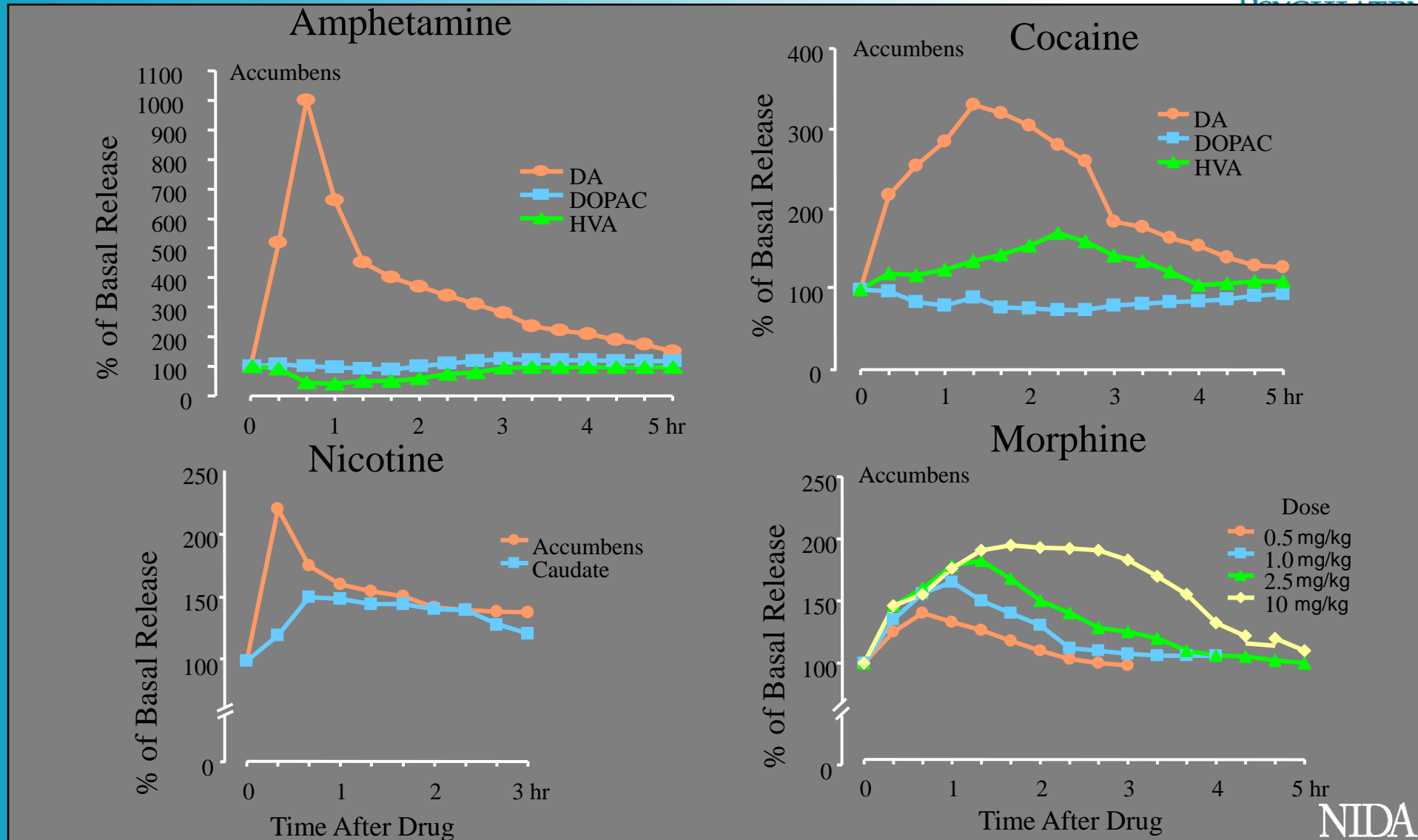
cocaine

Effects of Drugs on Dopamine Release



MASSACHUSETTS
GENERAL HOSPITAL

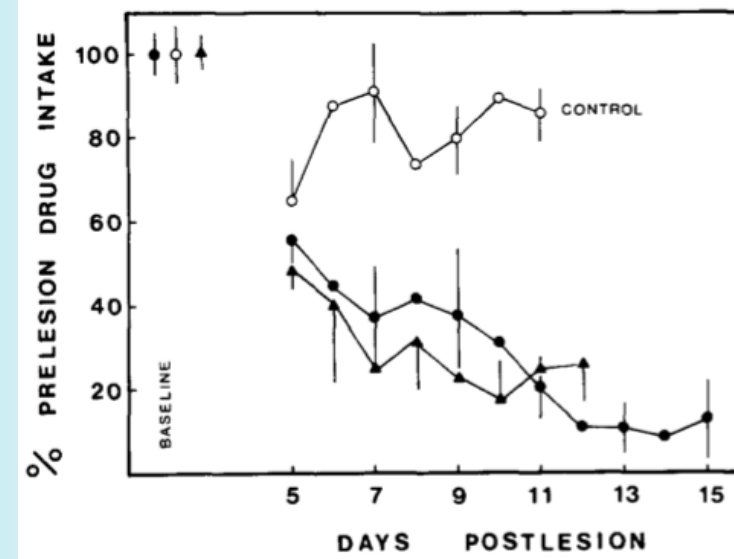
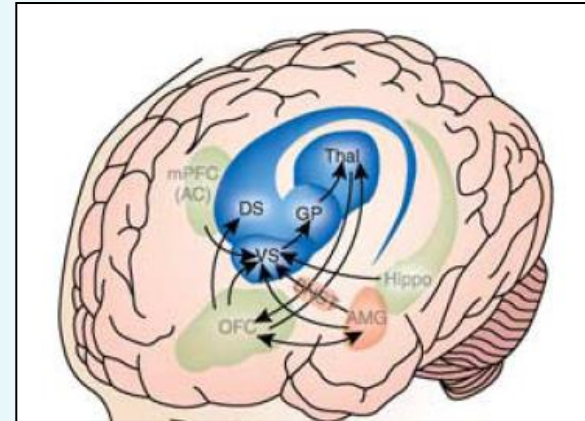
RECOVERY ACADEMY



Reward



- enhanced dopamine in the NA is responsible for **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

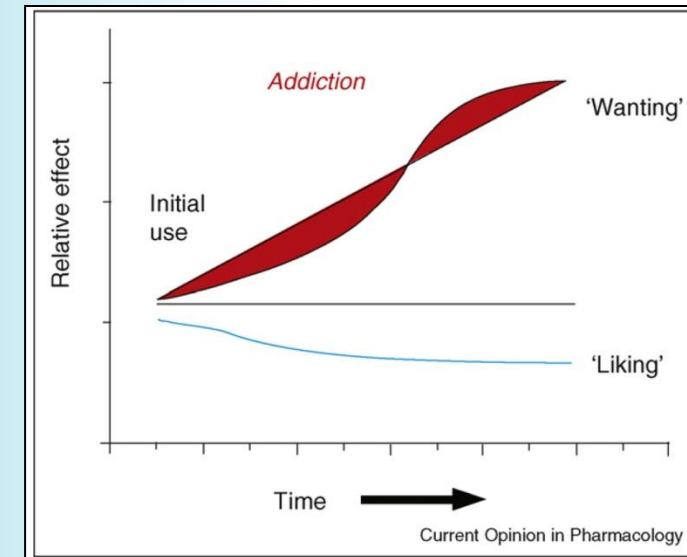
Is this Responsible for Addiction?



