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The Science of Addiction

CRIT/FIT 2016

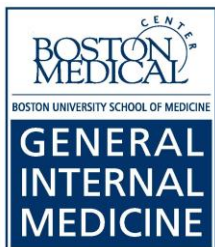
April 24-27, 2016

Daniel P. Alford, MD, MPH

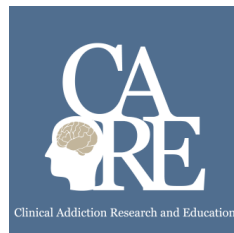
Associate Professor of Medicine

Assistant Dean, Continuing Medical Education

Director, Clinical Addiction Research and Education (CARE) Unit



Boston University School of Medicine



Agenda

- Definitions
- Trends in Substance Use, Use Disorders, Overdoses
- Understanding Addiction
- Prevention and Treatment
- And more...

Substance Use Disorder

Substance Use Disorder a diagnostic term in DSM-5 recurrent use of alcohol or other drugs causing significant impairment, such as health problems, disability and failure to meet major responsibilities.

It combines the DSM-IV categories of **substance abuse** and **dependence** into a single disorder measured on a continuum from **mild, moderate, or severe**.

Each specific substance is addressed as a separate use disorder, diagnosed based on the same overarching criteria.

Addiction

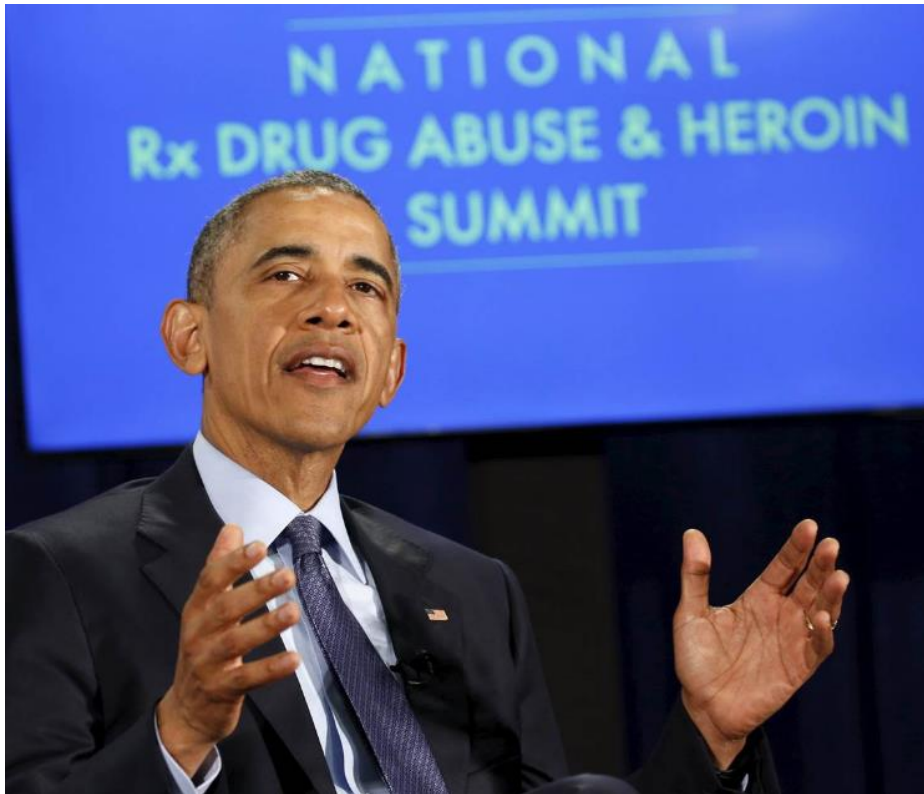
Addiction indicates the most severe, chronic stage of Substance Use Disorder (synonymous with “**severe Substance Use Disorder**”)

It is a primary, chronic disease of the brain reward, motivation, memory and related circuitry.

Like other chronic diseases, addiction often involves cycles of relapse and remission. Without treatment, addiction is progressive and can result in disability or premature death.

National Priority

Obama Seeks \$1 Billion to Fight Drug Abuse



“...the only way we reduce demand is if we're providing treatment and thinking about this as public health problem...”

