



The Neurobiology of Addiction

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What is Addiction?



- commonly associated with a chronic, relapsing course
- 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 (eg, dysphoria, anxiety, irritability) reflecting a motivational withdrawal syndrome when access to the drug is prevented

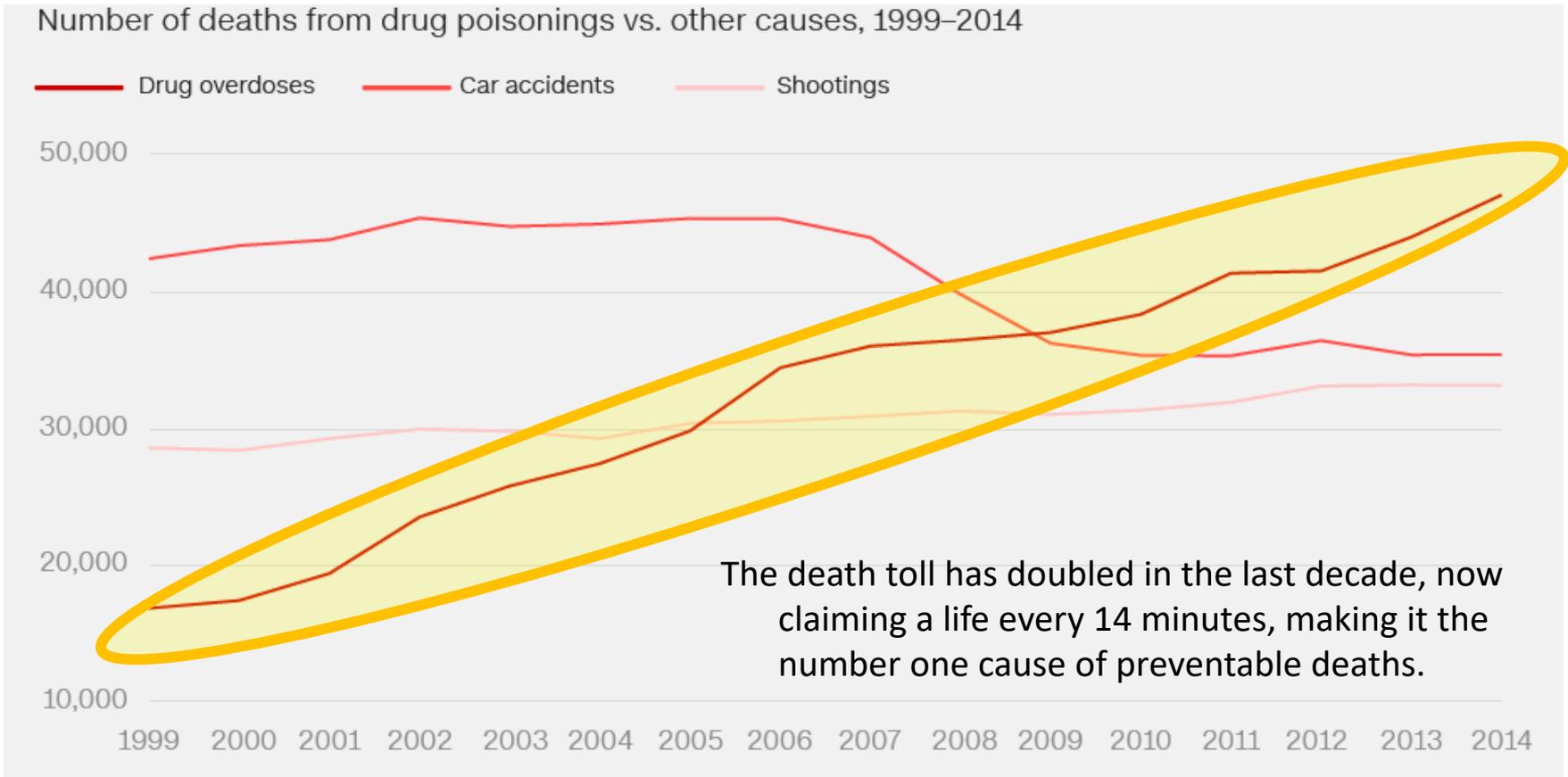
How Common is Addiction?



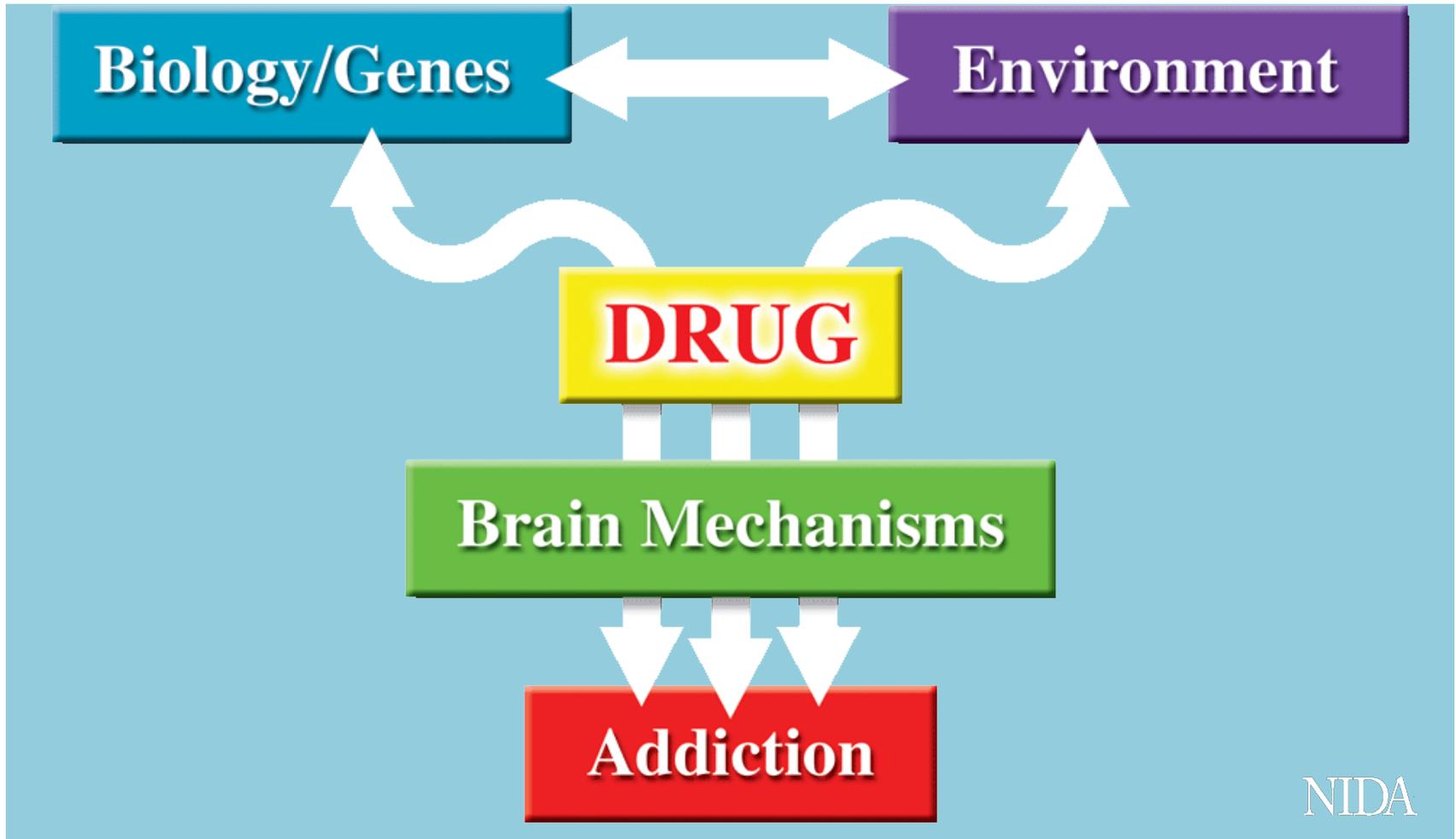
- **Alcohol:** 17 million Americans (11% of the population) are addicted (steady for the past few decades)
- **Nicotine:** 55 million Americans (21% of the population) are addicted (decreasing... For now... E-cigarettes may change this)
- **CANNABIS:** ~9 million (6% of the population) Americans are 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 opiates)



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



Addiction Involves Multiple Factors



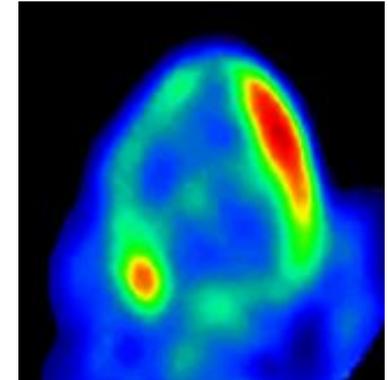
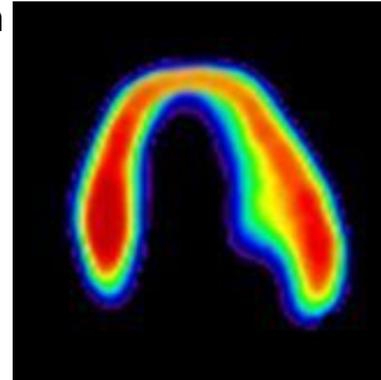
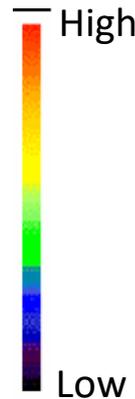
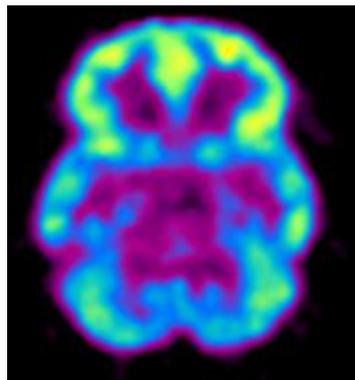
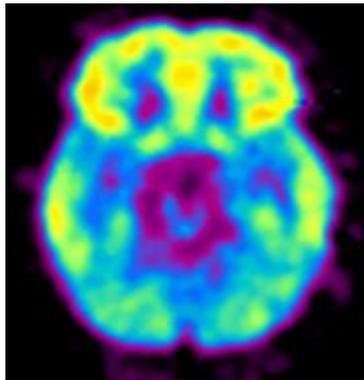
Addiction is Like Other Diseases...



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

Decreased Brain Metabolism
in *Cocaine-addiction Patient*

Decreased Heart Metabolism in
Heart Disease Patient



Healthy Brain

Diseased Brain/
Cocaine Abuse

Healthy Heart

Diseased Heart

NIDA

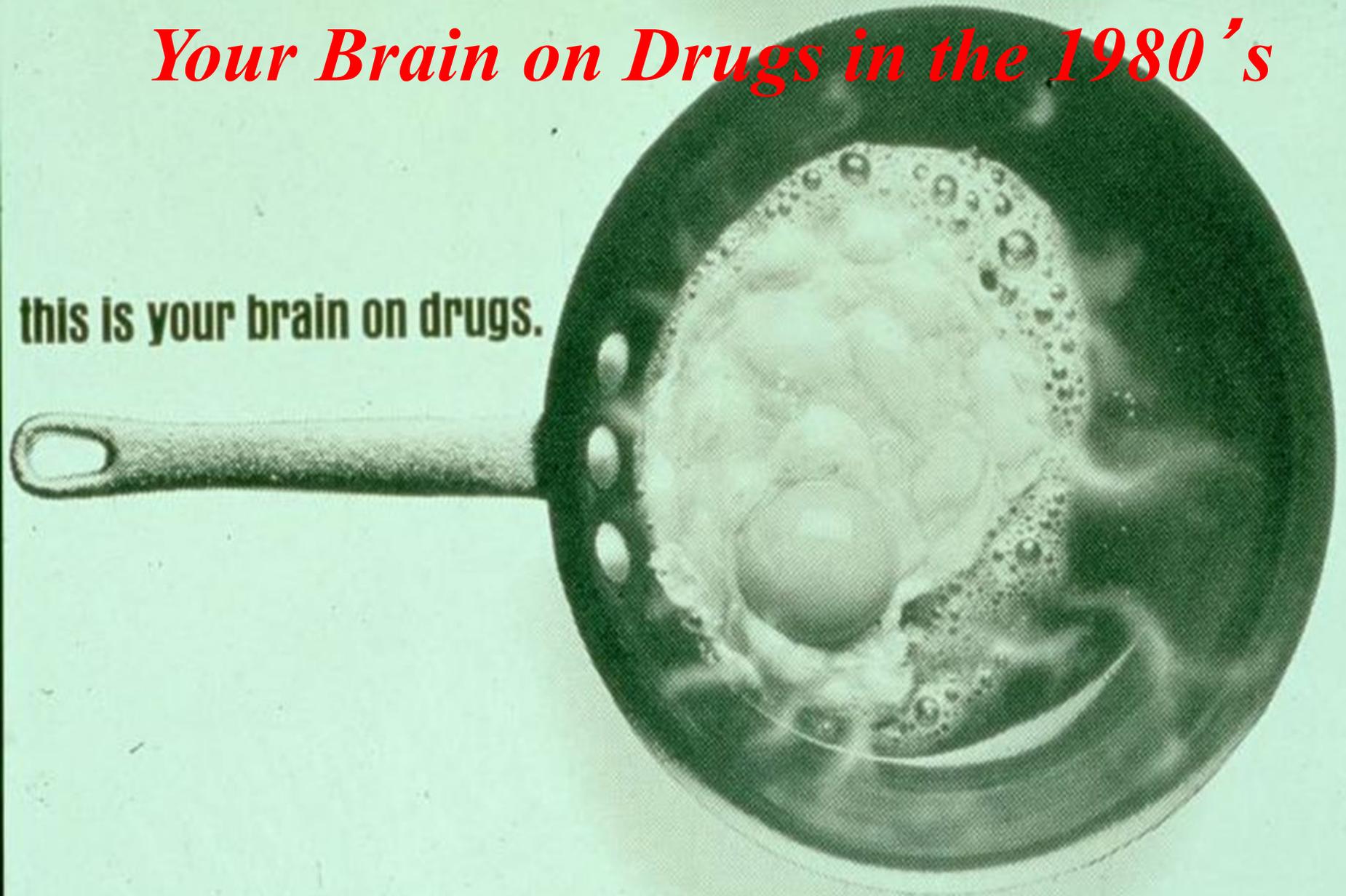


Advances in science have
revolutionized our fundamental
views of drug abuse and addiction.

NIDA

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



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

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PSYCHIATRY ACADEMY

Individual Variability



- Inhibitory control abnormalities? Reward Responsiveness/Anhedonia? Stress sensitivity Resilience?
- Mood, anxiety, psychotic disorders are clear risk factors
- Those with schizophrenia have cognitive impairments such as diminished prefrontal cortical control over behavior and increased limbic drive similar to those with addictions, perhaps conferring dual risk
- 40-60% of the risk for addiction attributed to genetic factors.
- Genetic factors also present in treatment response

Who is Predisposed to Addiction?

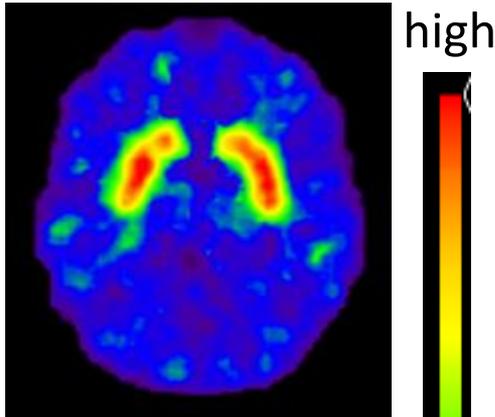


- The Marshmallow Test: Behavioral and Neural Correlates of Ability to Delay Gratification: 40 Years Later
- 4 year-olds who were able to resist eating one marshmallow in exchange for two marshmallows 15 minutes later showed lower rates of substance use 40 years later.