MASSACHUSETTS
GENERAL HOSPITAL

PSYCHIATRY ACADEMY

- 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)

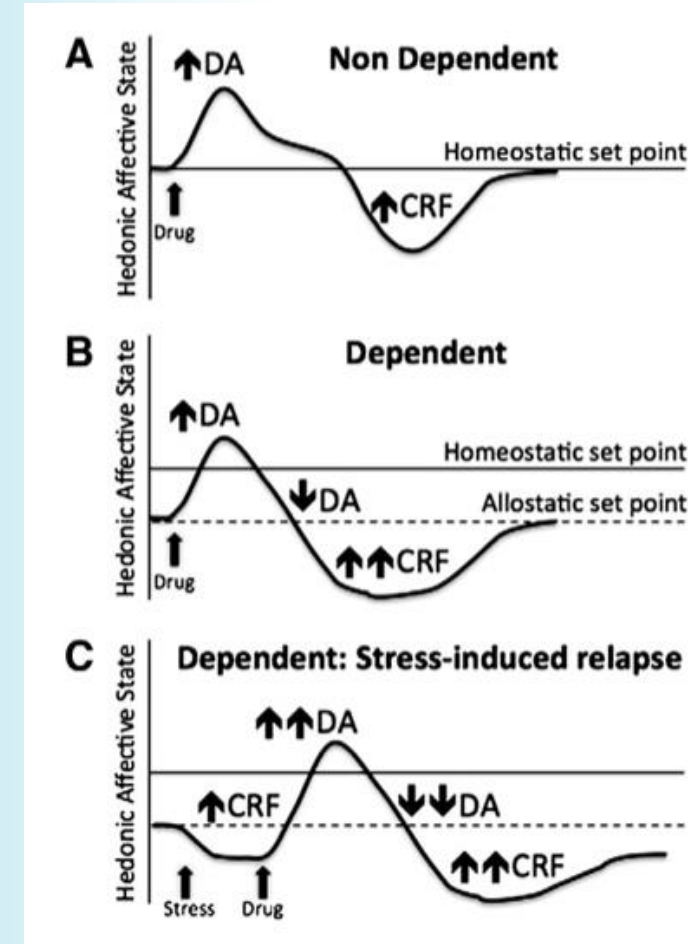
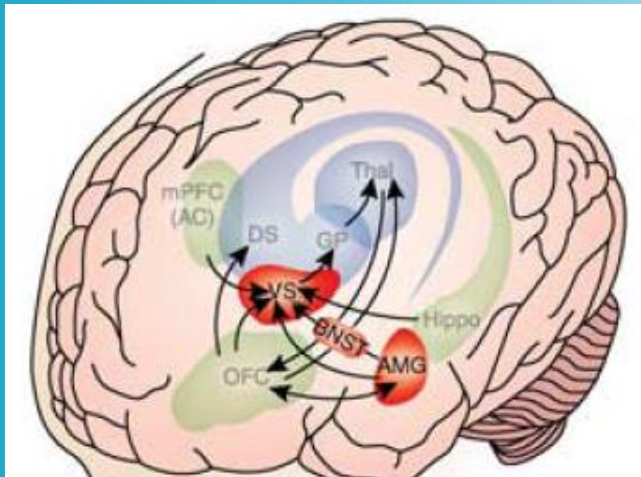


(Berridge et al., 2009)

The Switch from Reward to Negative Reinforcement/Withdrawal



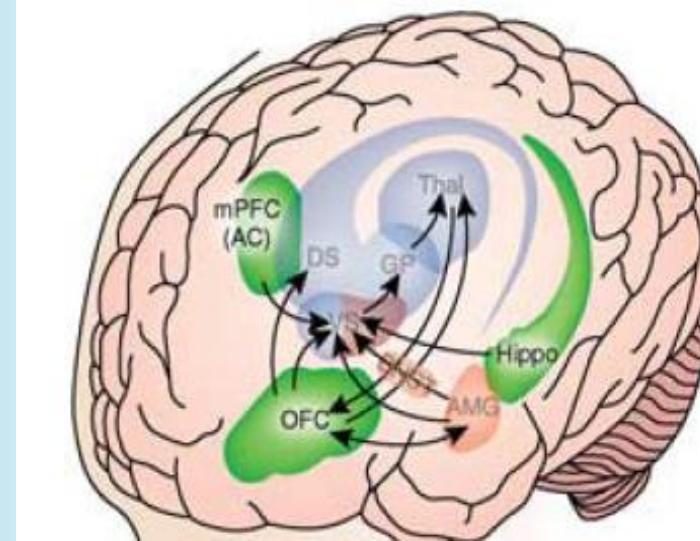
- enhanced dopamine in the NA is responsible for acute high or initial reinforcing effects (i.e., positive reinforcement) of drugs of abuse.
- All major drugs of abuse activate the brain stress systems
 - Elevated corticotrophin releasing factor (CRF) in the amygdala



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): role in inhibitory control of behaviors



Abnormal Activity in Two Brain Systems:

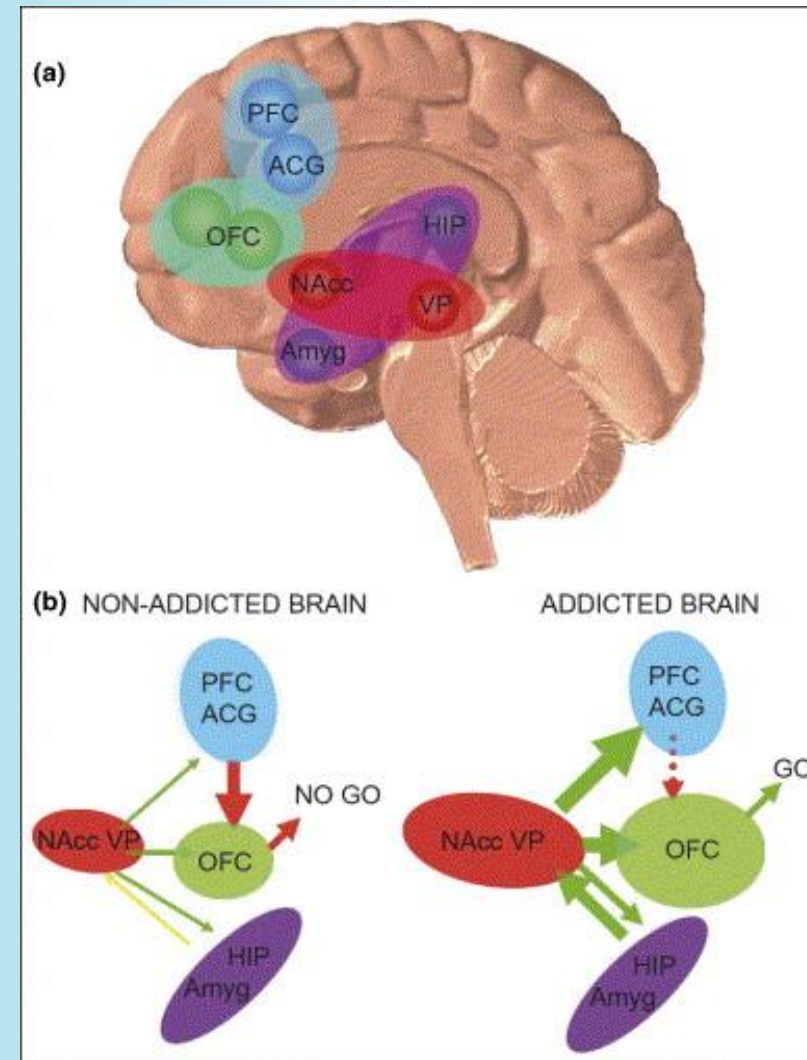


1) **Reward** (drive to meet goals)
- Strong urge to use drugs over natural rewards, associated with impulsivity

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?