March 26, 2016

Some Important Organizations (Acronyms)



- **NIDA** (National Institute on Drug Abuse)
 - part of NIH supports and conducts biomedical and behavioral research on the causes, consequences, treatment, and prevention research on drug abuse and addiction



- **NIAAA** (National Institute on Alcohol Abuse and Alcoholism)
 - part of NIH, supports and conducts biomedical and behavioral research on the causes, consequences, treatment, and prevention of alcoholism and alcohol-related problems

Some Important Organizations (Acronyms)

- **SAMHSA** (Substance Abuse and Mental Health Services Administration)



- a branch of the U.S. Department of Health and Human Services charged with improving the quality and availability of prevention, treatment, and rehabilitative services for substance abuse and mental illnesses

- **ONDCP** (Office of National Drug Control Policy)

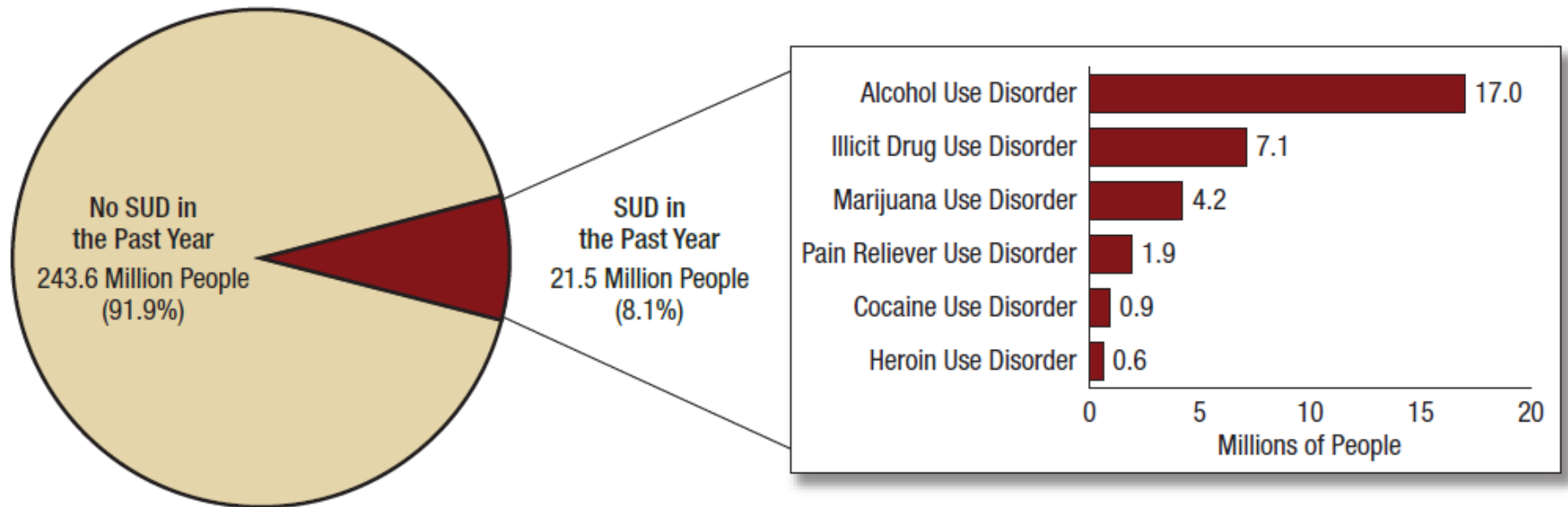


- a former cabinet-level component of the Executive Office of the President, was established in 1989 with the goal to establish policies, priorities, and objectives to eradicate illicit drug use, manufacturing, and trafficking, drug-related crime and violence, and drug-related health consequences