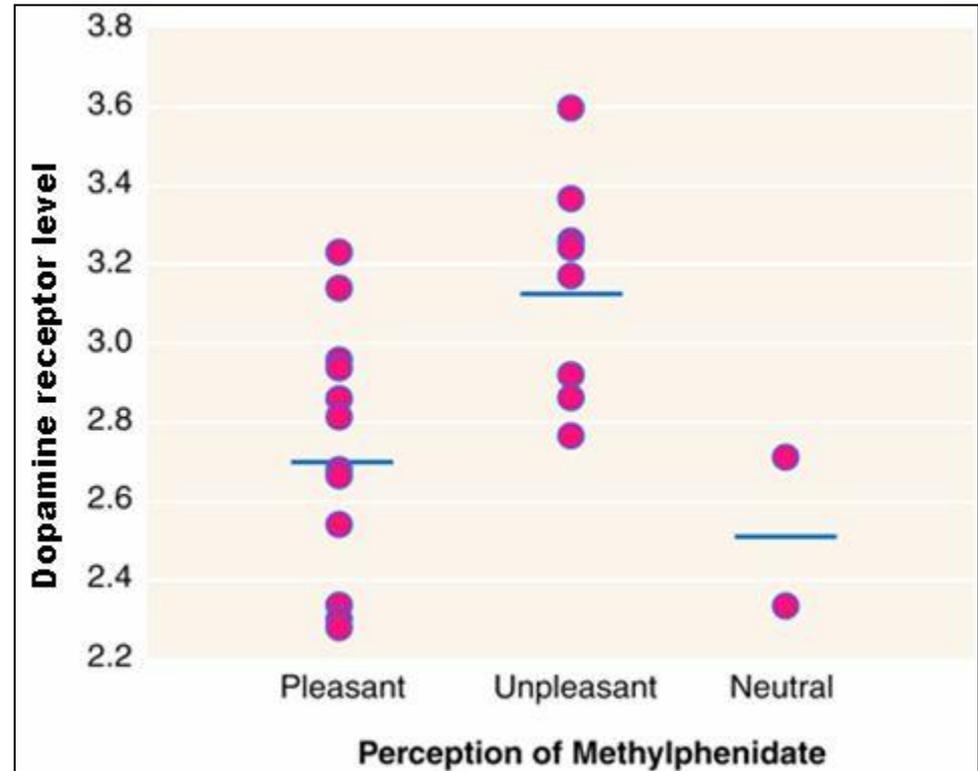
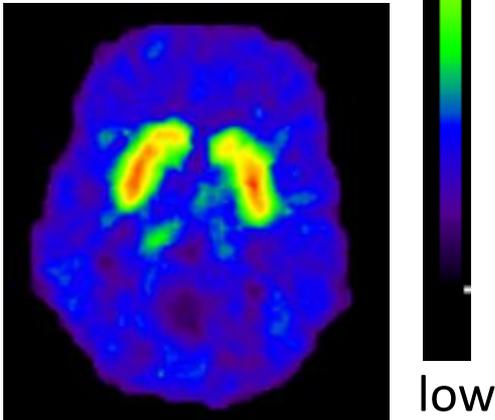
Individual Differences in Response to Drugs: DA Receptors influence drug liking



High DA
receptor



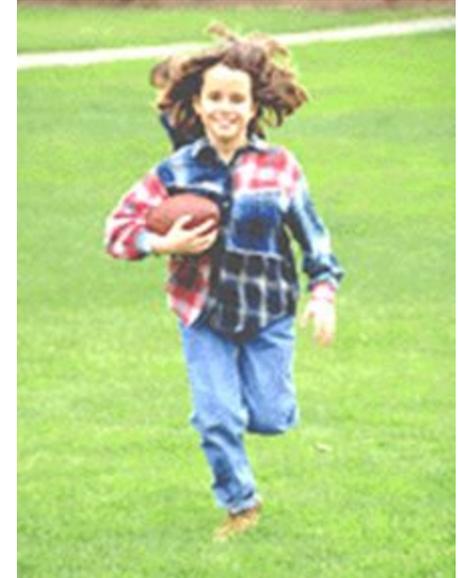
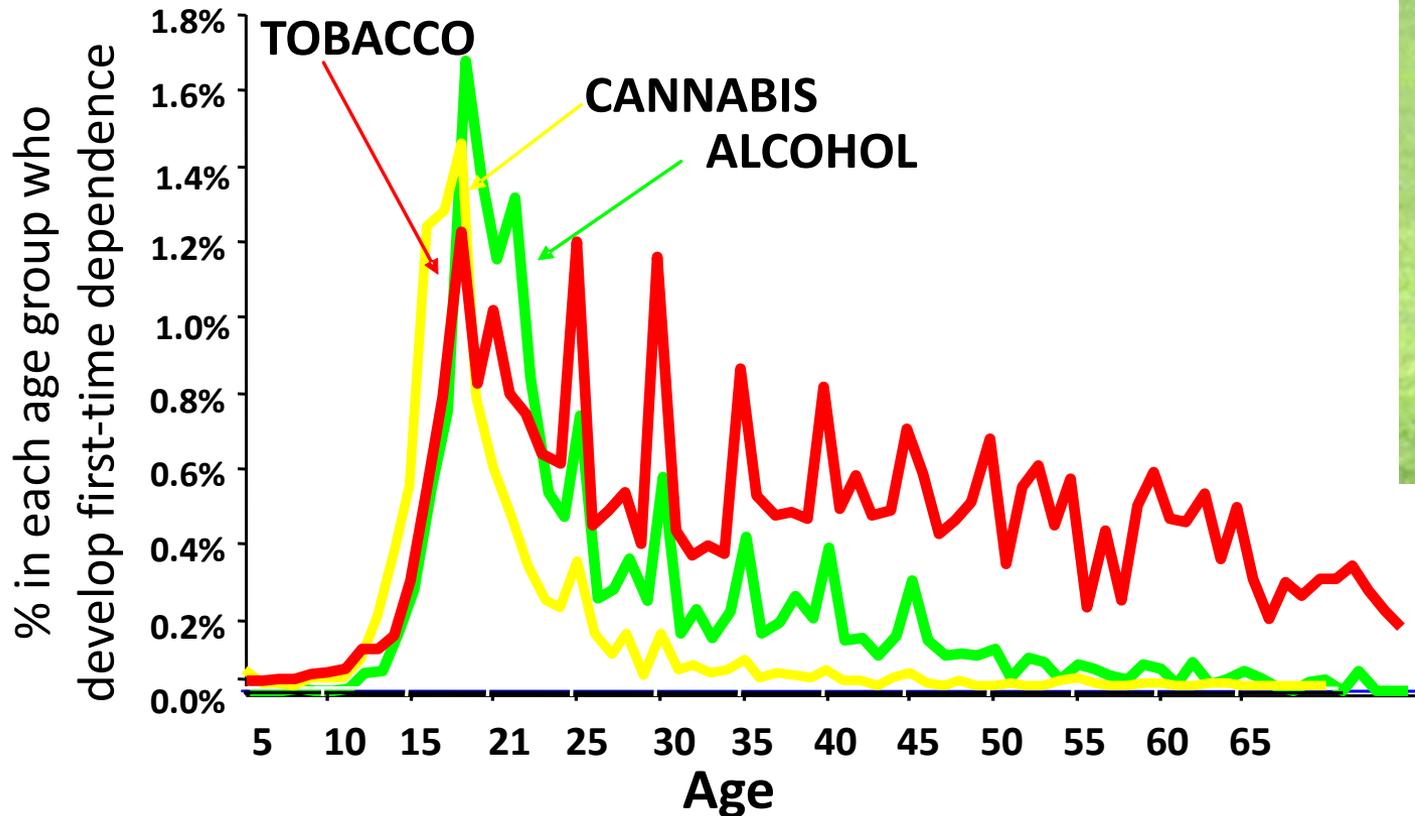
Low DA
receptor



As a group, subjects with low receptor levels found MP pleasant while those with high levels found MP unpleasant

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Addiction is a Developmental Disease that starts in adolescence and childhood



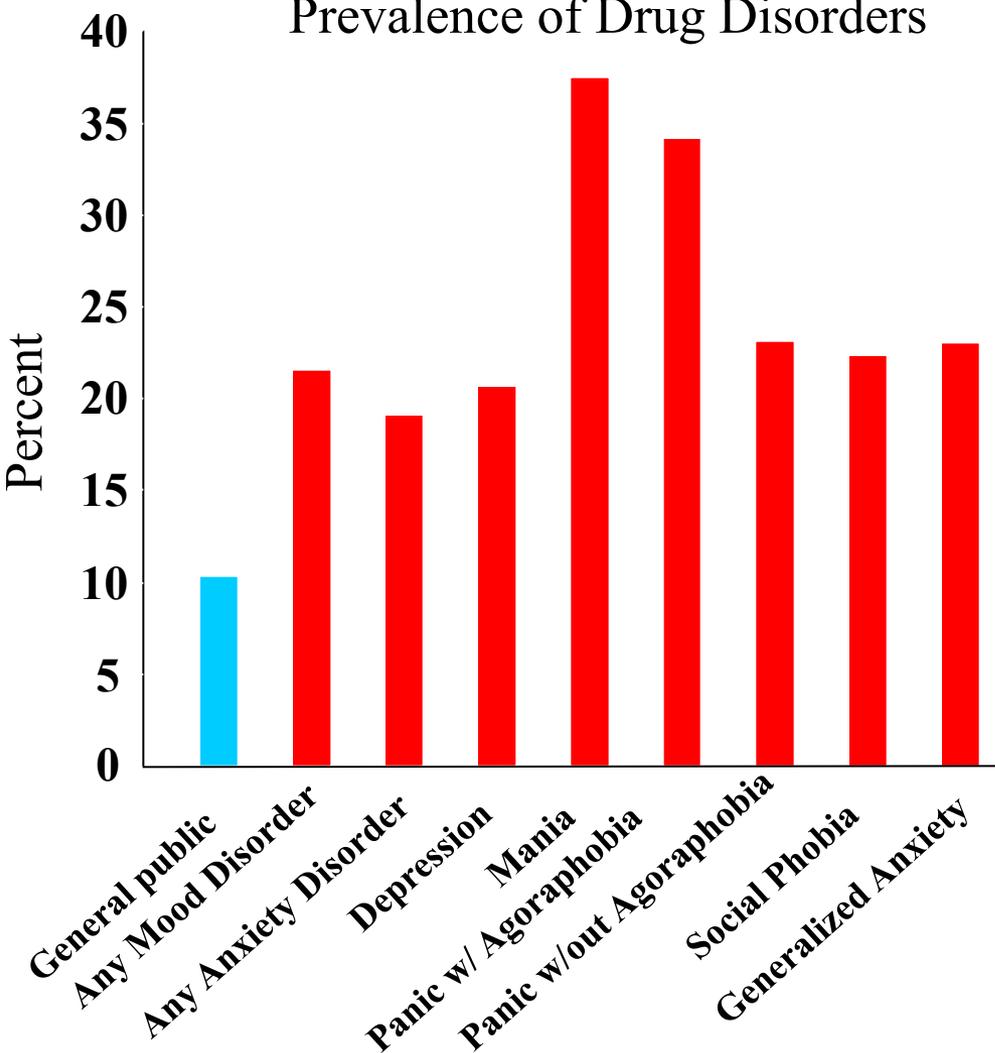
Age at **tobacco**, **alcohol**, and **cannabis** dependence per DSM IV

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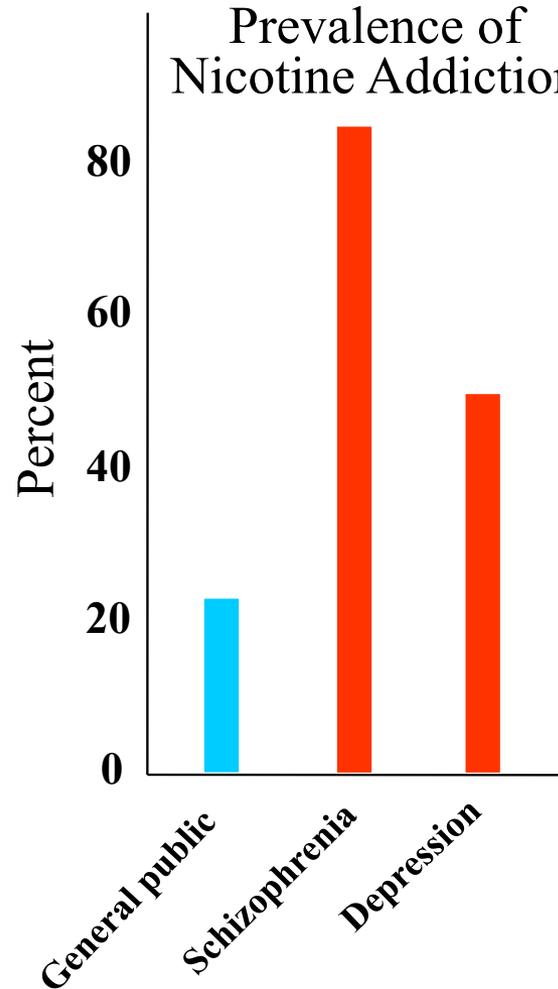


What Other Biological Factors Contribute to Addiction-- Comorbidity

Prevalence of Drug Disorders



Prevalence of Nicotine Addiction



Why do Mental Illnesses and Substance Abuse Co-occur?

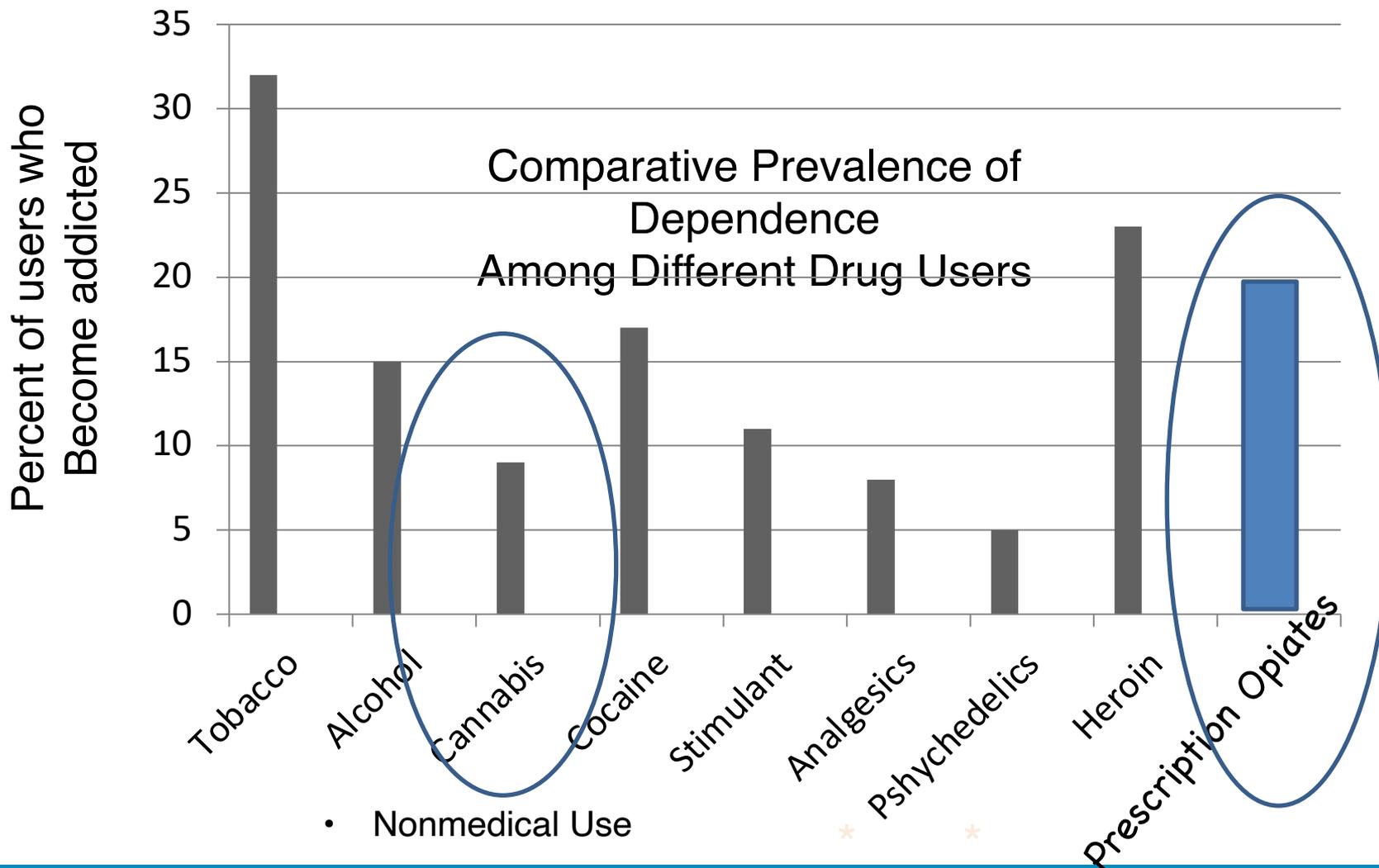


- **Self-medication**
 - substance abuse begins as an attempt to alleviate symptoms of mental illness
- **Causal effects**
 - Substance abuse may increase vulnerability to mental illness
- **Common or correlated causes**
 - the risk factors that give rise to mental illness and substance abuse may be related or overlap