MASSACHUSETTS
GENERAL HOSPITAL

PSYCHIATRY ACADEMY

- 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



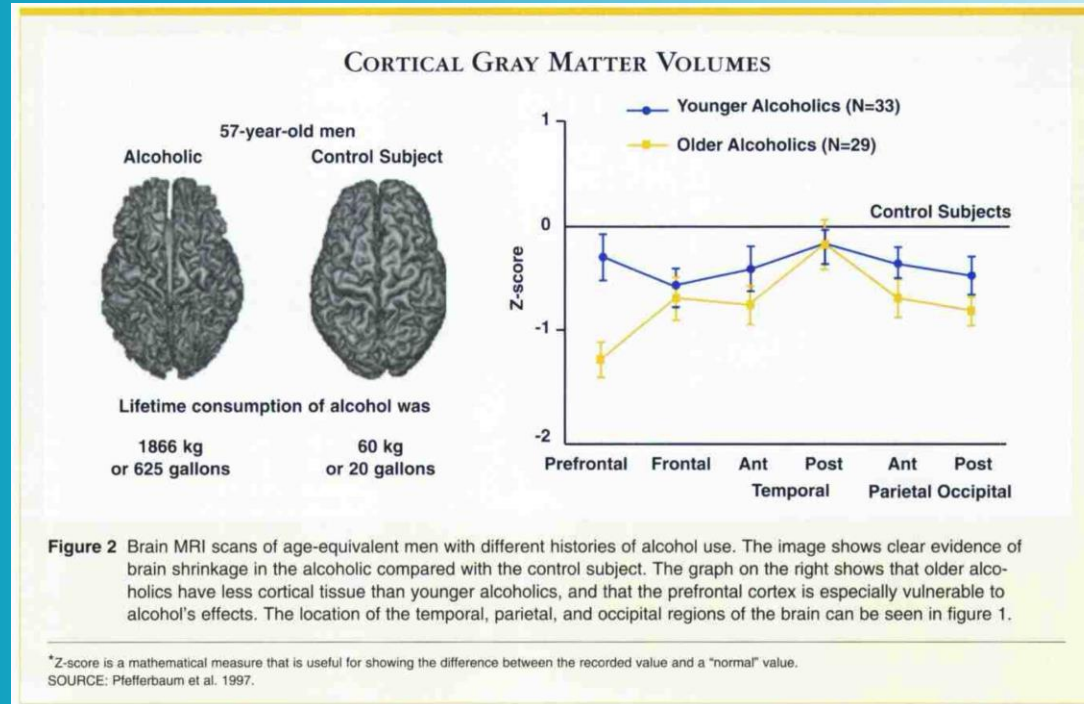
MASSACHUSETTS
GENERAL HOSPITAL

PSYCHIATRY ACADEMY

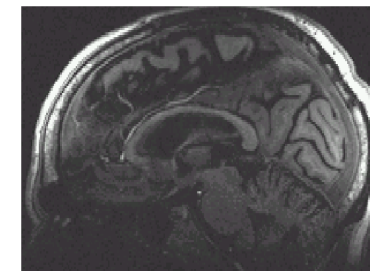
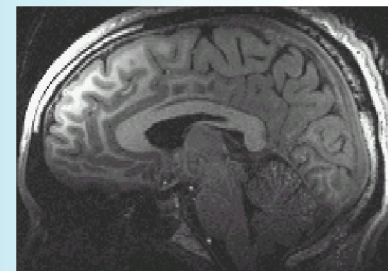
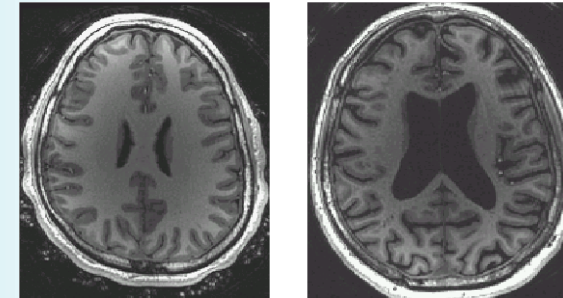
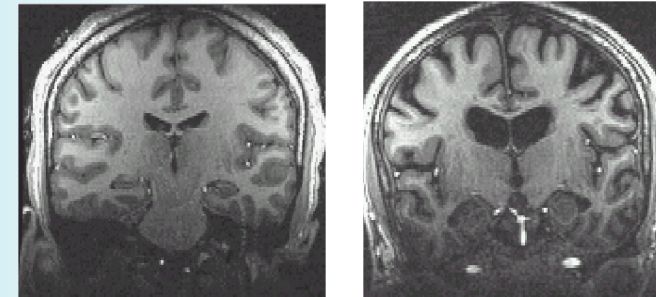
Prolonged Drug Use Changes the Brain In Fundamental and Long-Lasting Ways