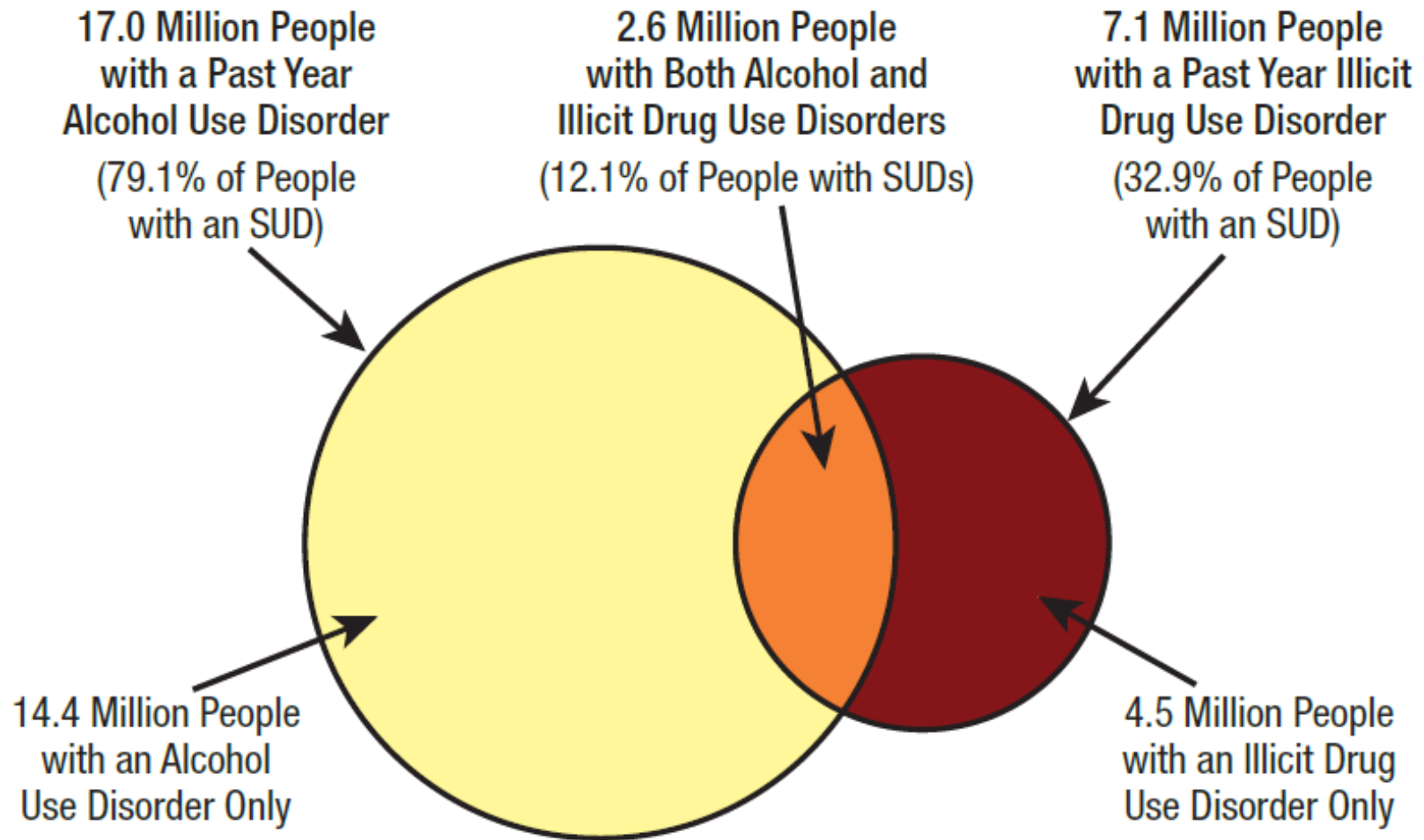
Trends: Sources of Data

- **National Survey on Drug Use and Health (NSDUH)**
 - annual since 1971 SAMHSA survey on use of illicit drugs, alcohol, and tobacco in the US civilian, noninstitutionalized population aged ≥ 12 years. Questionnaires to a representative sample of the population through face-to-face interviews at their place of residence obtained from approximately 67,500 individuals.
- **Monitoring the Future (MTF)**
 - annual since 1975 NIDA funded survey of 8th, 10th, and 12th graders measuring drug, alcohol, and cigarette use by the University of Michigan. The 2015 MTF survey involved about 44,900 8th-10th-, and 12th-grade students in 382 secondary schools