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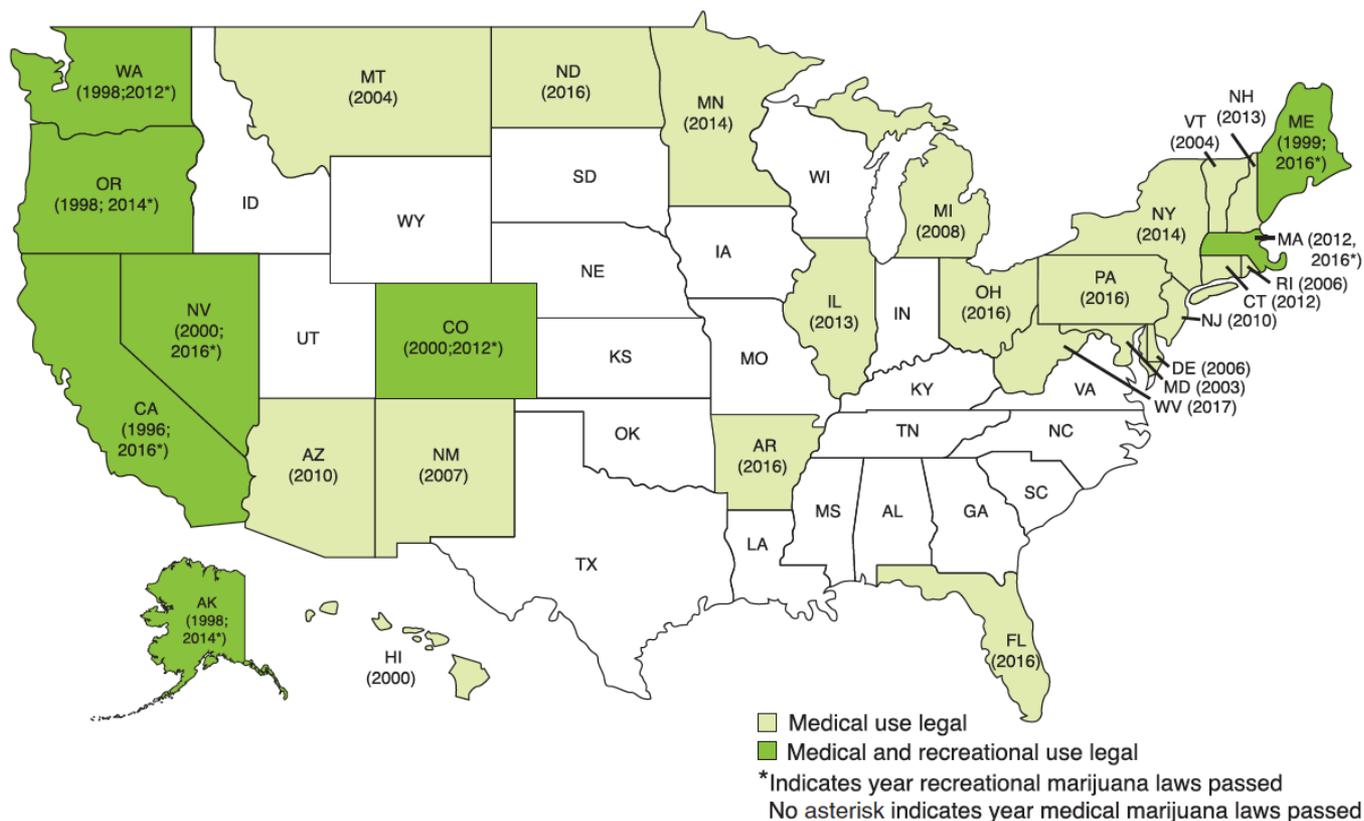
Addictiveness by Drug Type



Source: Anthony et al. Exp. Clin. Psychopharmacol. 2(3), pp 244-268 (1994)



US STATES, MEDICAL AND RECREATIONAL MARIJUANA 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



*“Green Crack”
wax*



“Ear Wax”



Butane Hash Oil
(BHO)



Hash Oil Capsules



“Budder”

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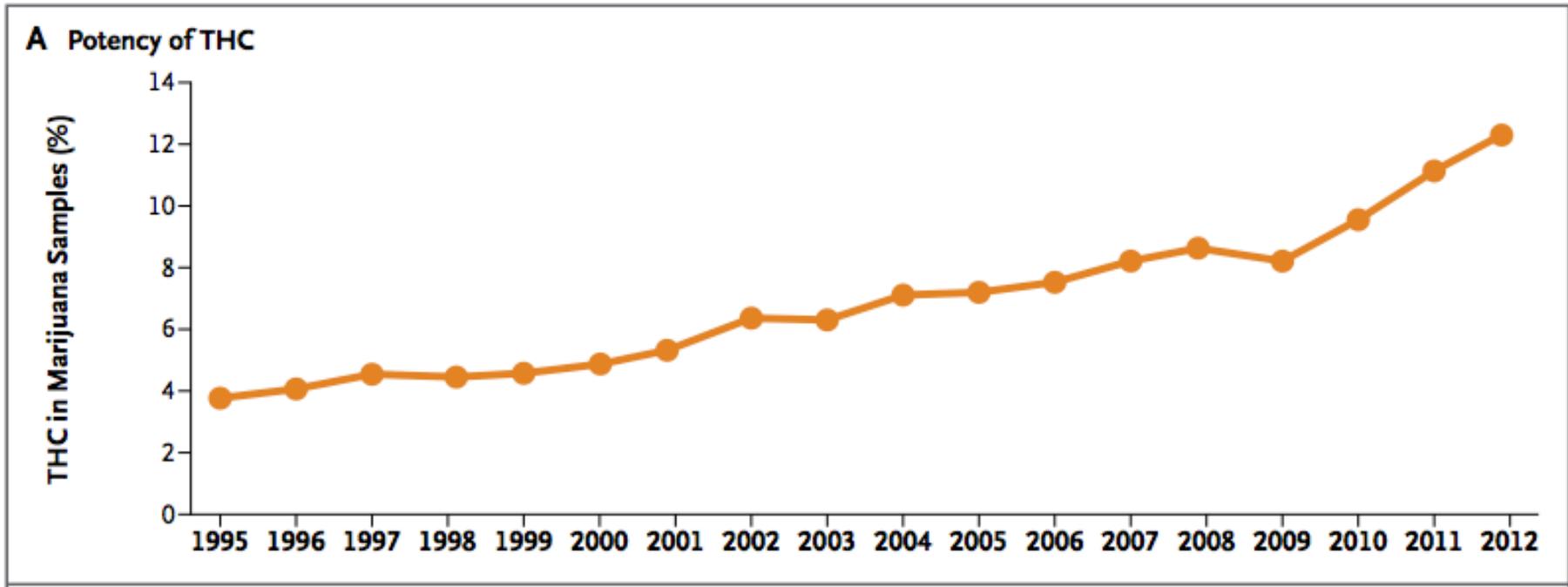
“Shatter”





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

Marijuana 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 Marijuana may lead to psychosis

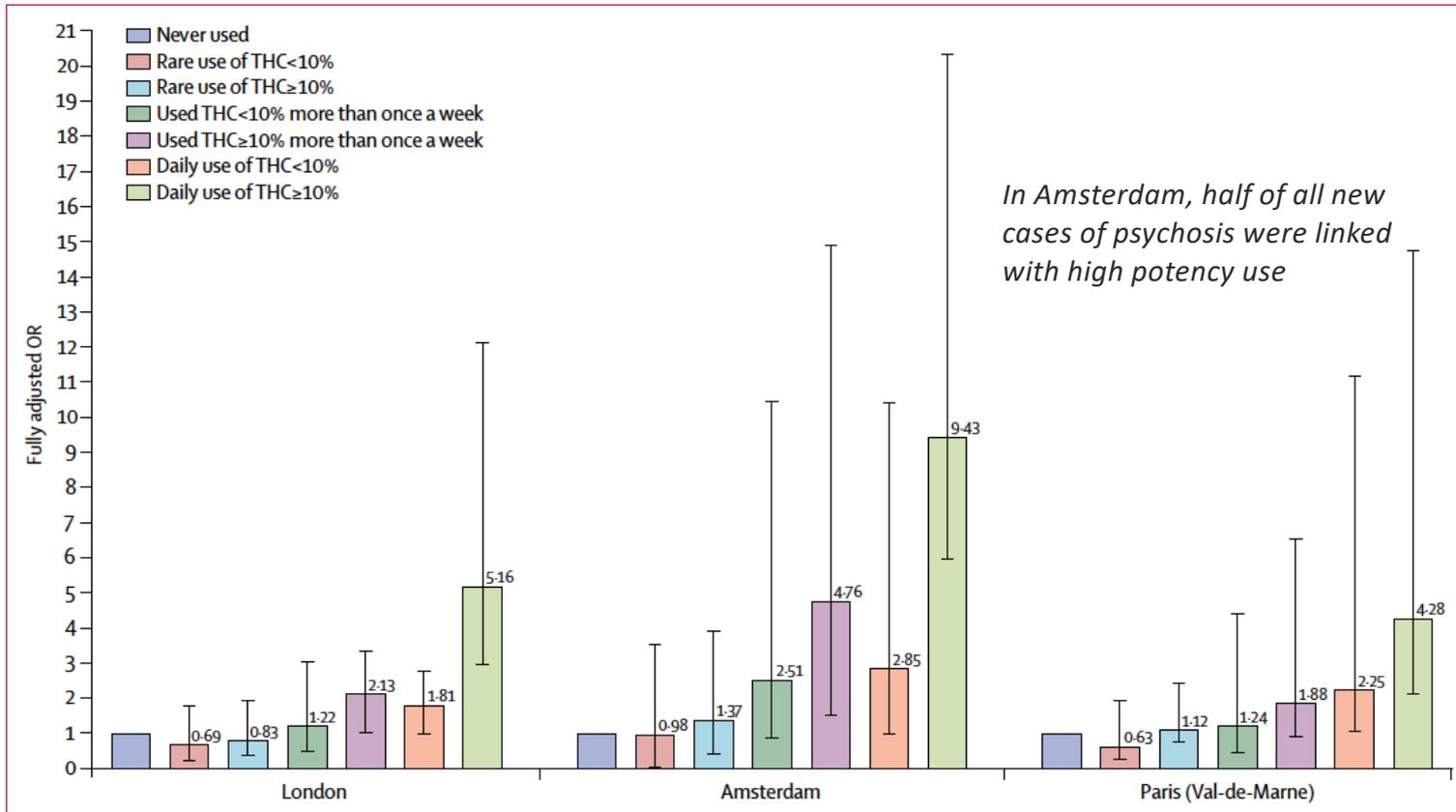


Figure 2: Fully adjusted ORs of psychotic disorders for the combined measure of frequency plus type of cannabis use in three sites

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 Opiate Epidemic

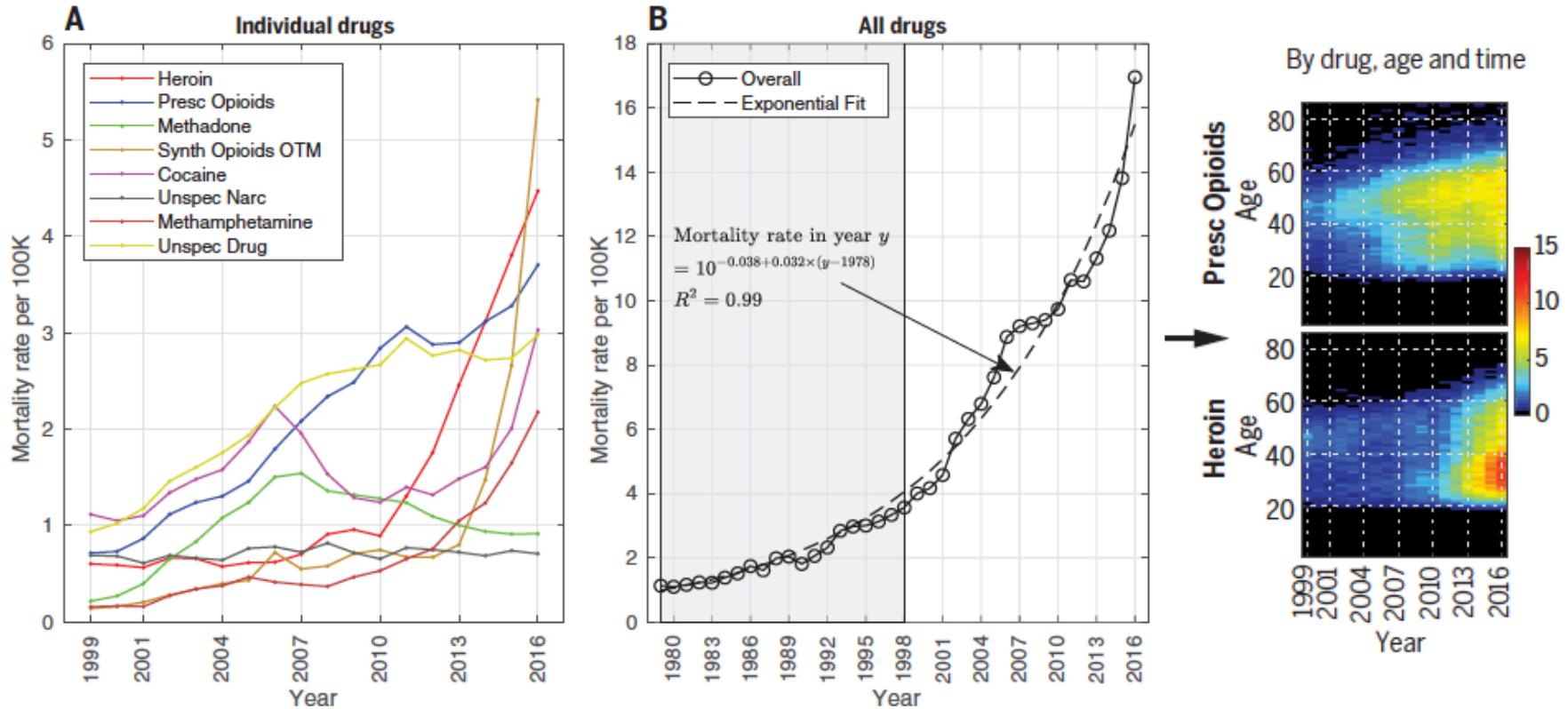
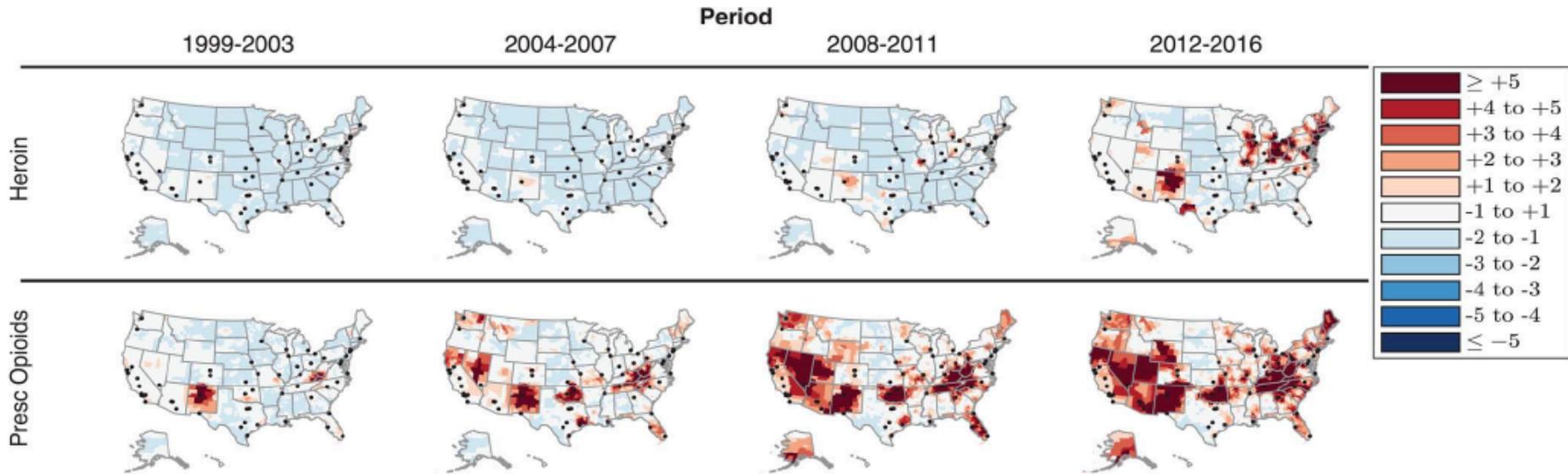
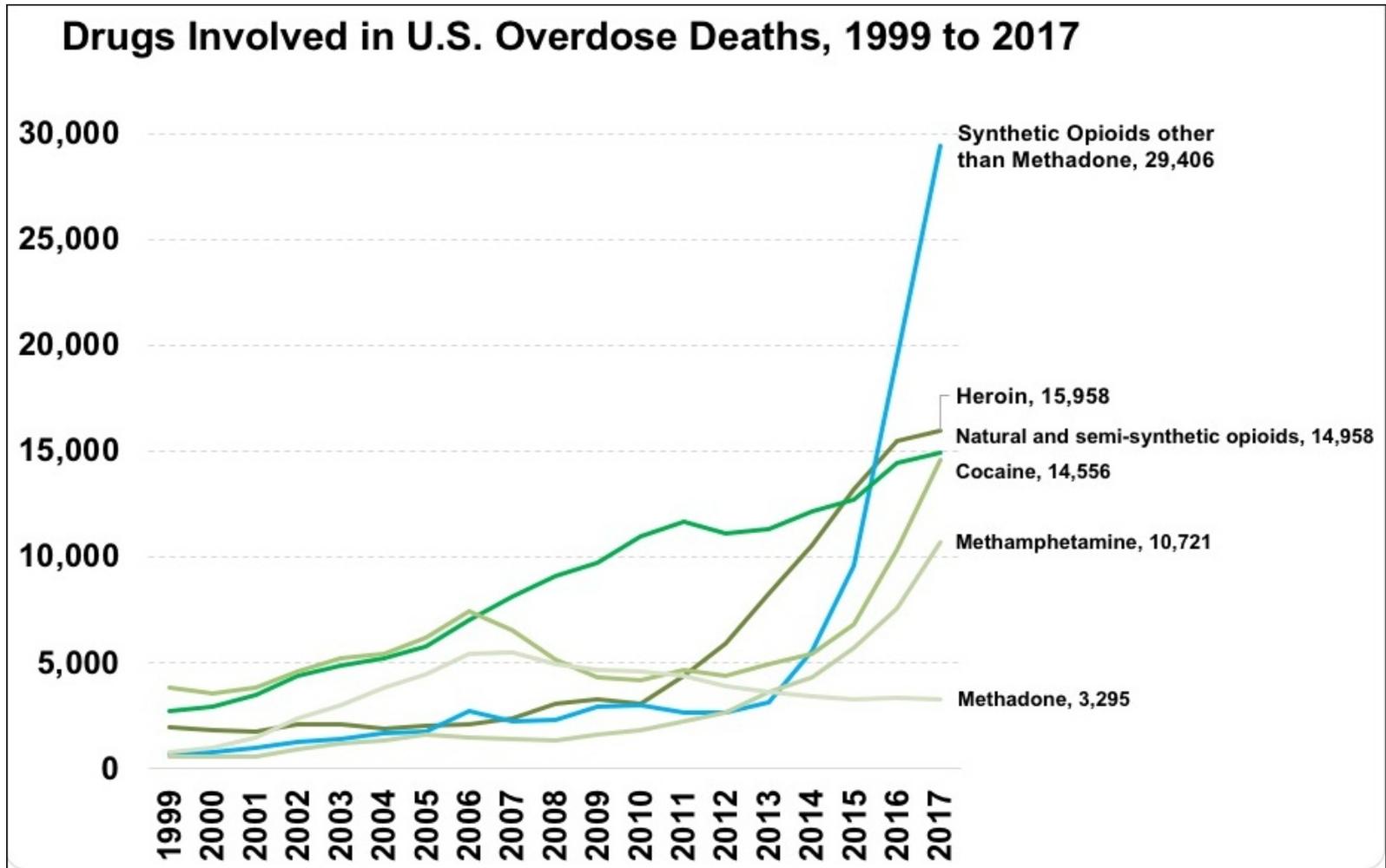