NIDA

Structural Effects of Addiction



Pfefferbaum et al. 1997

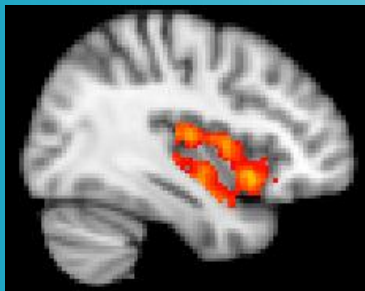


Control brain

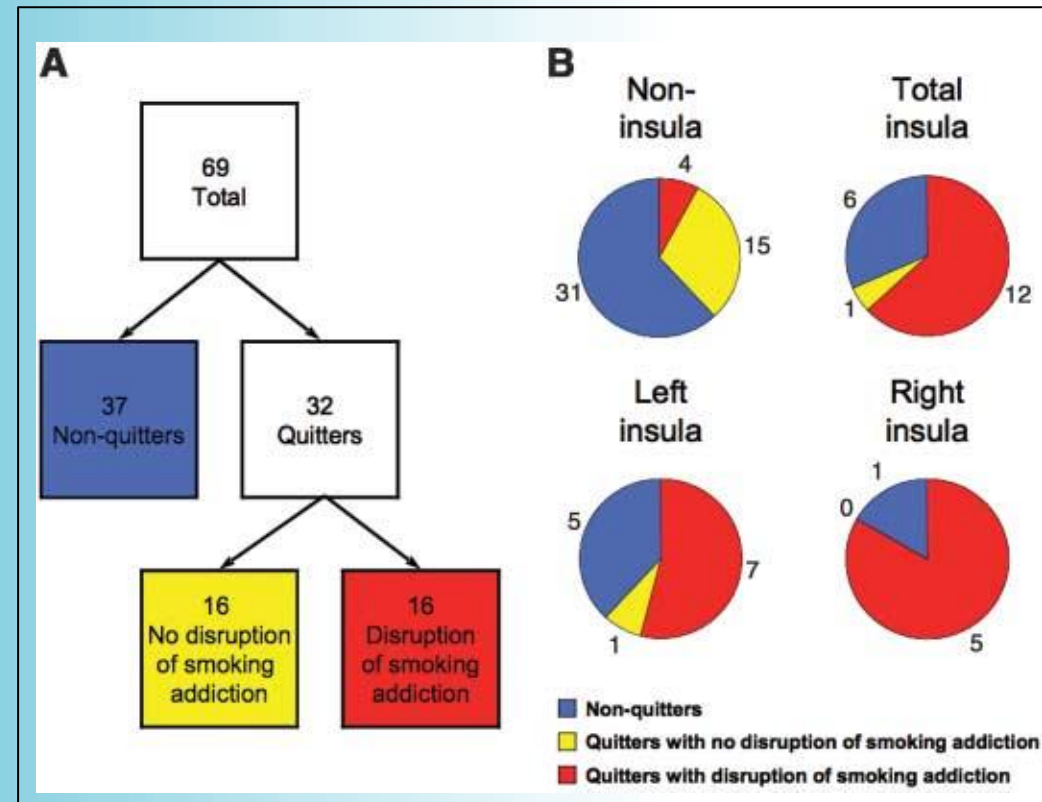
Alcoholic brain

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

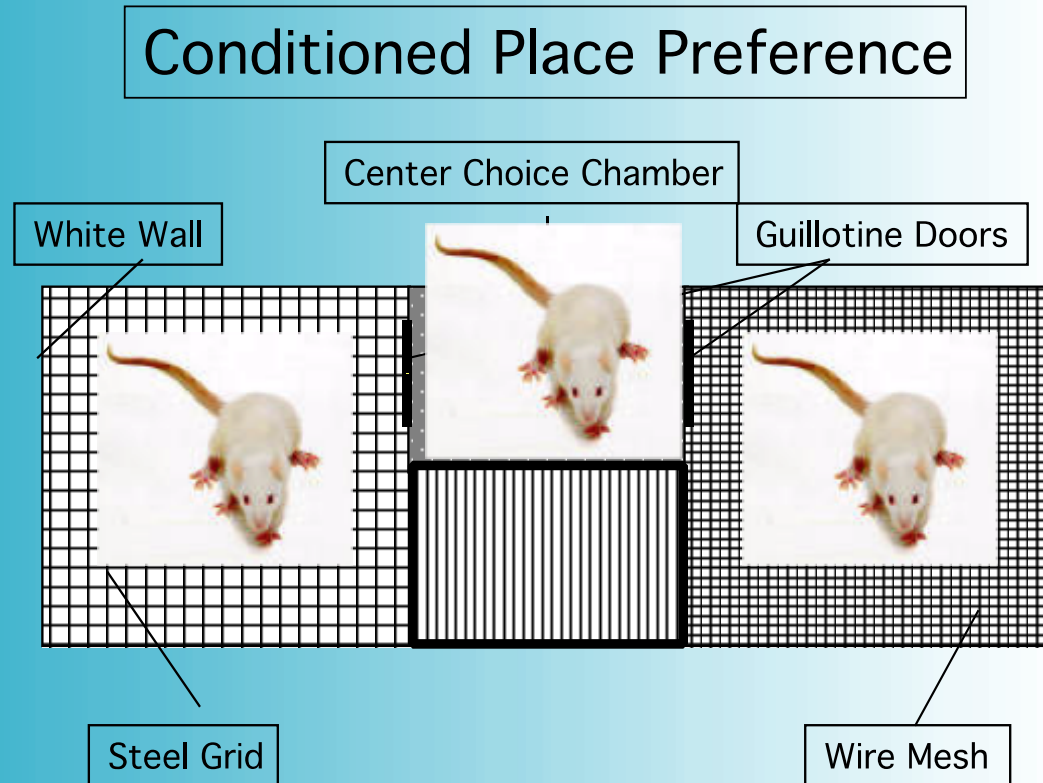
Overview of consequences of repeated adolescent exposure to ethanol (EtOH), nicotine (NIC), cannabinoids (CBs) and MDMA and methamphetamine stimulants (STIM).

General Age Vulnerability	EtOH Adol > Adult	NIC Adol > Adult	CB Adol > Adult	COC ?	STIM Adol < Adult
Cognitive/behav.					
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	↑				
Affective/Social behavior					
Depression-like behaviors	↑		↑		
Social interactions	↓		↓	=	↓
Social anxiety-like behaviors	↑		↑		↑
Other anxiety-like behaviors	↑, ↓	↑	↑, ↓, =	=	↑, ↓
Later self-admint. (same/different drugs)	↑, =	↑, =	↑, =		
Neural					
Neurogenesis	↓				
Cell death	↑	↑			↑
Spines/dendritic branching	↑ "immature spines"	↑			
Electrophysiol. Alterations	Y			Y	
Neuroimmune activation	Y				
Histone acetylation/epigenetic regulat.	Y			Y	
Alterations in:					
Ach	Y	Y			Y
Glutamate/GABA	Y	Y	Y	Y	Y
DA	Y	Y	Y	Y	Y
5HT		Y	Y		Y
CB			Y		
Affected brain regions:					
PFC	Y	Y	Y	Y	Y
HPC	Y	Y	Y	Y	Y
nAc	Y	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 alterations 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