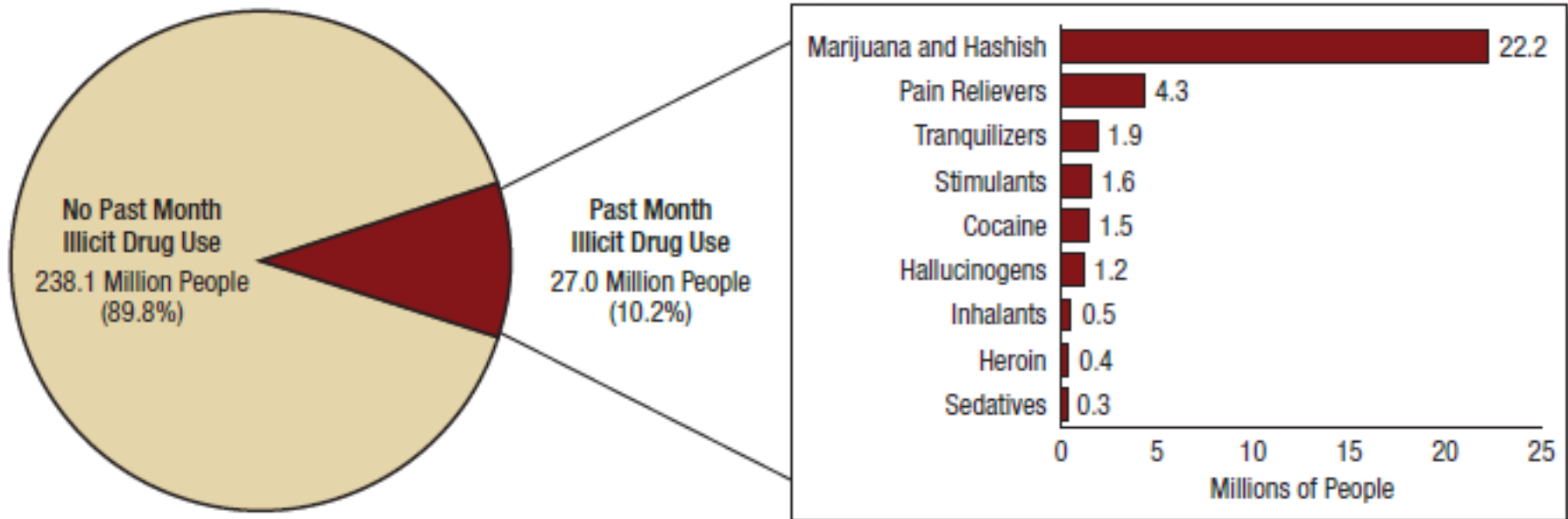
Past Year Substance Use Disorder: 2014



Past Year Substance Use Disorder: 2014

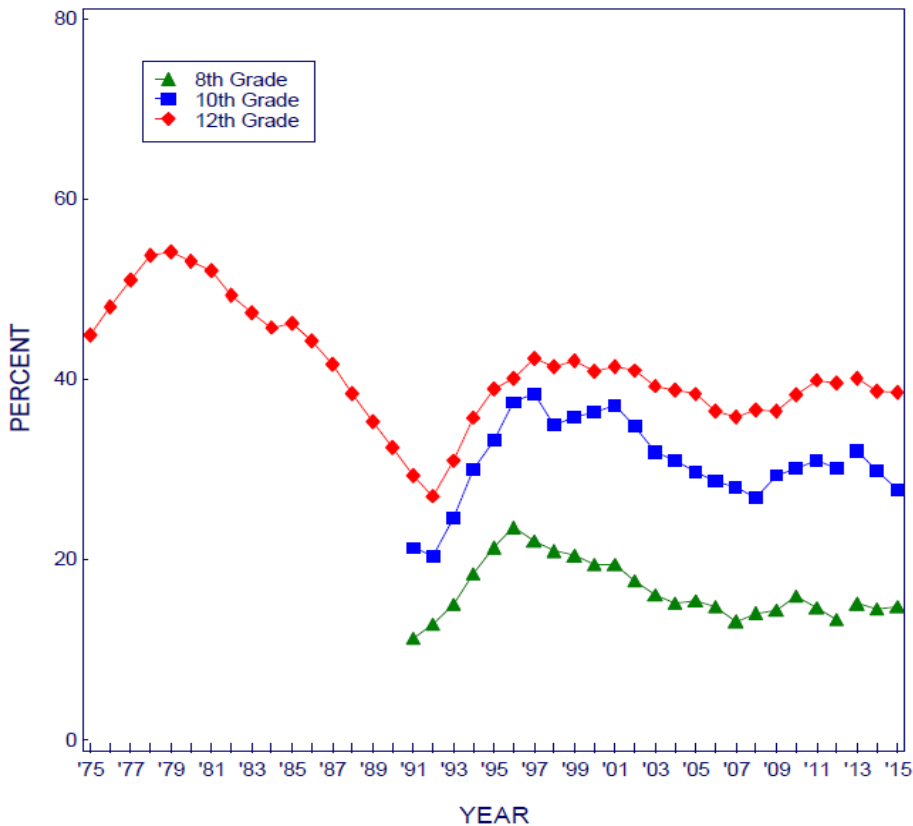