Fig. 1. Mortality rates from unintentional drug overdoses. (A and B) Mortality rates for (A) individual drugs and (B) all drugs. Detailed data for individual drugs are only available from 1999 to 2016, although additional data for all drugs are available since 1979 (this area is grayed out). The exponential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

The Opiate Epidemic



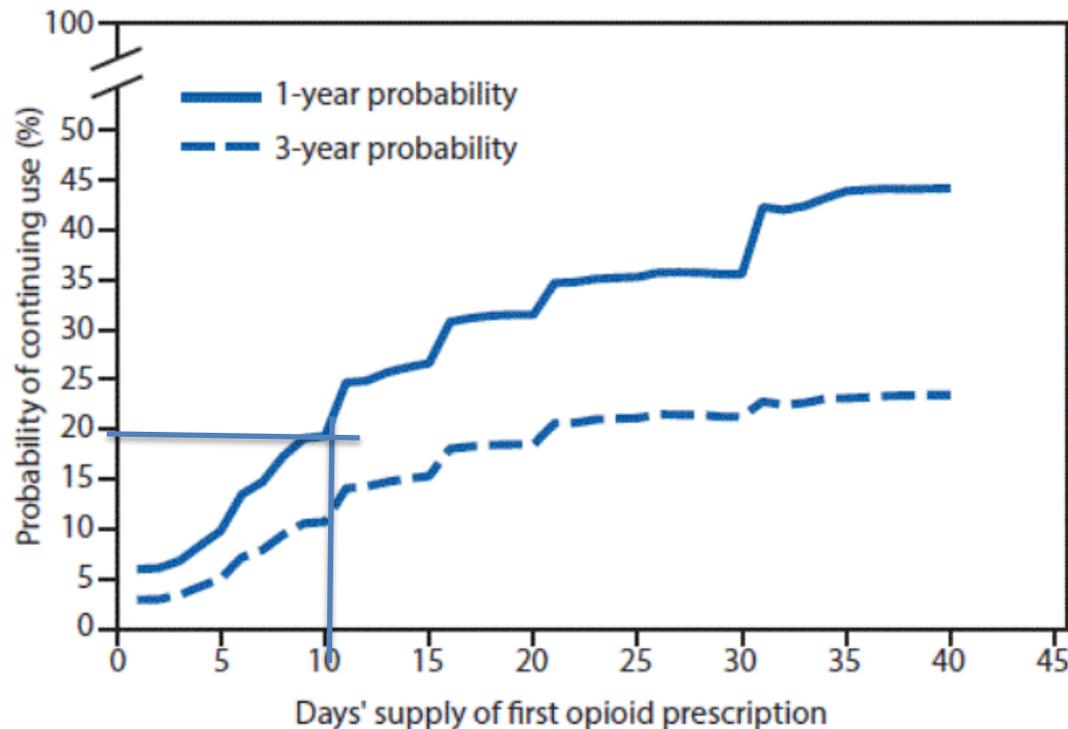
TYPES OF OPIATE OVERDOSES



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



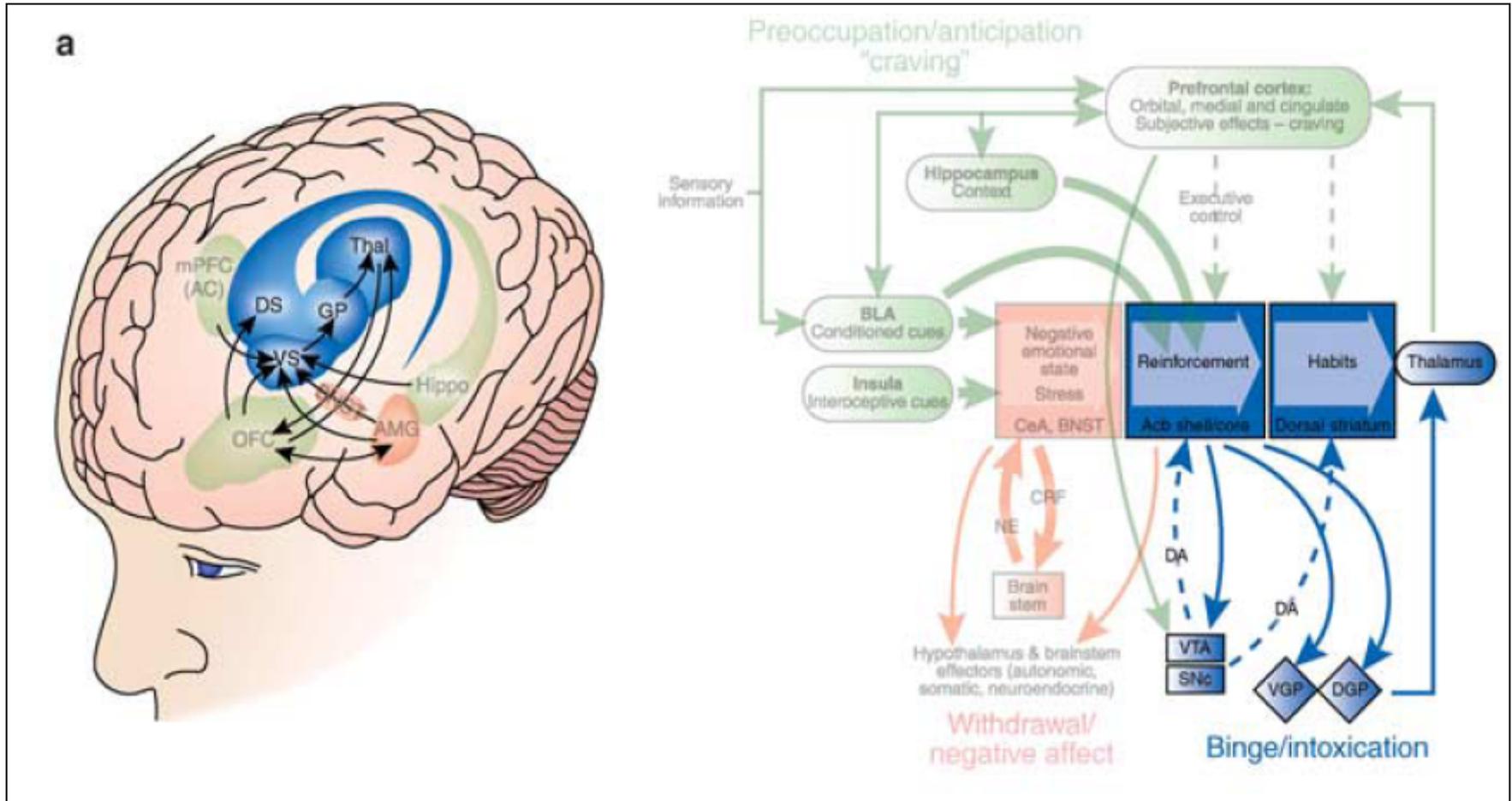
* Days' supply of the first prescription is expressed in days (1–40) in 1-day increments. If a patient had multiple prescriptions on the first day, the prescription with the longest days' supply was considered the first prescription.

Today's Talk



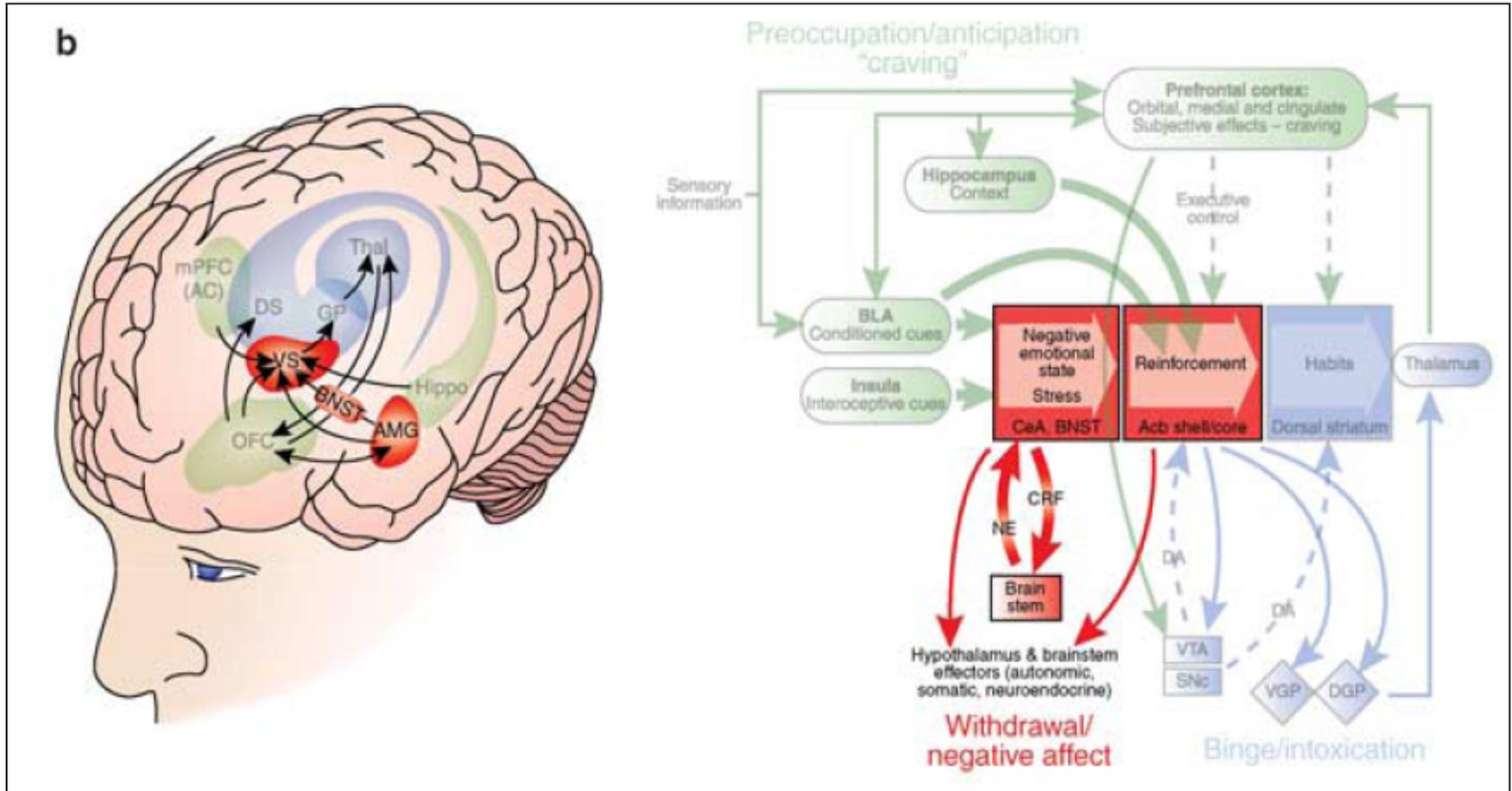
- Who gets Addicted?
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The addiction cycle



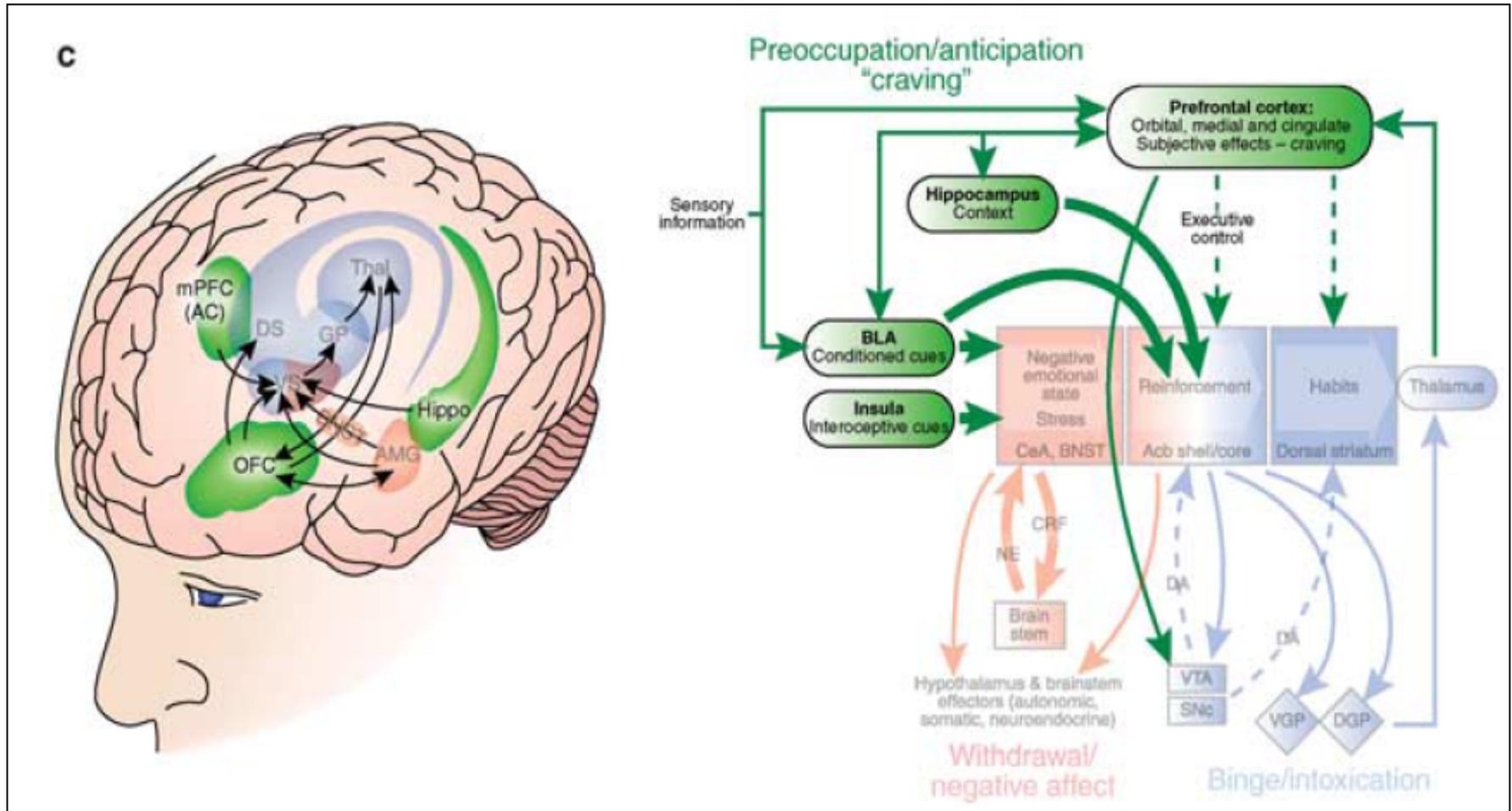
Koob and Volkow 2010

The addiction cycle



Koob and Volkow 2010

The addiction cycle

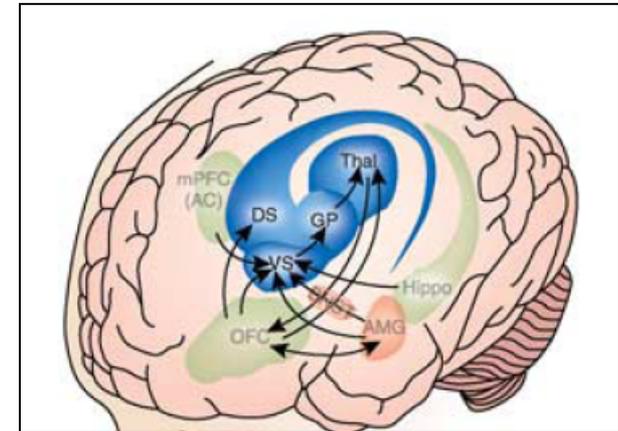


Koob and Volkow 2010

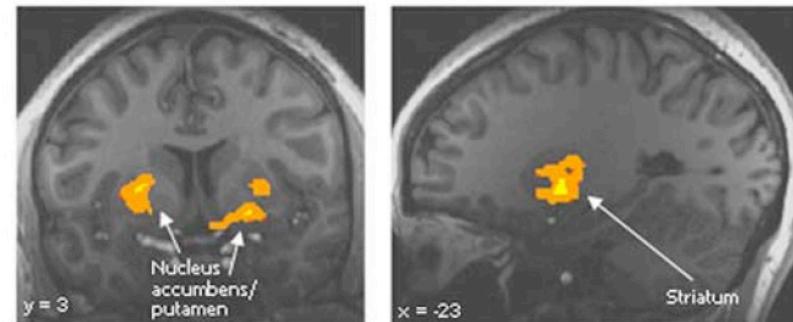
Reward, Dopamine, and the Nucleus Accumbens (NAc)