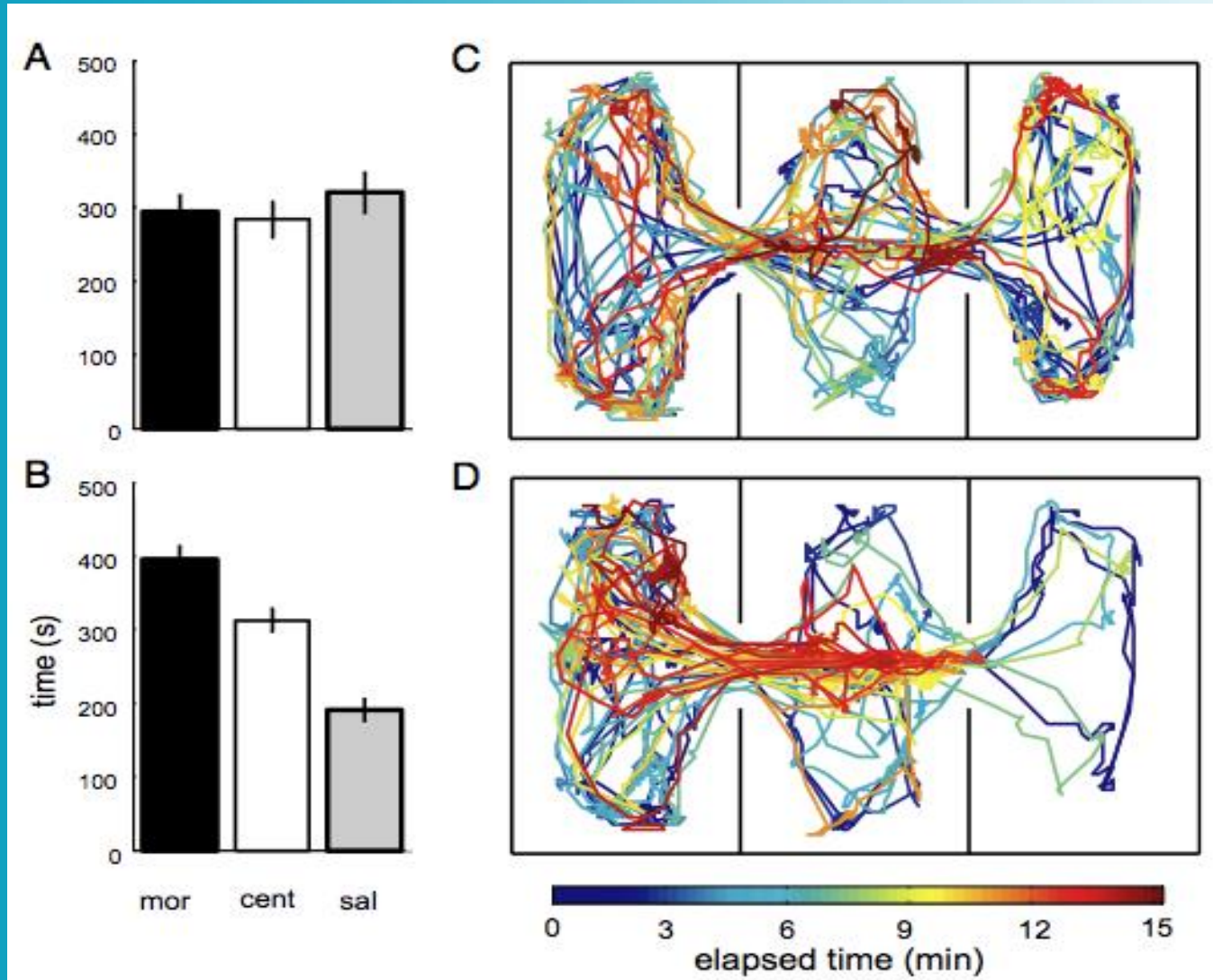


Morphine-induced Conditioned Place Preference



MASSACHUSETTS
GENERAL HOSPITAL

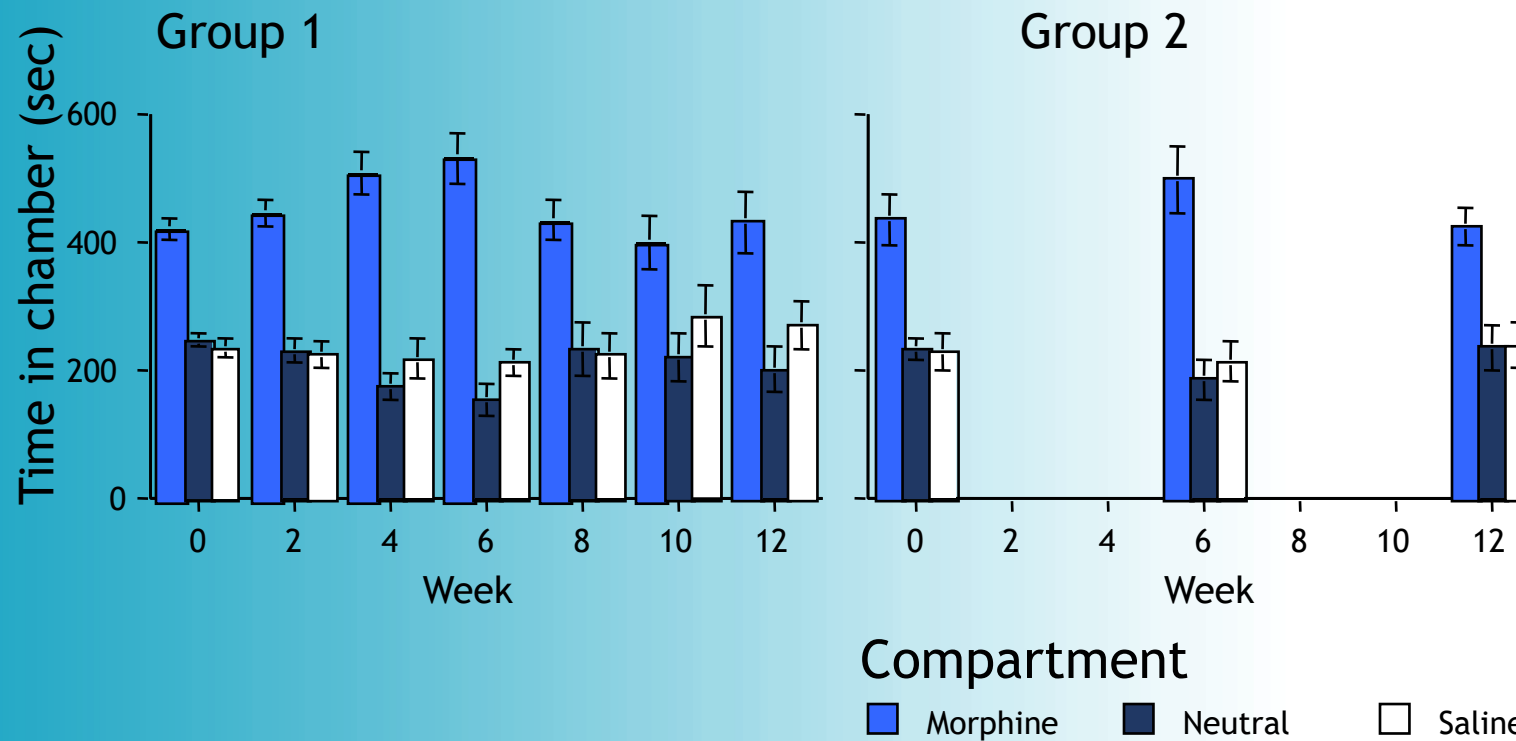
PSYCHIATRY ACADEMY



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??