Past Month Illicit Drug Use: 2014

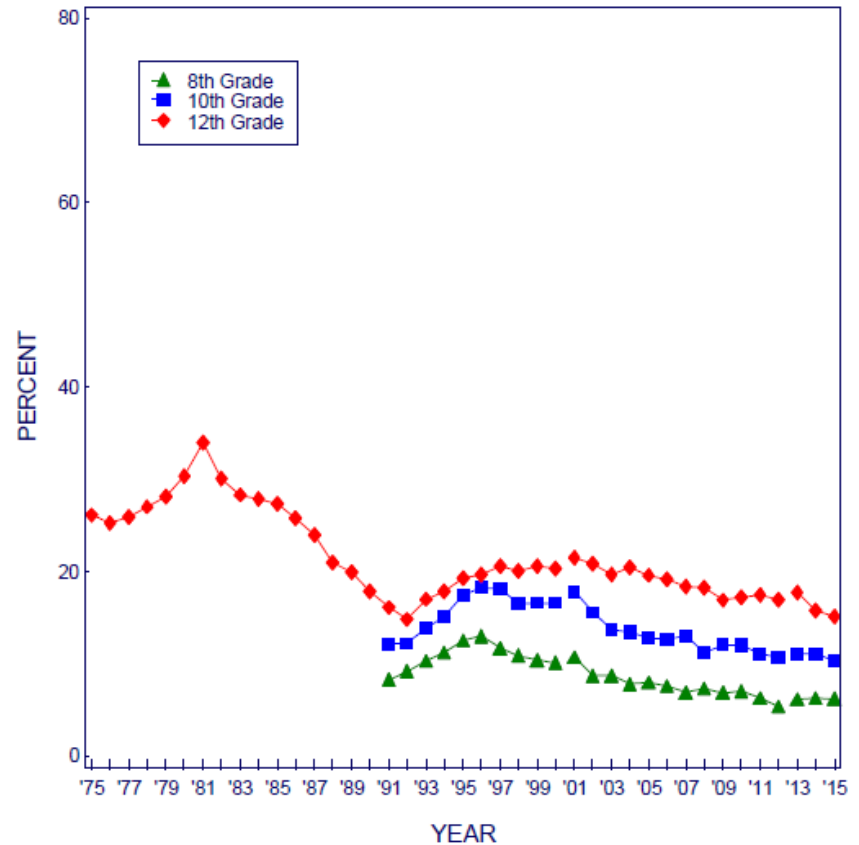


Trends in Annual Prevalence of Illicit Drug Use by Teens