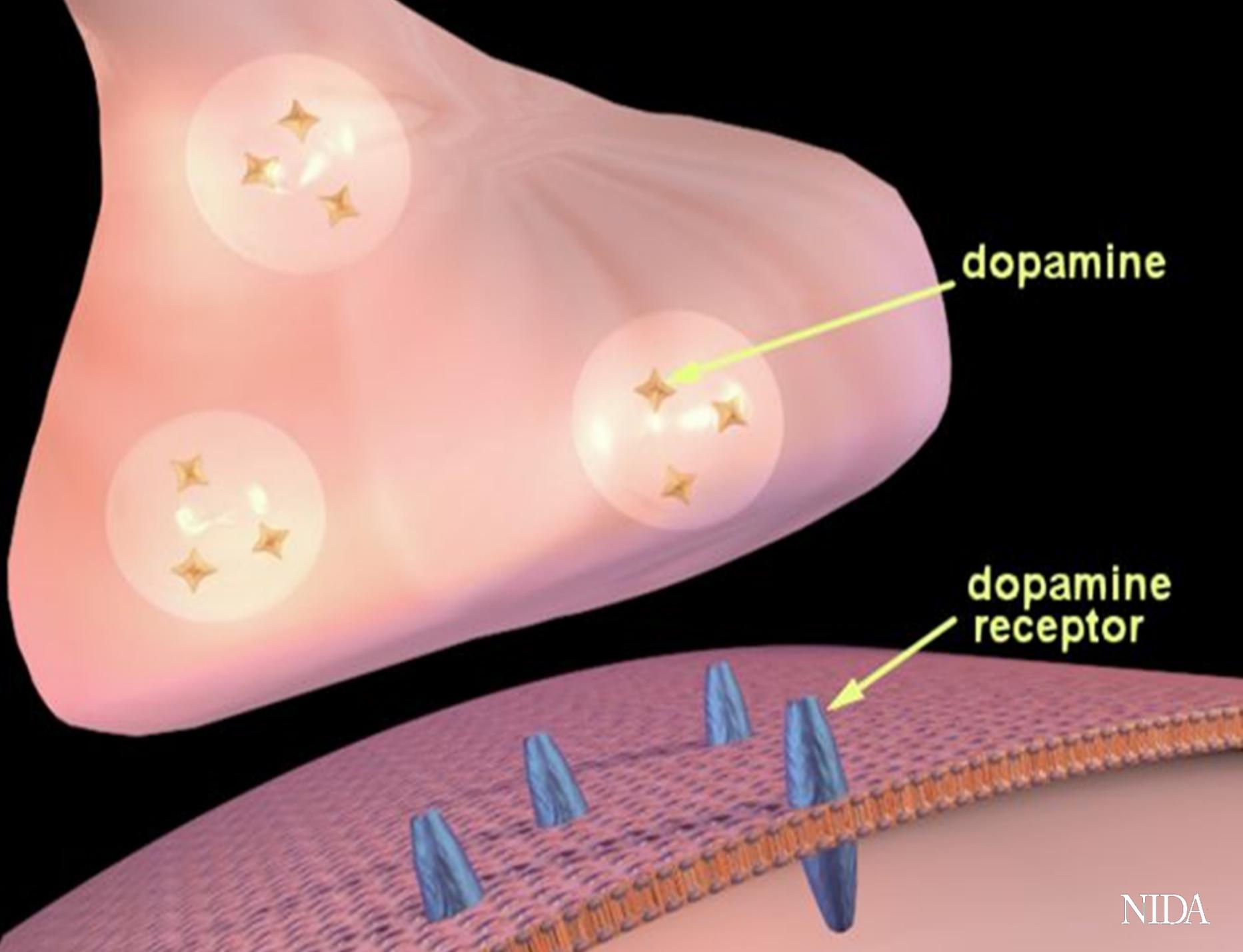
- Reward: stimulus that induces subjective feelings of pleasure.
- Rewarding stimuli activate the mesocorticolimbic reward circuit.
- All drugs of abuse share the ability to activate the this circuit.
 - increase extracellular dopamine (DA) levels in the NAc



Alcohol:

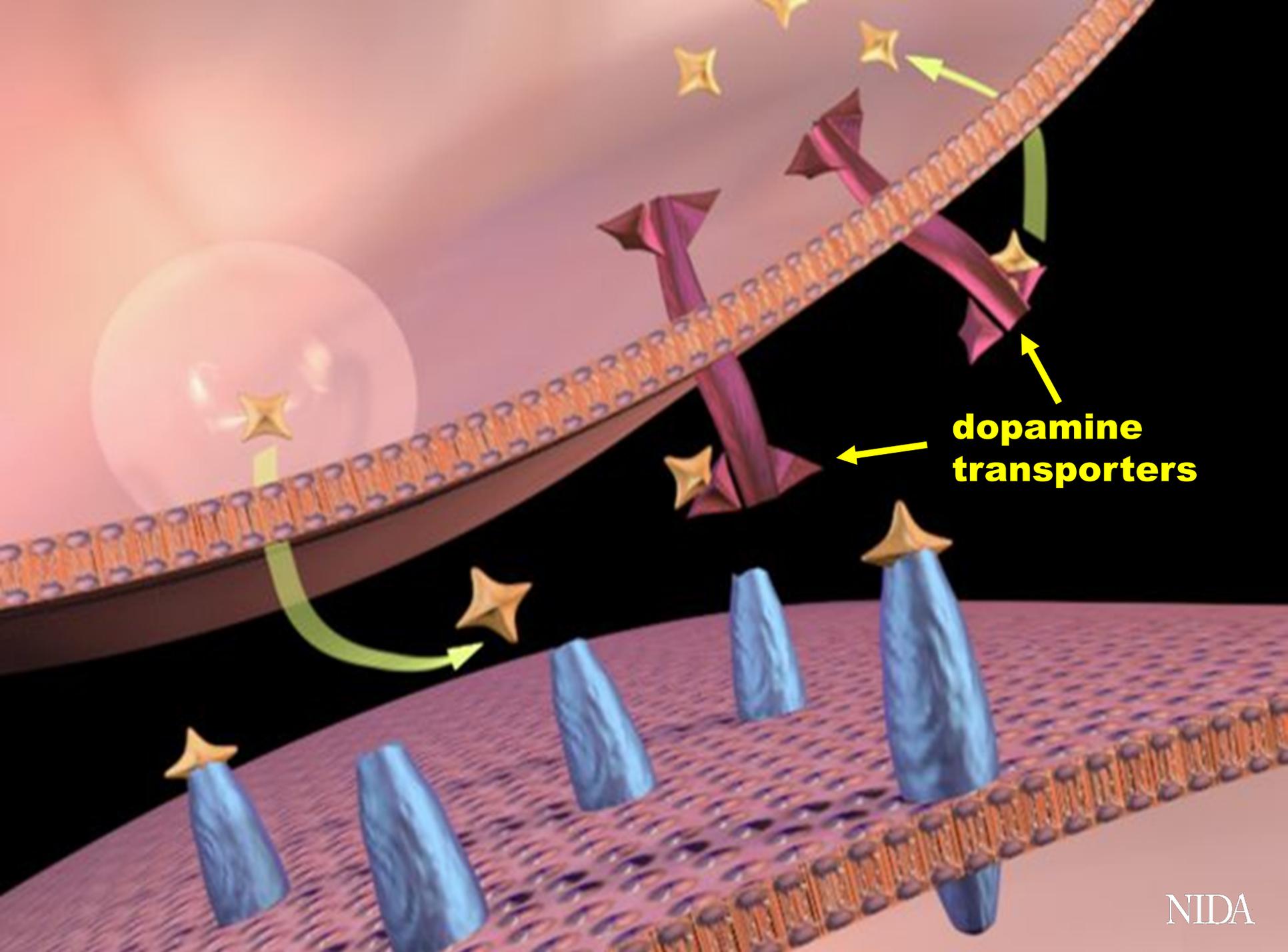


Gilman et al. 2008



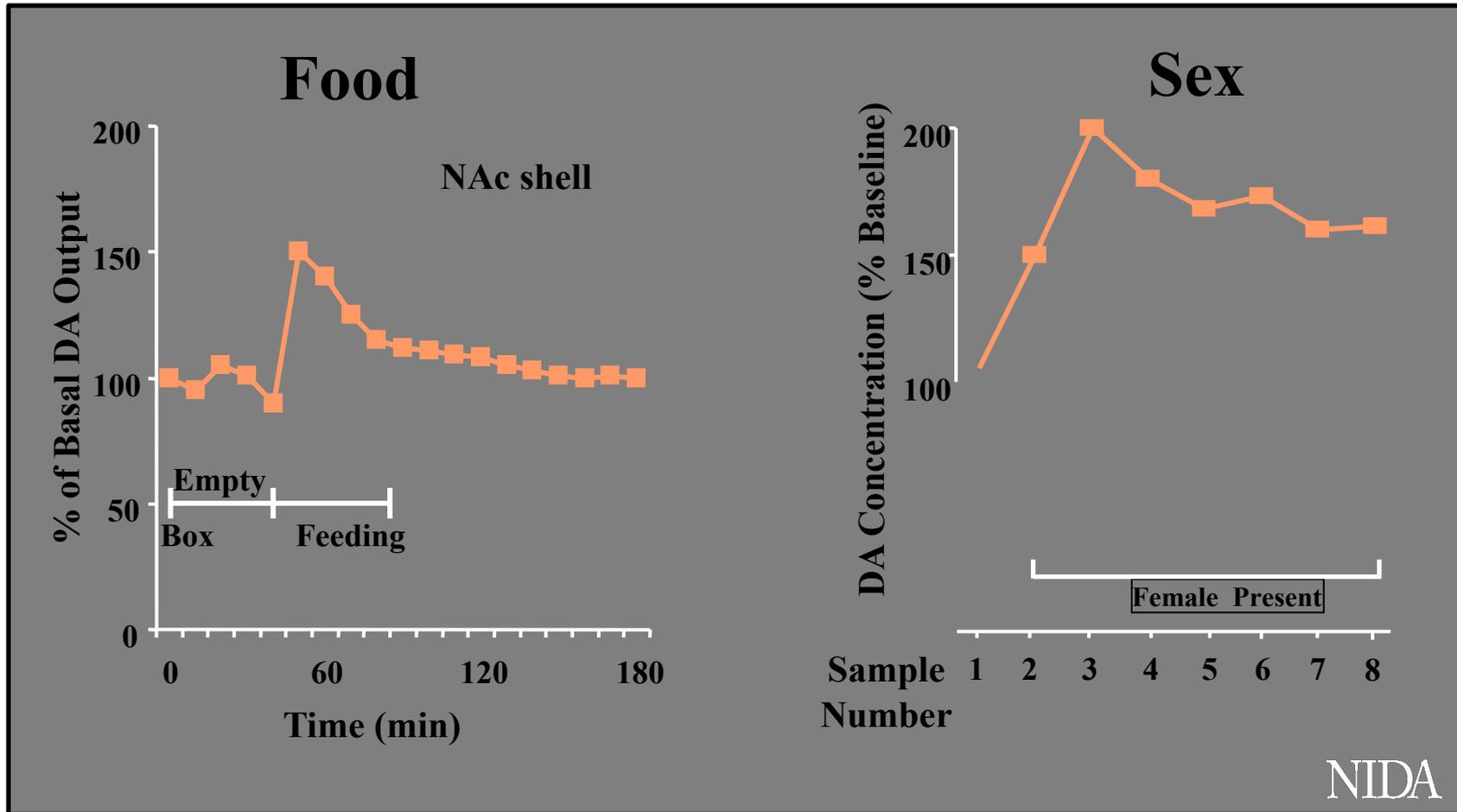
dopamine

dopamine receptor

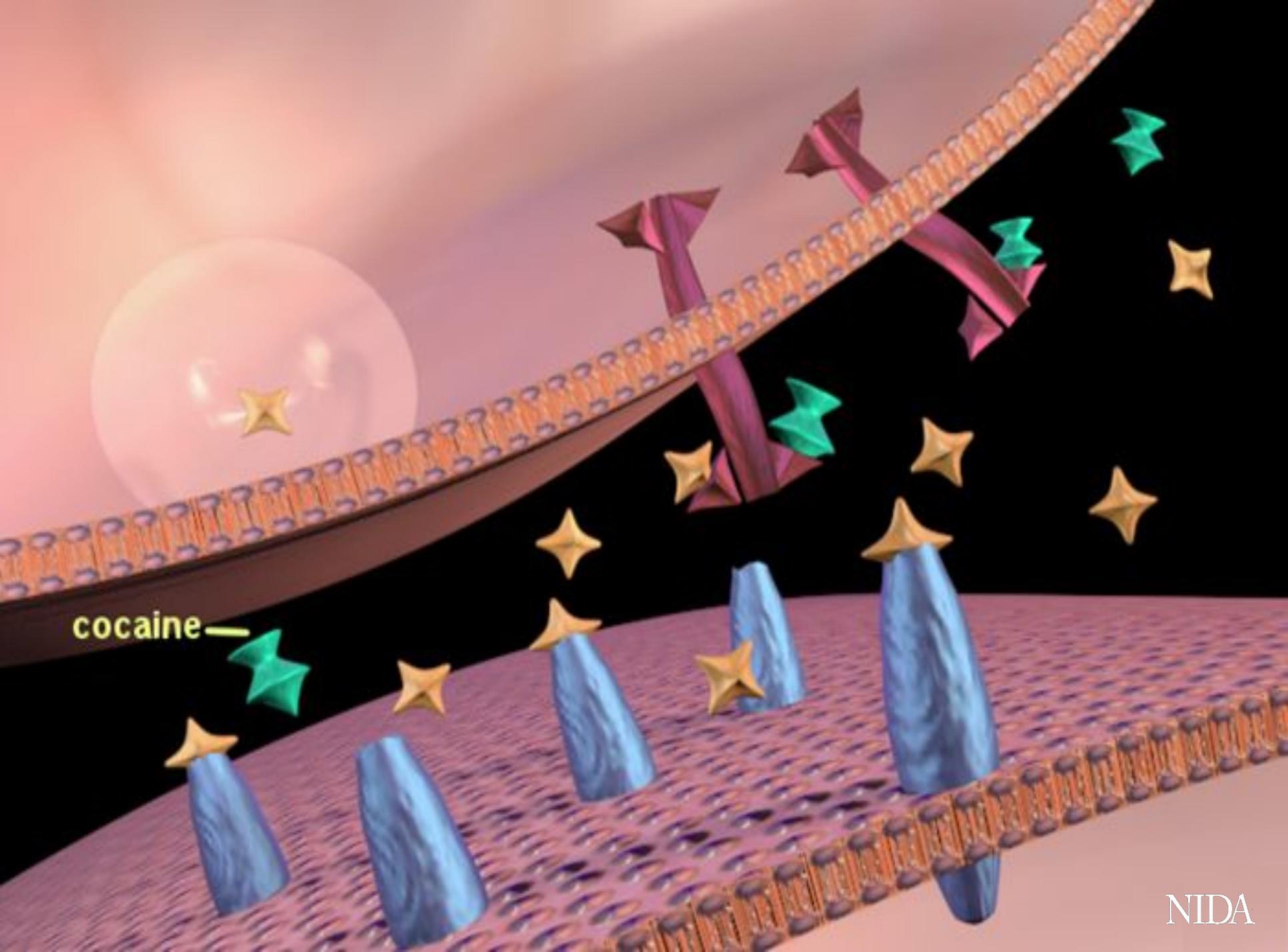


**dopamine
transporters**

Natural Rewards Elevate Dopamine Levels



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

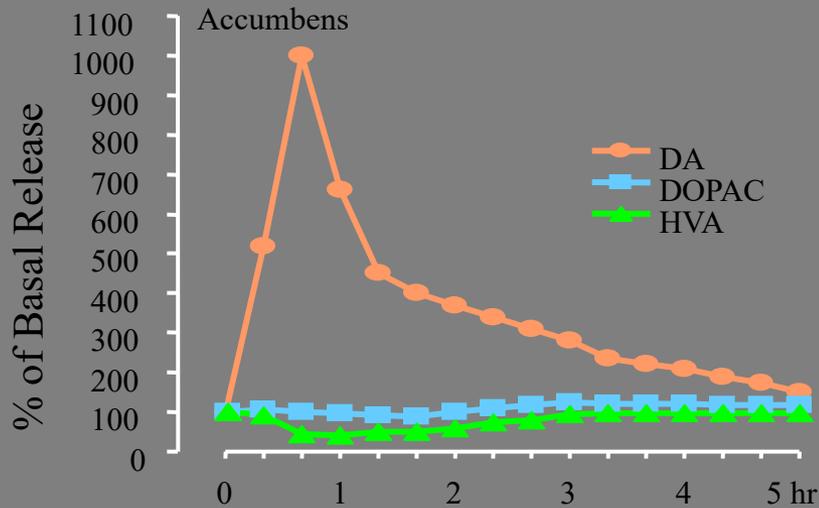


cocaine

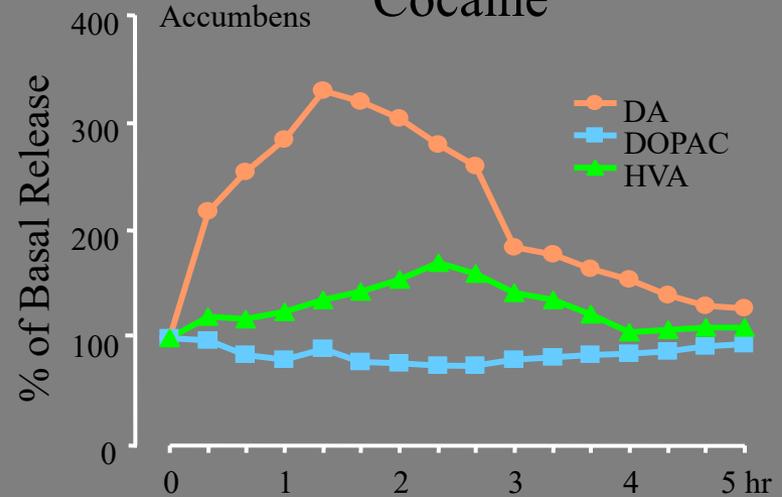
Effects of Drugs on Dopamine Release



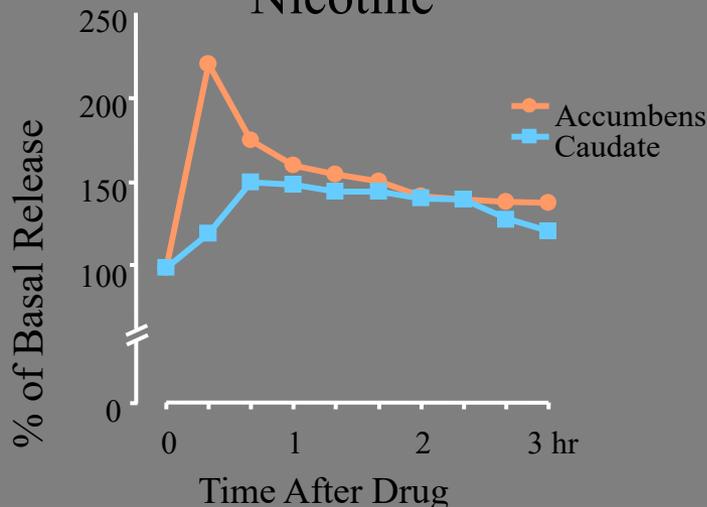
Amphetamine



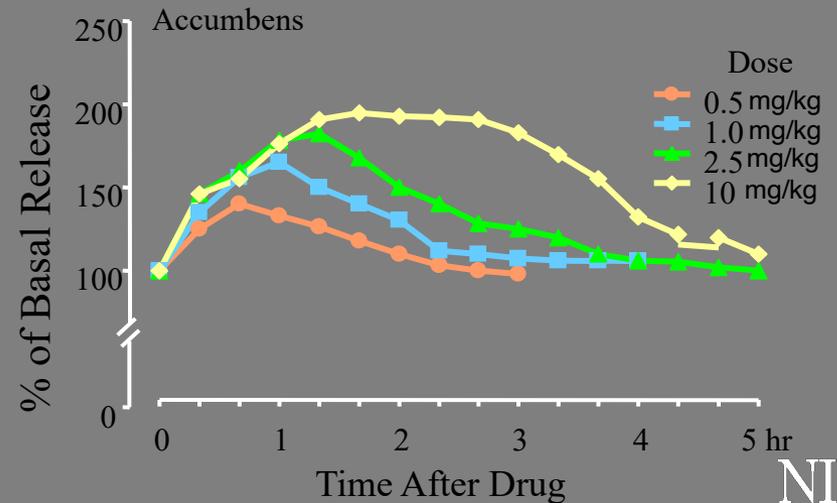
Cocaine



Nicotine



Morphine



NIDA

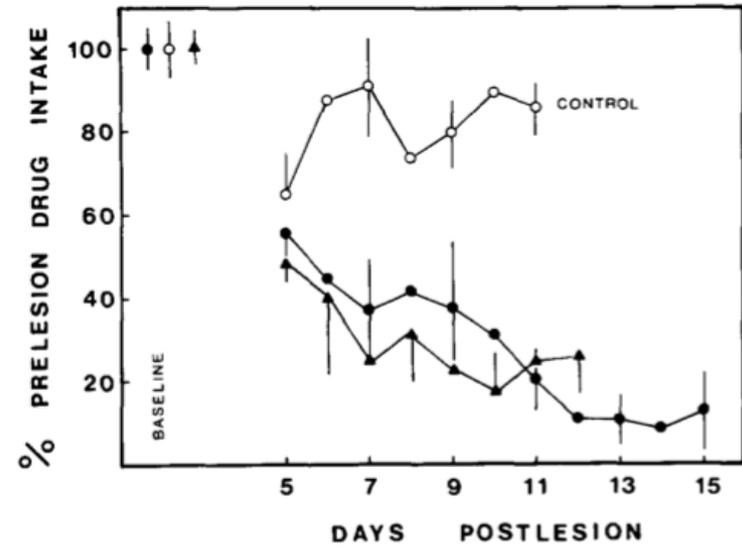
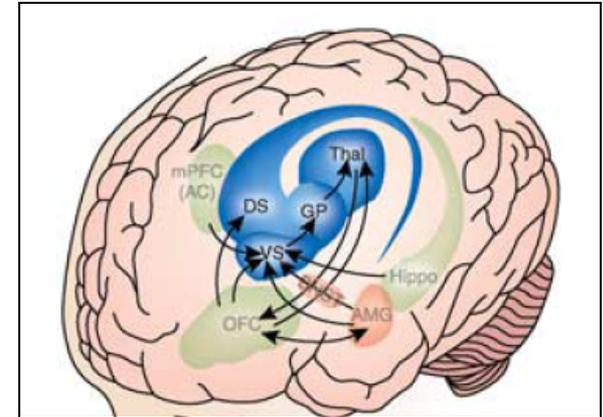
Di Chiara and Imperato, PNAS, 1988

www.mghcme.org

Reward



- enhanced dopamine in the NA is responsible for **acute high or initial reinforcing effects** of drugs of abuse.
- Drugs of abuse are able to **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.

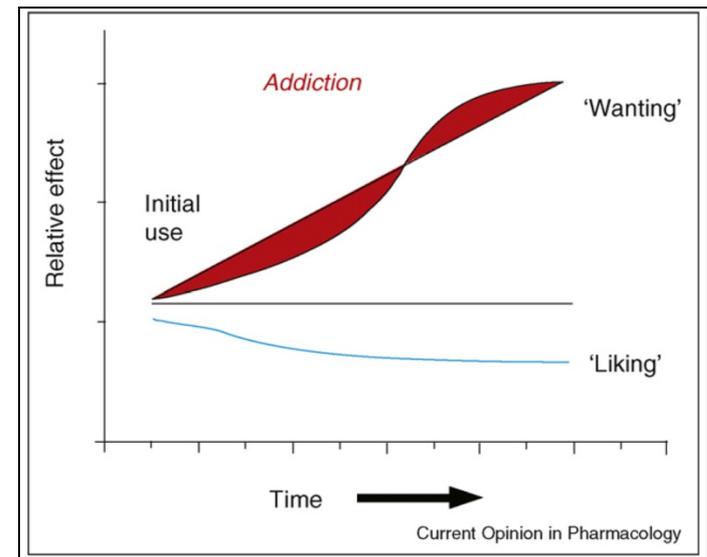


Roberts & Koob, 1980

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)

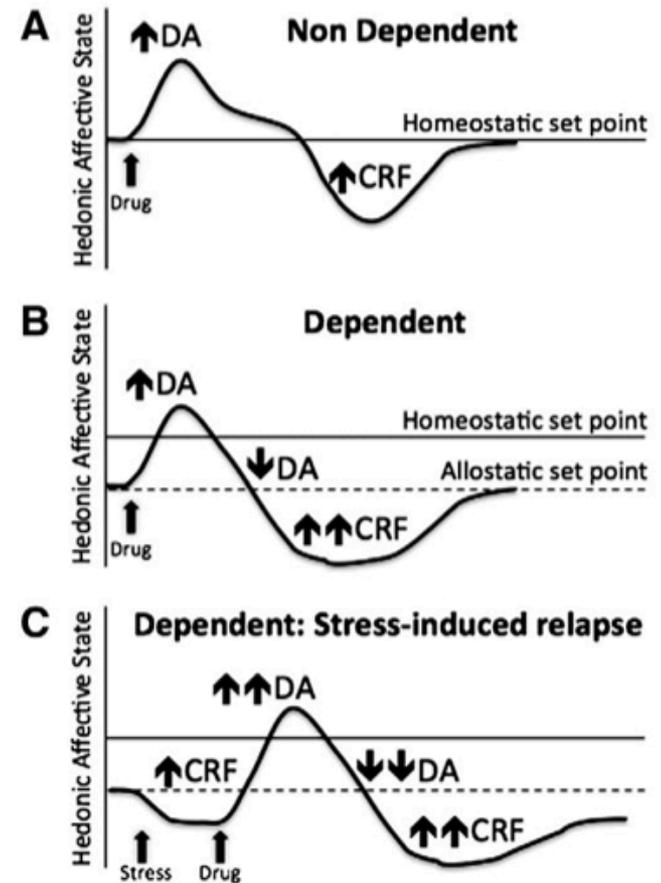
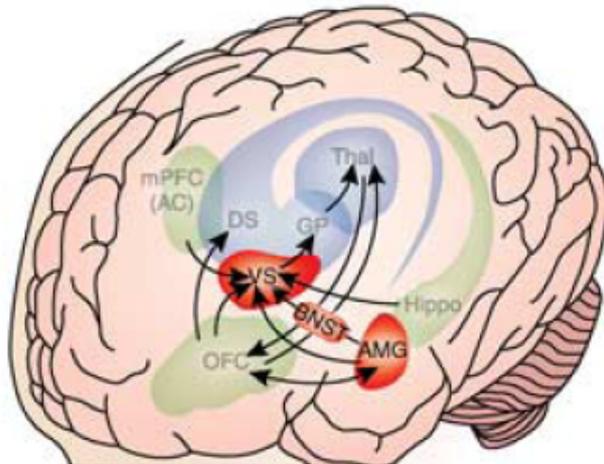


(Berridge et al., 2009)

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 corticotrophin releasing factor (CRF) in the amygdala

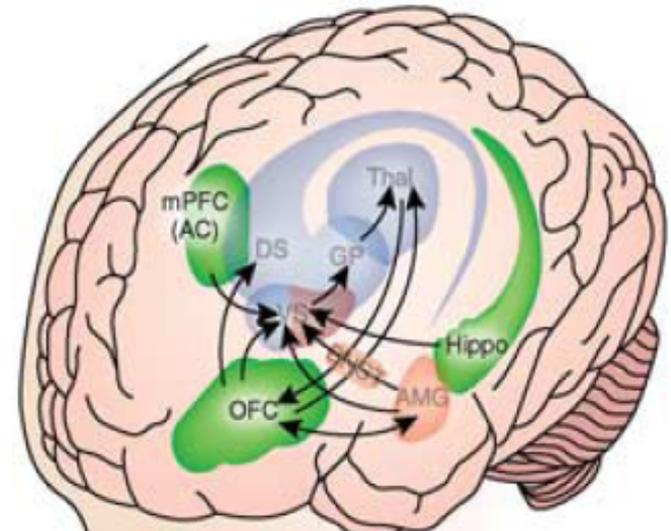


George, Le Moal, and Koob,
2012

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



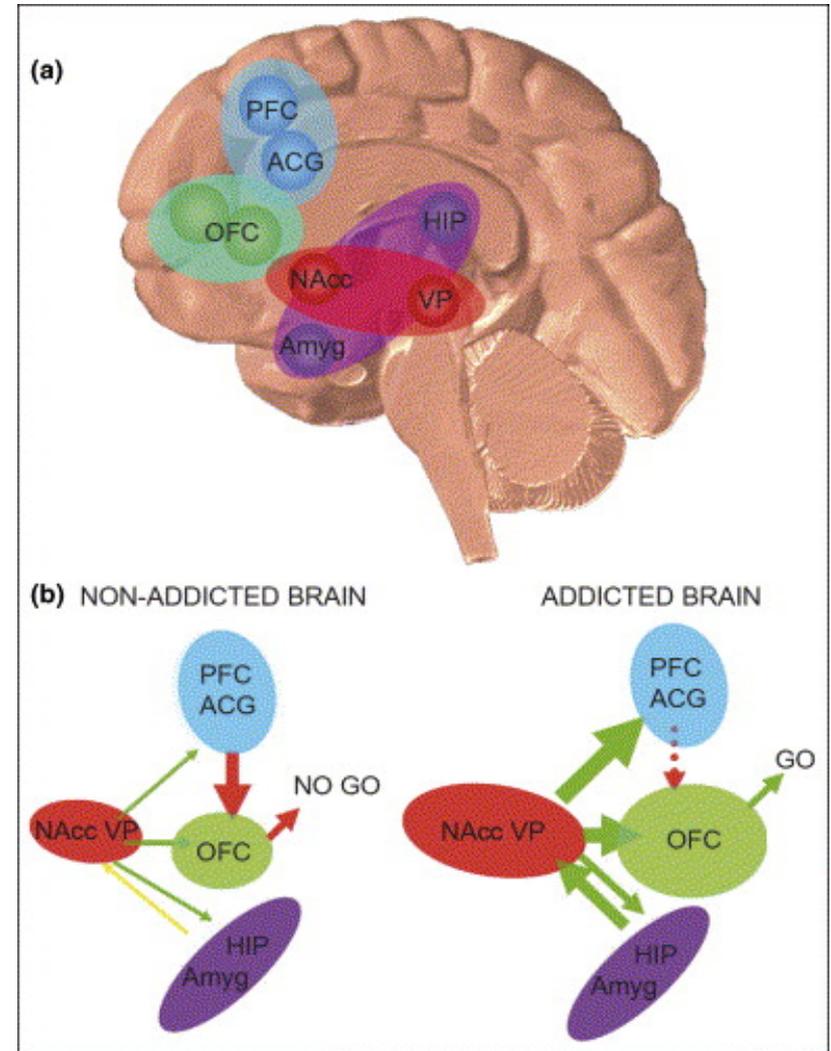
Abnormal Activity in Two Brain Systems:



- 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?