MASSACHUSETTS
GENERAL HOSPITAL

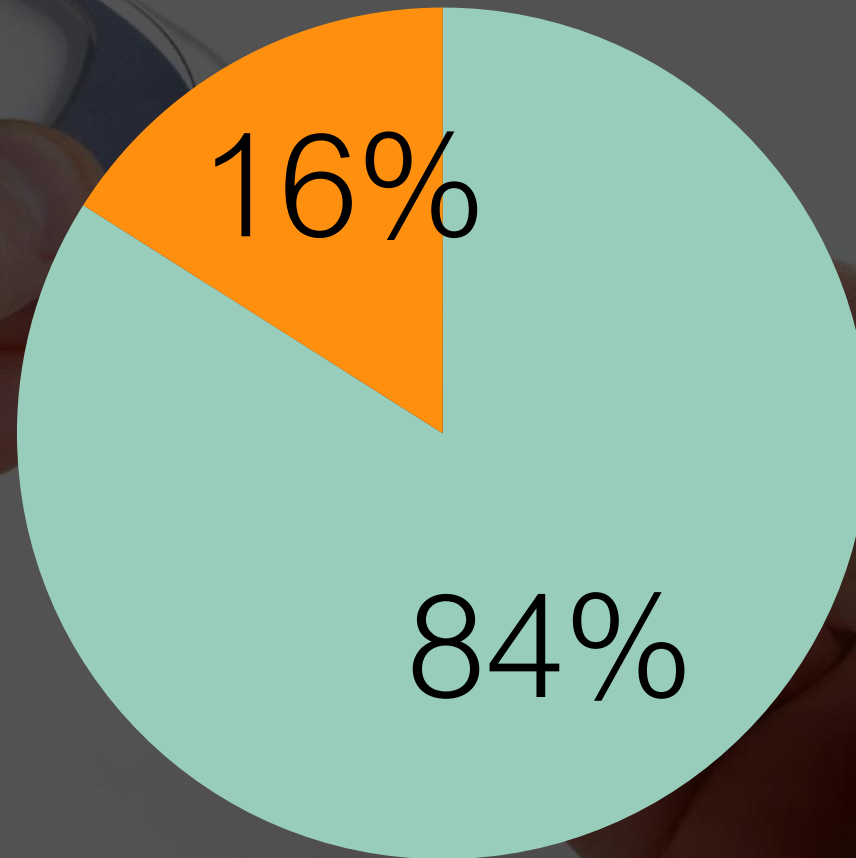
PSYCHIATRY ACADEMY

8.3% of Americans have diabetes





■ Any diabetes treatment ■ No treatment





MASSACHUSETTS
GENERAL HOSPITAL

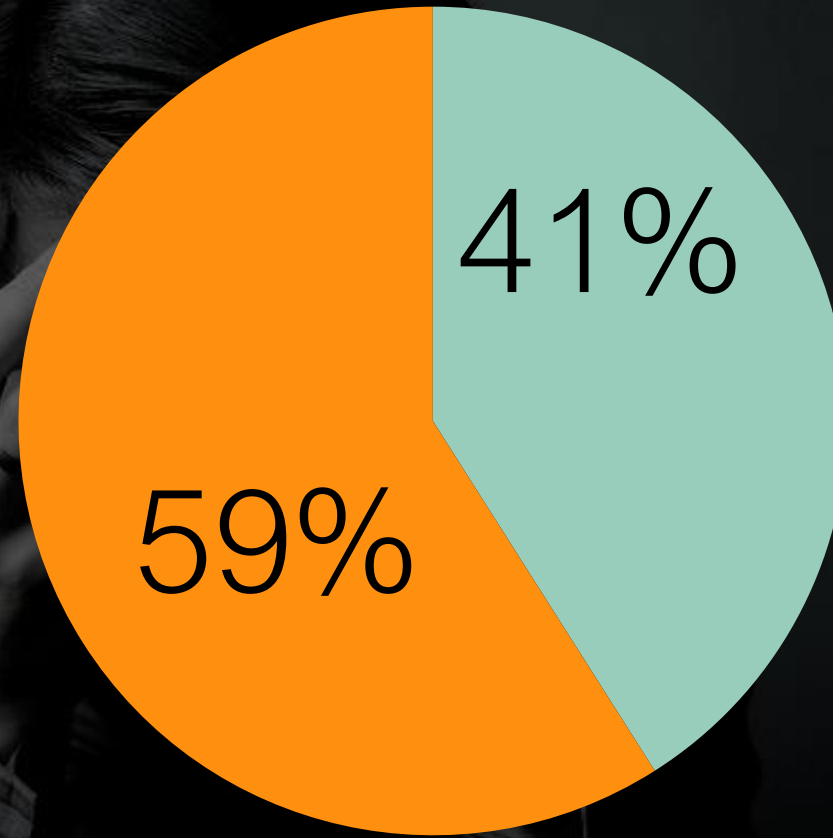
PSYCHIATRY ACADEMY



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



■ Any MH treatment ■ No treatment

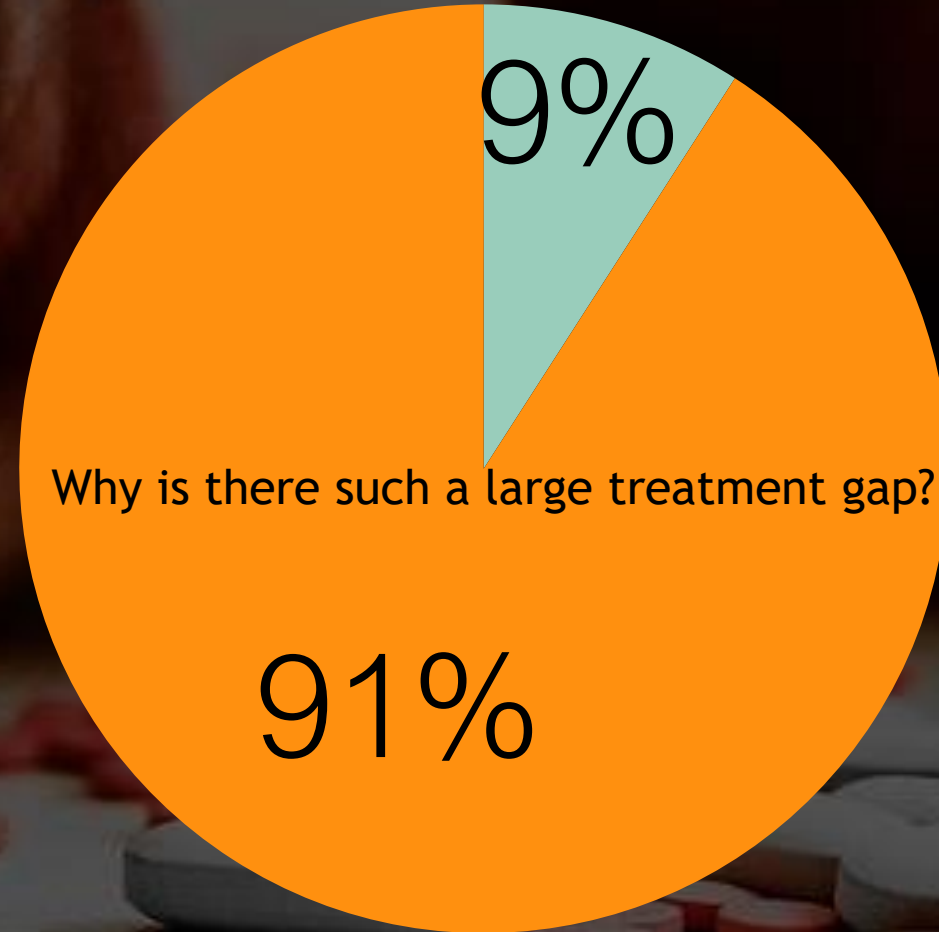




7.4% of Americans have a
substance use disorder in a
given year



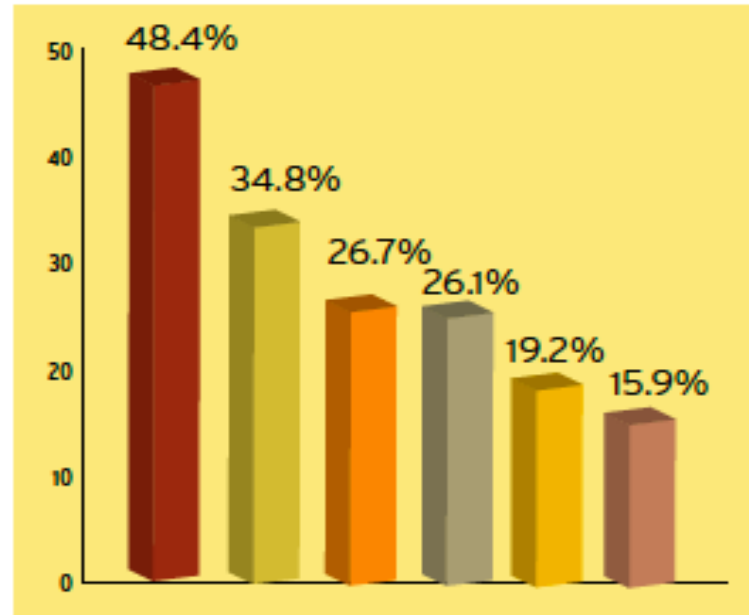
■ Any addiction treatment ■ No treatment



1) People can't afford treatment



How People Pay for Treatment

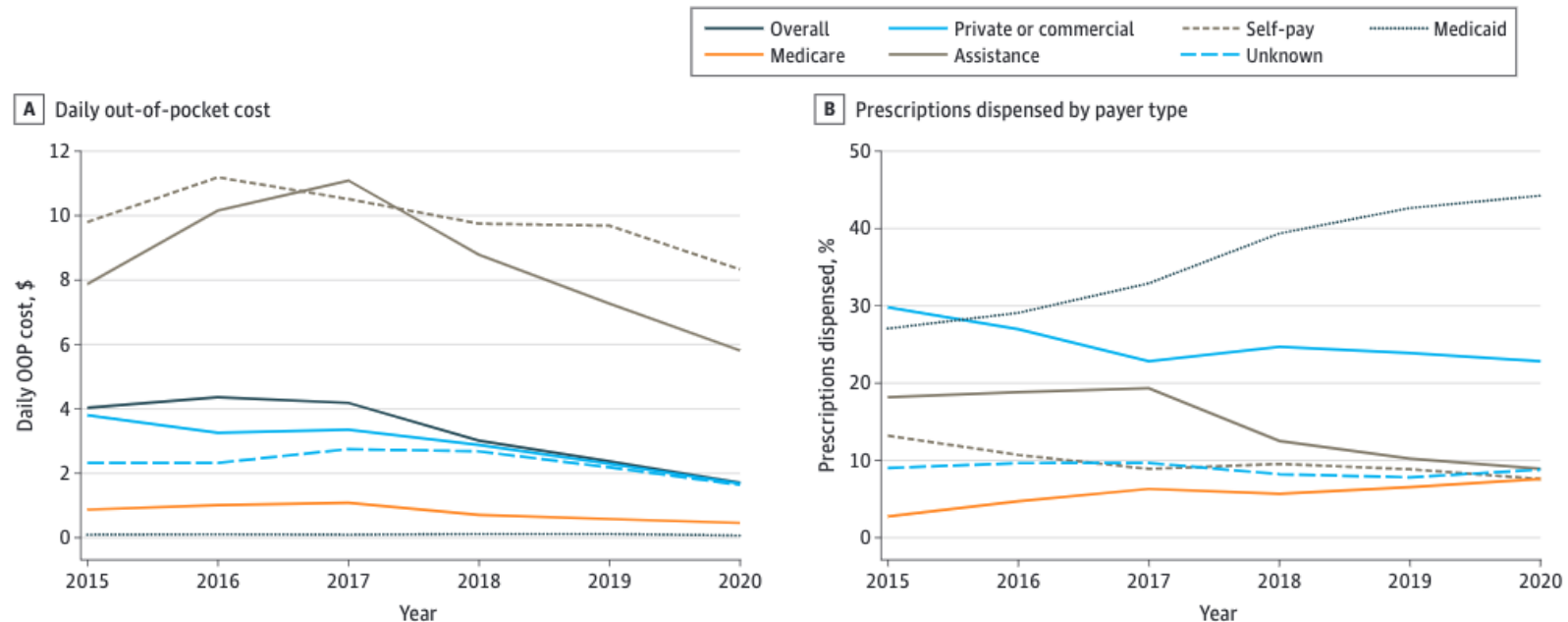


- Own savings and earnings
 - Private health insurance
 - Medicaid
 - Public assistance other than Medicaid
 - Medicare
 - Funds from family members
- [note: individuals could report multiple sources of funding for treatment]

Suboxone costs are high for those who self-pay



Figure. Mean Daily Out-of-Pocket (OOP) Cost and Proportion of Prescriptions Dispensed by Payer Type for Retail Pharmacy-Dispensed Buprenorphine, 2015 to 2020



Total prescriptions dispensed decreased from 39 319 in 2015 to 32 408 in 2020. Private or commercial payer included employer-sponsored health insurance, plans purchased through health insurance exchanges, and those administered by pharmacy benefit managers. Self-pay indicates a prescription was paid for entirely with cash. Medicaid includes Medicaid managed care or fee-for-service

Medicaid. Medicare indicates prescriptions paid by Medicare Part D. The assistance category indicates payment using a discount card (including non-Medicare senior discount cards), a coupon, or a voucher. The unknown category consisted of prescriptions that were missing payer type or had unspecified third-party or unknown for payer type.



2) Not enough doctors treat addiction (ex: Suboxone)

Train more psychiatrists?

- <1% are current prescribers
- Many psychiatric clinics will not prescribe buprenorphine

Train more PCPs?

- <0.01% are prescribers
- Majority of primary care clinics will not prescribe buprenorphine

Train more addiction psychiatrists?

- About 20-40 new board-certified addiction psychiatrists per year in the US



Targeting addiction treatments to specific stages of the addiction cycle

Preoccupation or anticipation ('craving')

Existing medications:

- Acamprosate
- Bupropion

Potential pharmacotherapies:

- GABA modulators (homeostatic resetters)
- CRF₁ antagonists (stress reducers)
- Glutamate modulators (habit reducers)

Withdrawal or negative affect

Existing medications:

- Methadone
- Buprenorphine
- Varenicline
- Nicotine patch

Potential pharmacotherapies:

- GABA modulators (homeostatic resetters)
- CRF₁ antagonists (stress reducers)
- κ -opioid antagonists (dysphoria reducer)

Binge or intoxication

Existing medications:

- Disulfiram
- Naltrexone
- Methadone
- Buprenorphine

Potential pharmacotherapies:

- Partial agonists of the relevant receptor system (intoxication blockers)
- Drug vaccines (intoxication blockers)

Koob et al., 2009. Nat. Rev. Drug Disc.