- 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

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

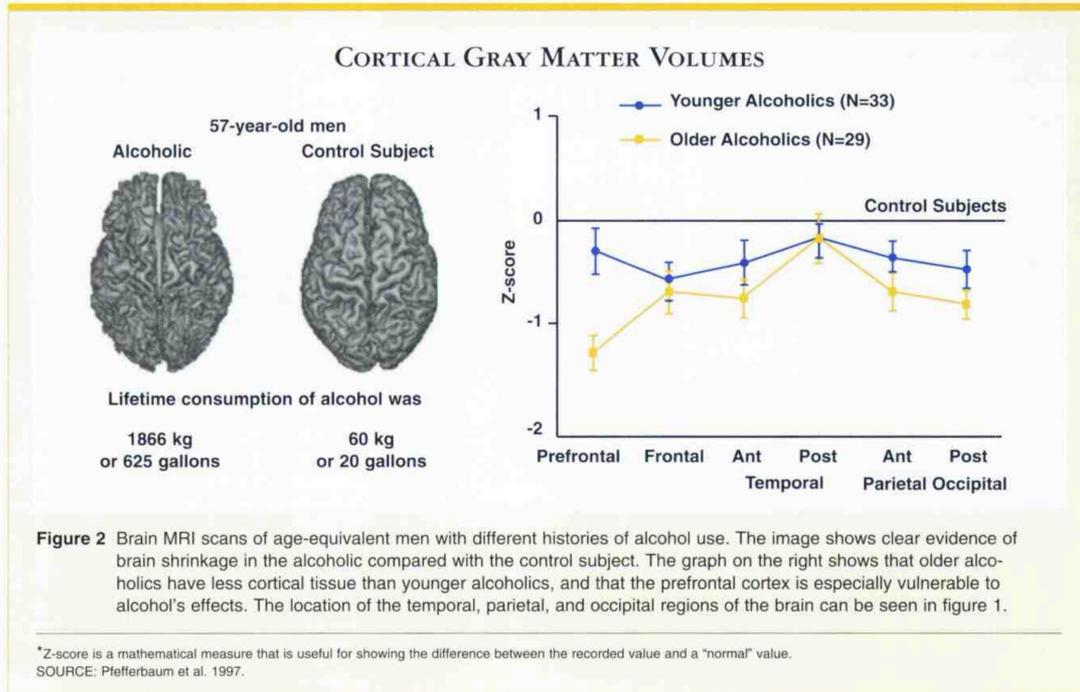
Volkow & Fowler, 2000; Koob & Volkow, 2010

Today's Talk

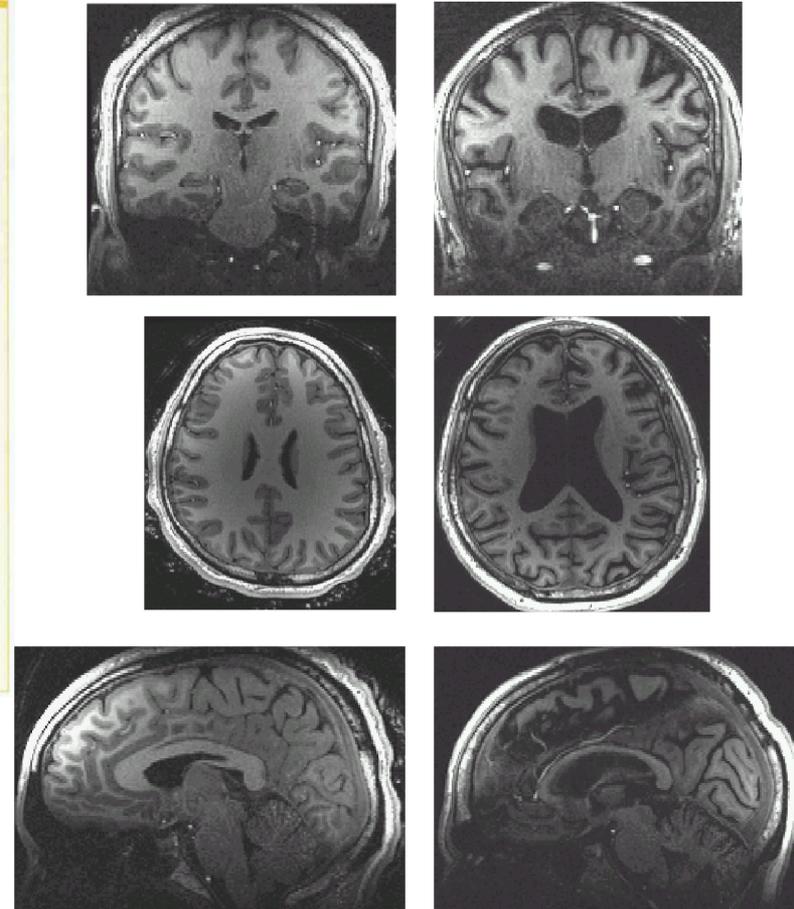


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Structural Effects of Addiction



Pfefferbaum et al. 1997



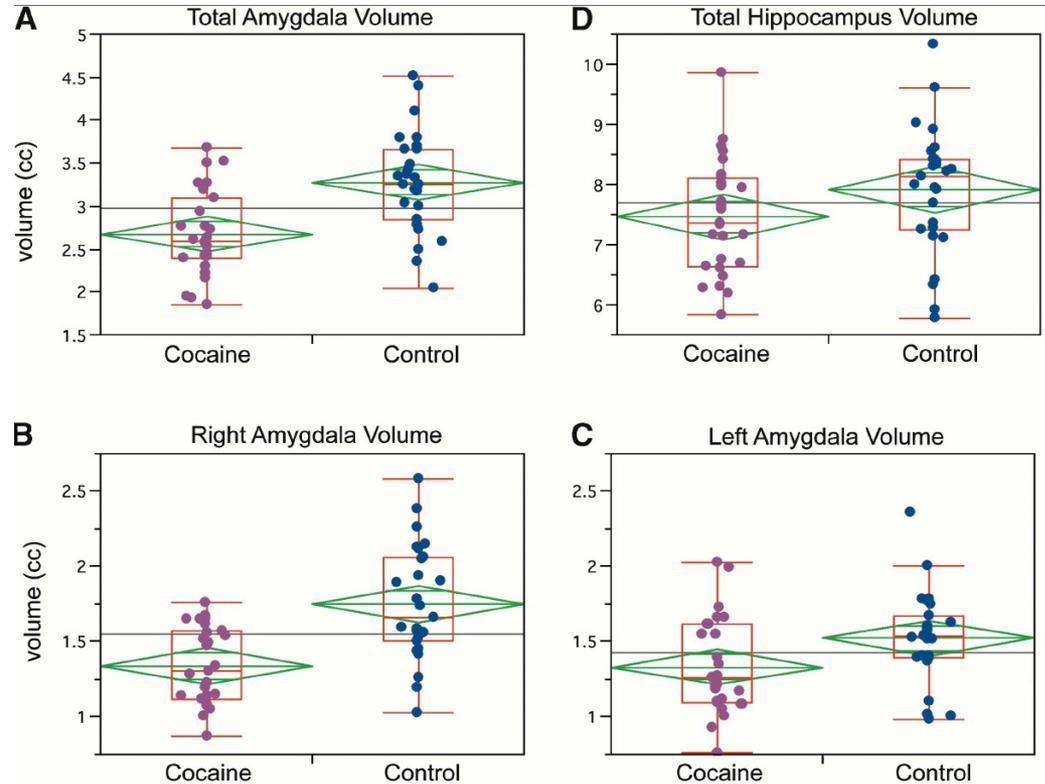
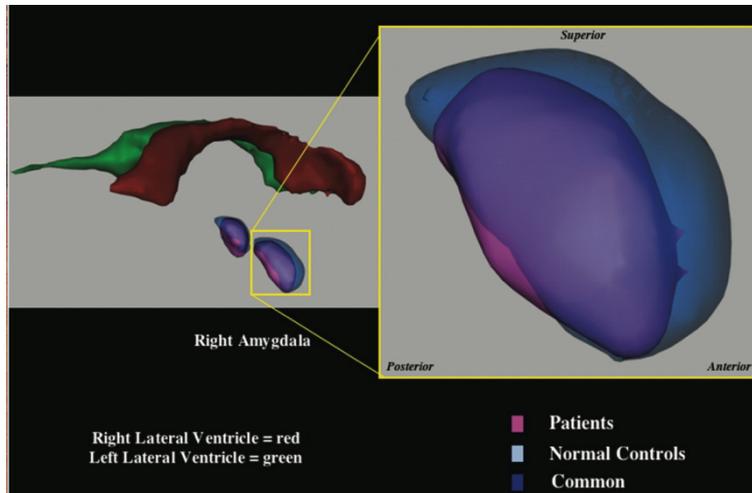
Control brain

Alcoholic brain

Gilman et al. 2008

www.mghcme.org

Reduction in Amygdala Size in Cocaine Users

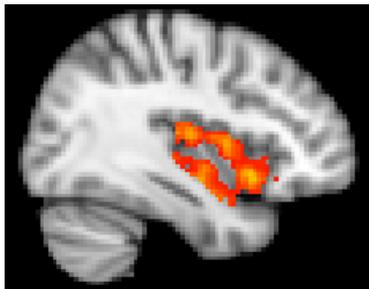


Makris et al. 2004

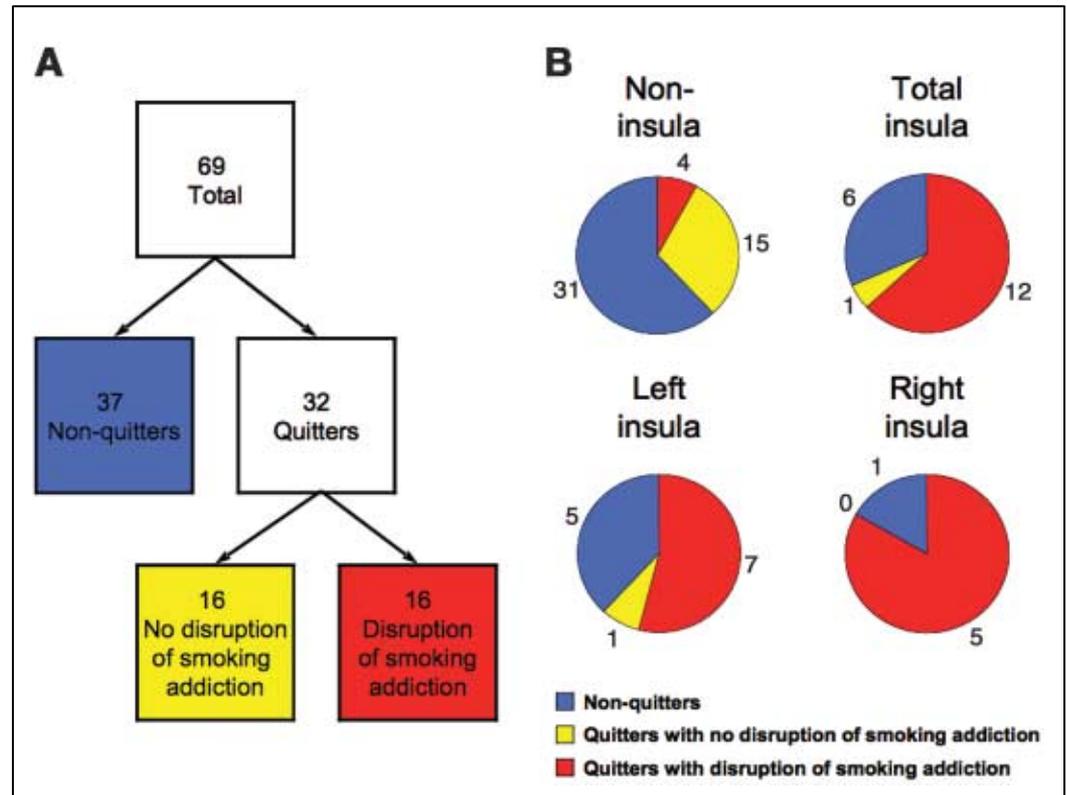
Certain brain regions such as the Insula are especially important in the maintenance of addictive behavior



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., *Science*, 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	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).

Today's Talk



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***Science Has Generated Much
Evidence Showing That...***

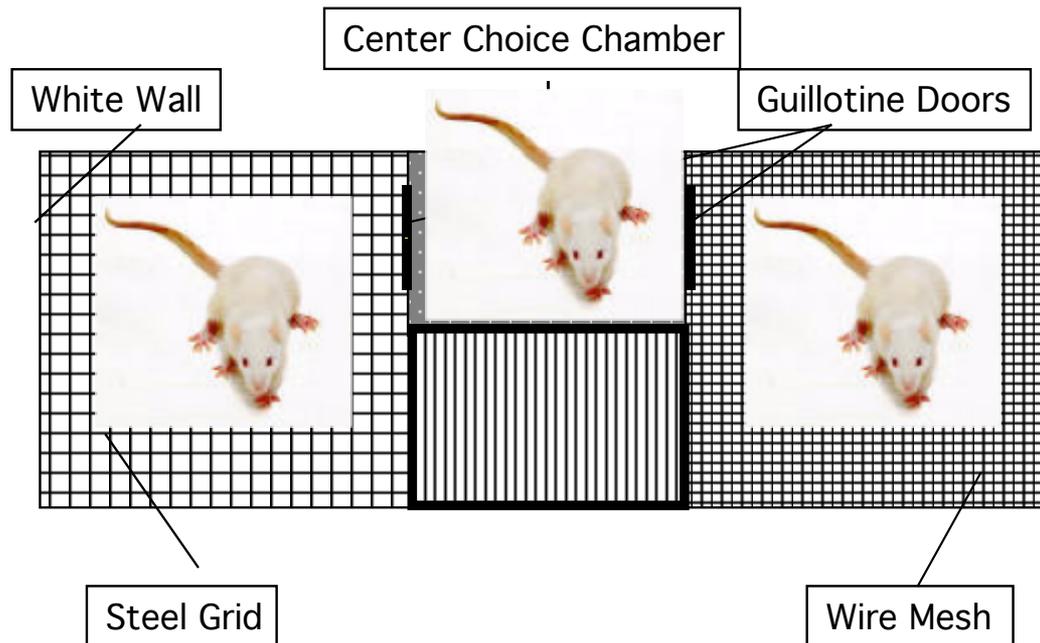
**Prolonged Drug Use Changes
the Brain In Fundamental
and Long-Lasting Ways**