Addiction is Similar to Other Chronic Illnesses Because:



MASSACHUSETTS
GENERAL HOSPITAL

PSYCHIATRY ACADEMY

- 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





MASSACHUSETTS
GENERAL HOSPITAL

PSYCHIATRY ACADEMY

*Full recovery is a challenge
but it is possible ...*

NIDA

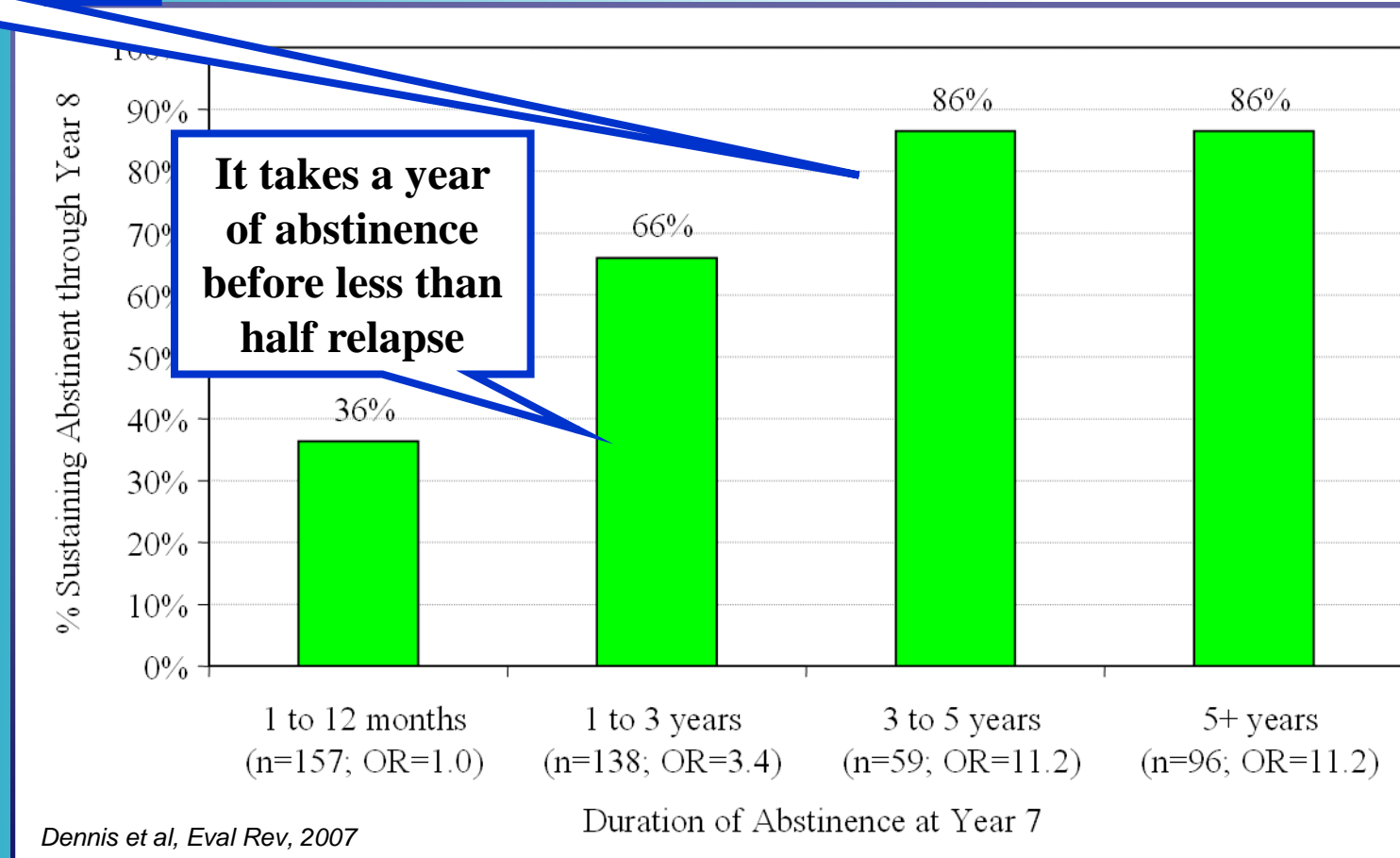
Extended Abstinence is Predictive of Sustained Recovery



MASSACHUSETTS
GENERAL HOSPITAL

PSYCHIATRY ACADEMY

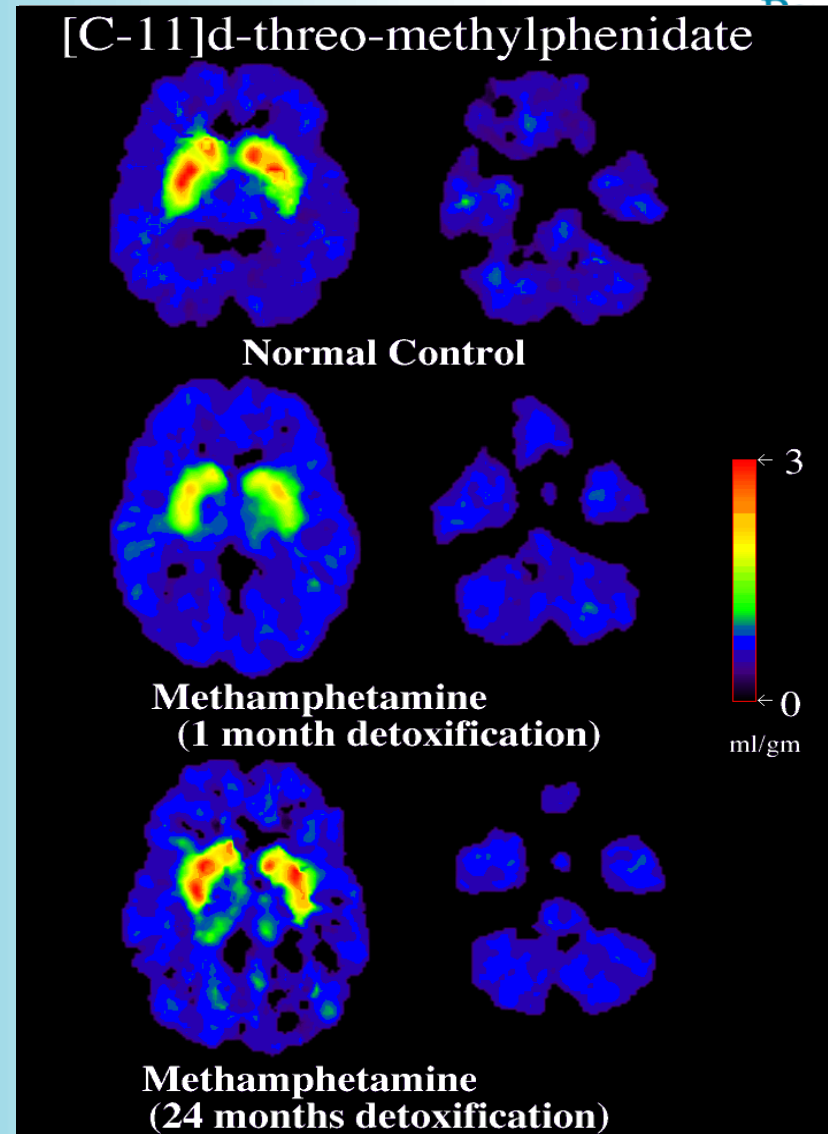
After 3 years – if you are sober,
you probably will stay that way.



*It takes time, but
the brain can
recover*

DAT Recovery
with prolonged
abstinence from
methamphetamine

Volkow et al., J. Neuroscience, 2001.



Conclusions



MASSACHUSETTS
GENERAL HOSPITAL

PSYCHIATRY ACADEMY

- Addiction is a brain disease, with both biological and behavioral risk factors
- Addiction consists of specific stages, that each involve different brain regions and different neurotransmitters
- Addiction disrupts brain circuits involved in judgment and decision-making, so that “saying no” becomes very difficult
- These disruptions of brain circuitry are long-lasting
- Specific treatments of addiction exist, and those treatments work to help patients maintain abstinence

- Thank you for your attention!!!