NIDA

These changes are long-lasting



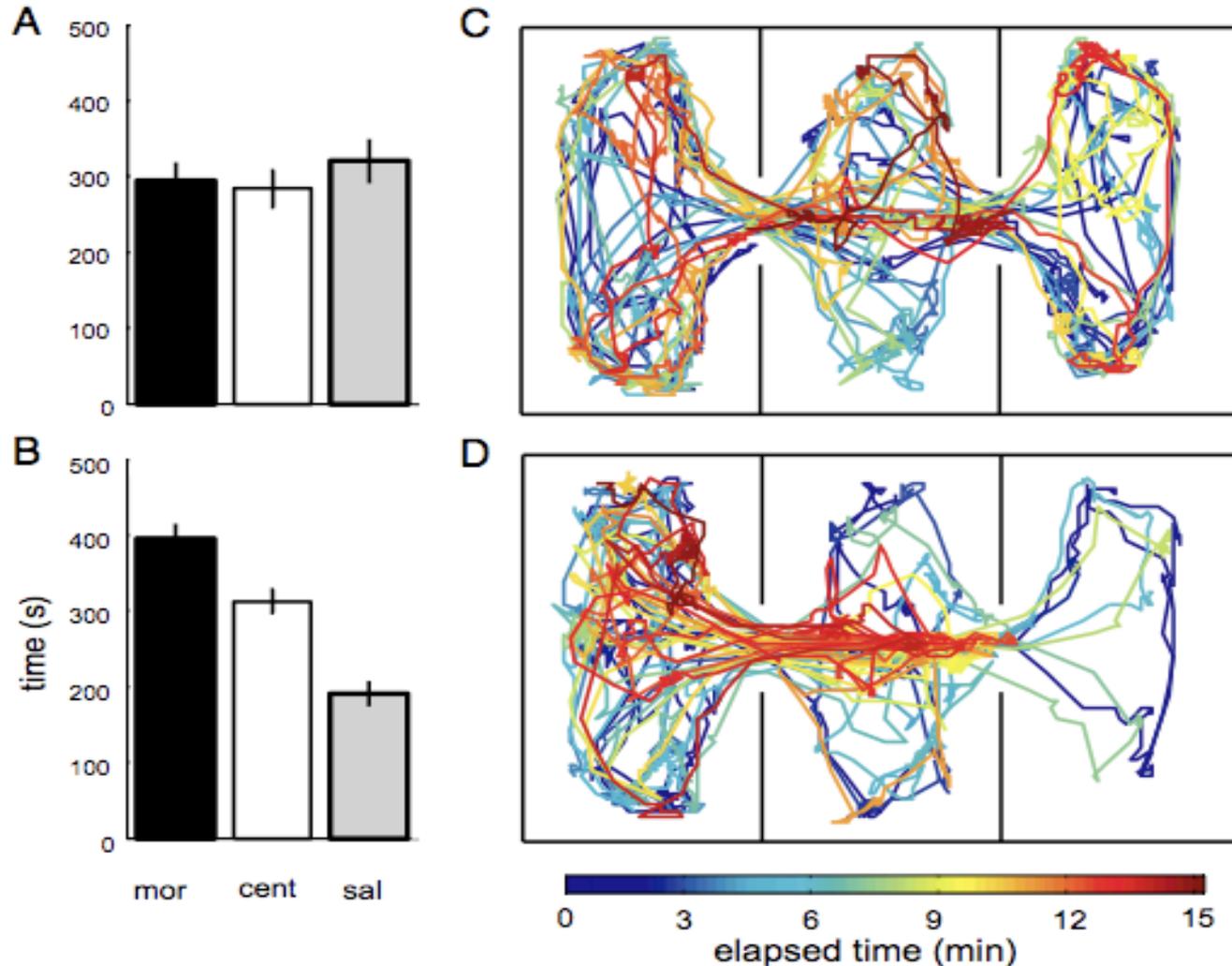
Conditioned Place Preference



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



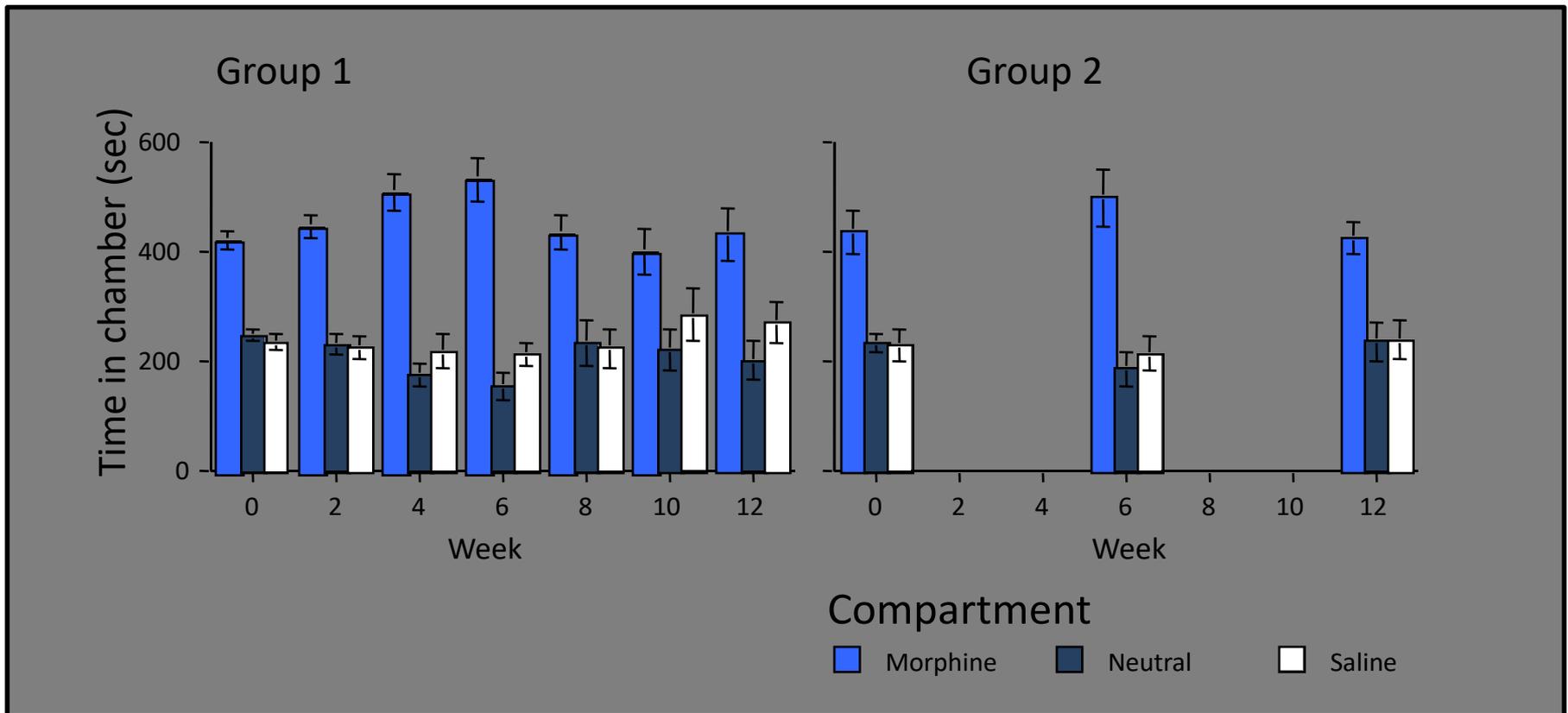
S.C.



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

Who Gets Treatment??

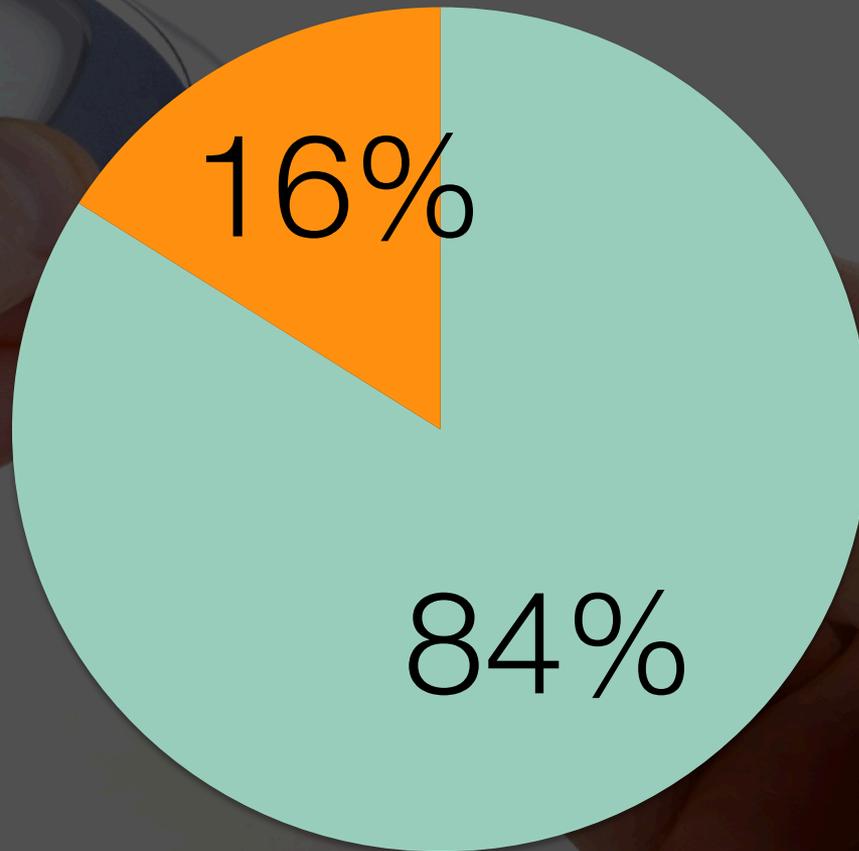


8.3% of Americans have diabetes





■ Any diabetes treatment ■ No treatment



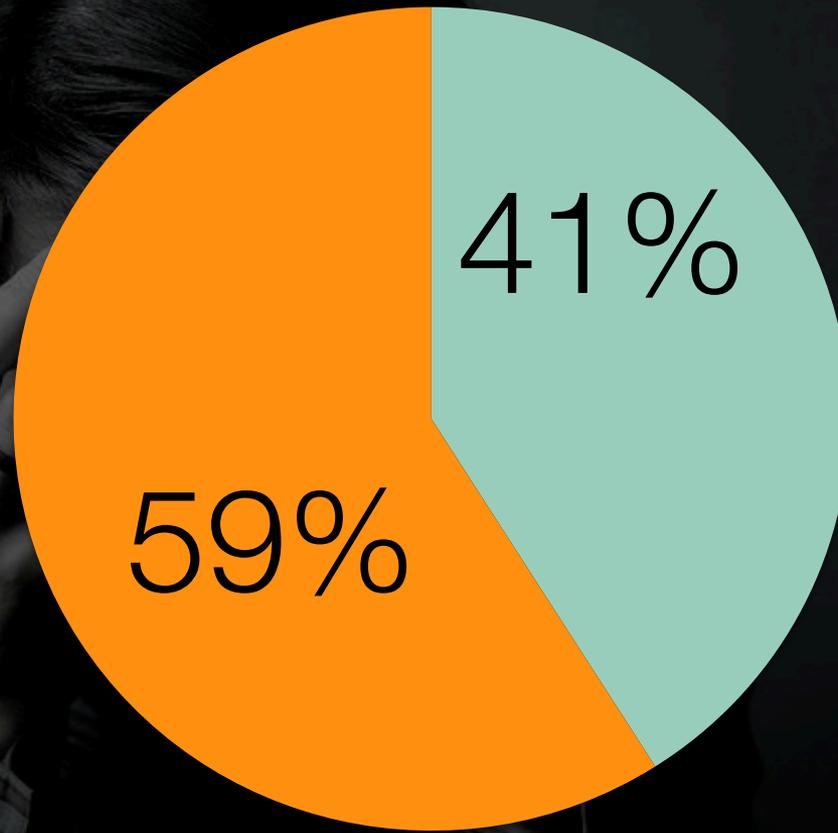


9.5% of Americans have
a mood disorder in a
given year





■ Any MH treatment ■ No treatment



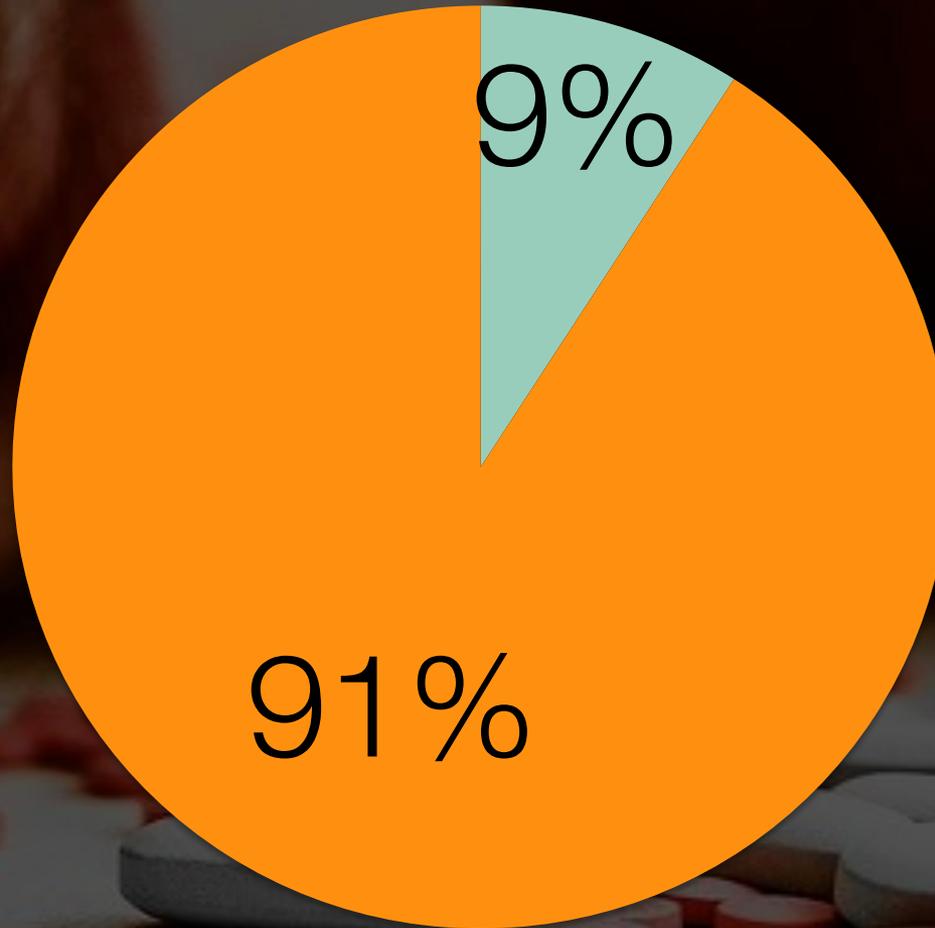


7.4% of Americans have a
substance use disorder in a
given year





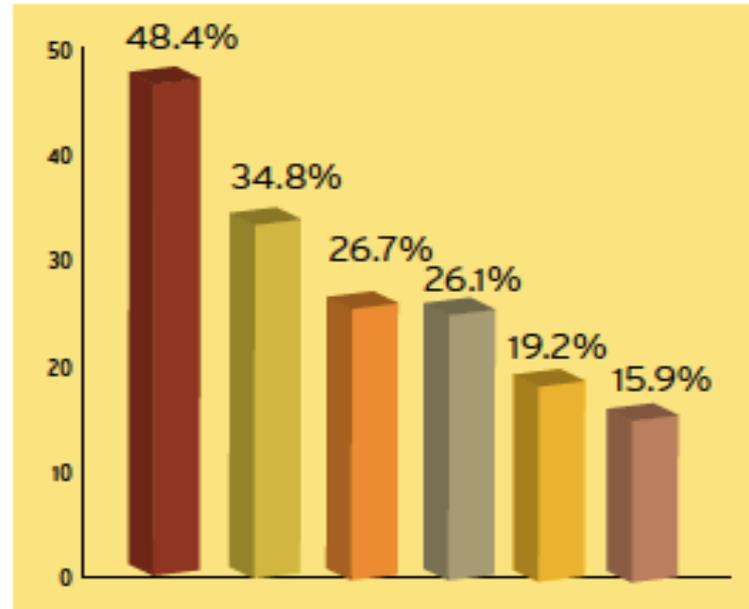
■ Any addiction treatment ■ No treatment



WHY?? 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]

WHY?? Not enough doctors! (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

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

NIDA



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

NIDA



MASSACHUSETTS
GENERAL HOSPITAL

PSYCHIATRY ACADEMY

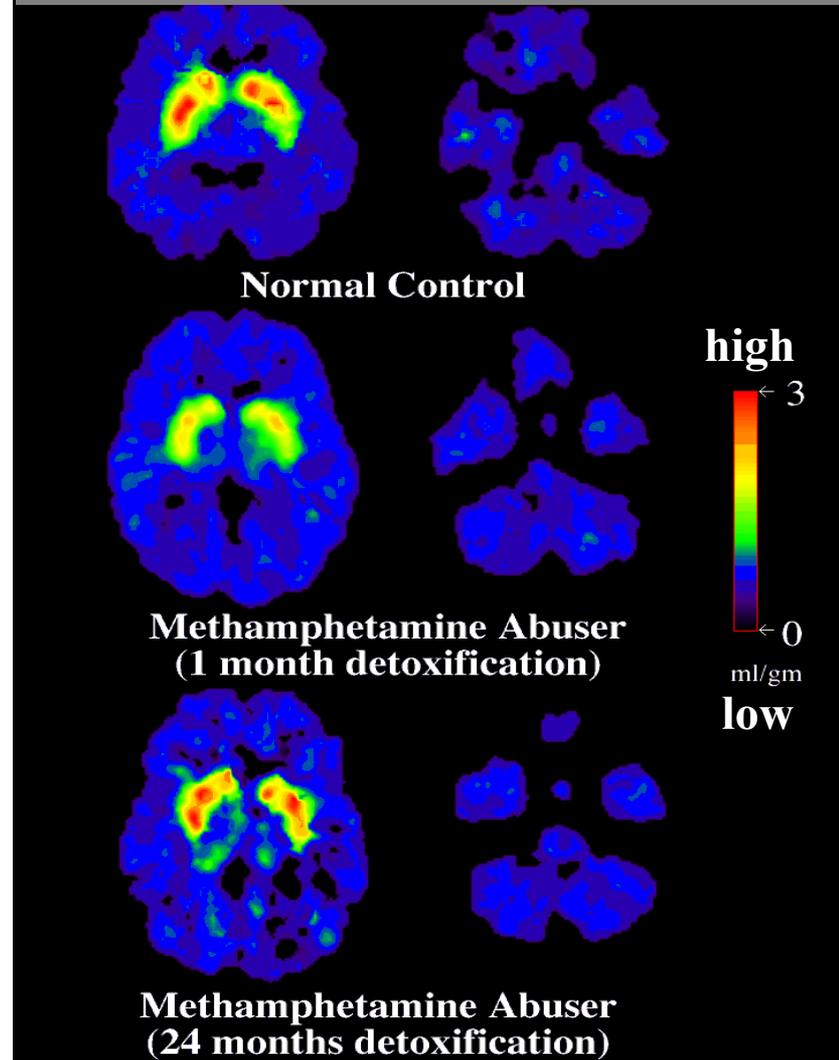
www.mghcme.org



[C-11]d-threo-methylphenidate

*It takes time, but
the brain can
recover*

DAT Recovery
with prolonged
abstinence from
methamphetamine



Volkow et al., *J. Neuroscience*, 2001.

Conclusions



- 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!!!