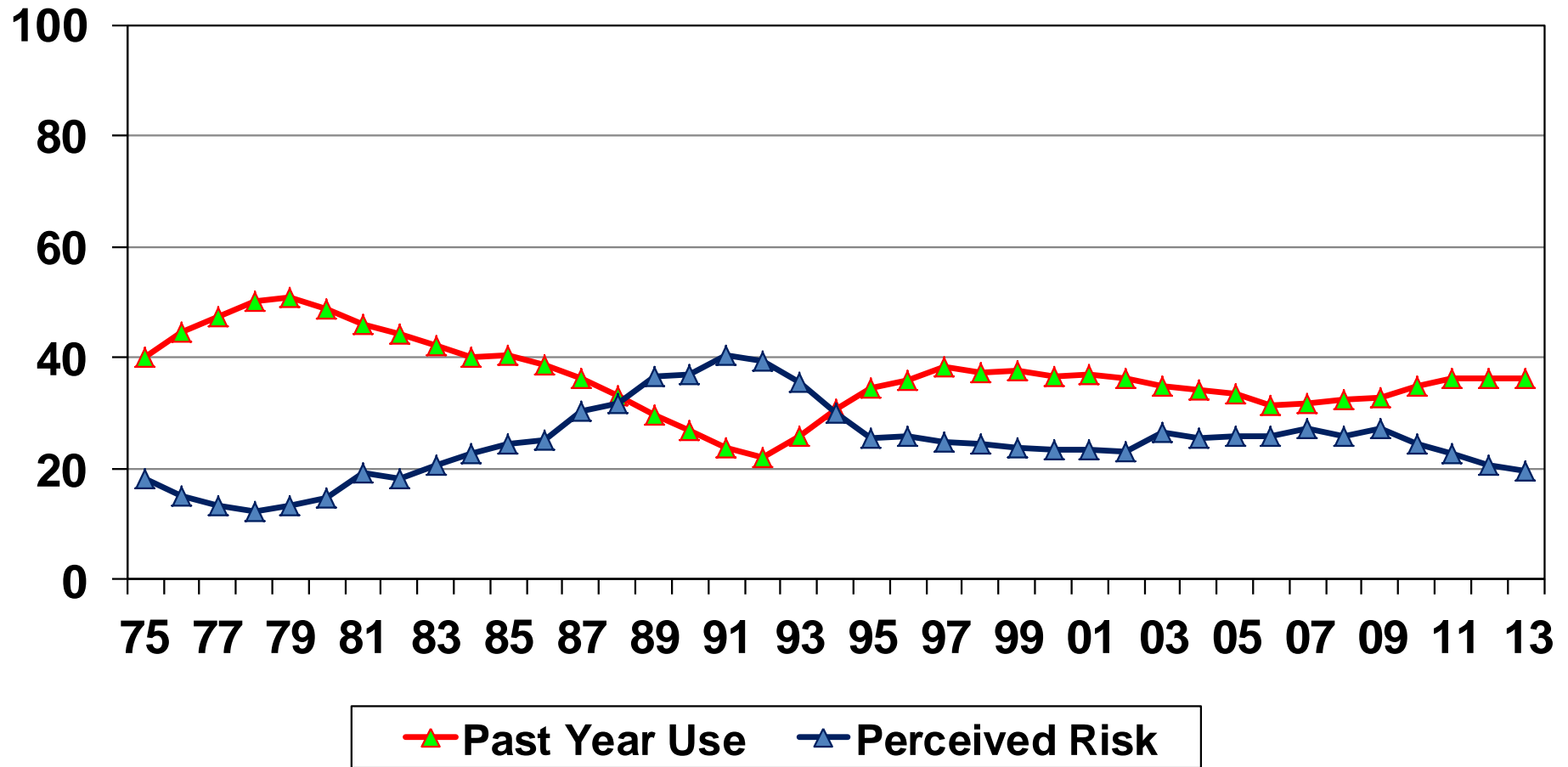
Illicit Drug Use



Illicit Drug Use *excluding* Marijuana



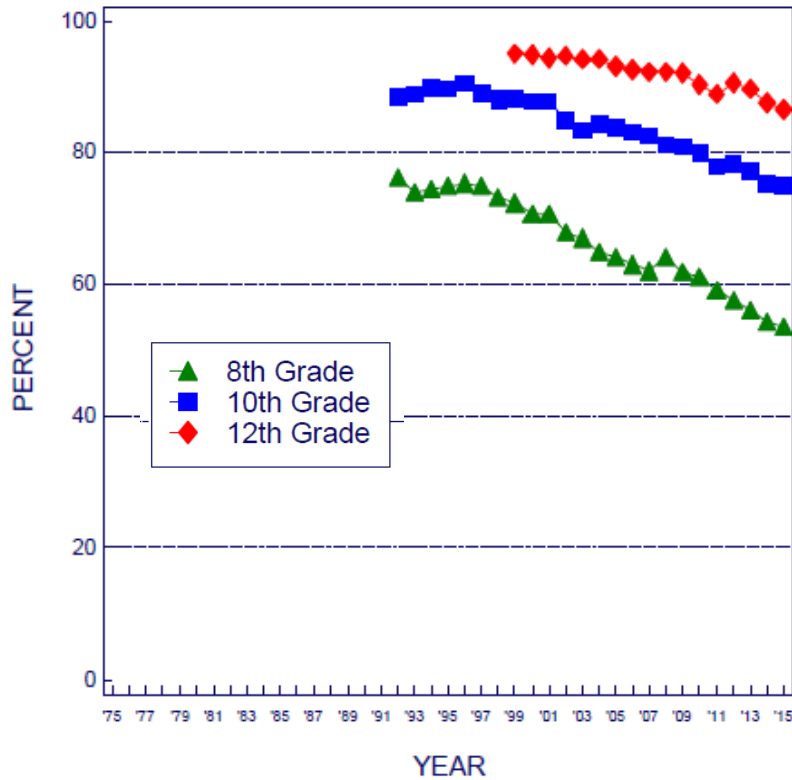
12th Graders' Past Year Marijuana Use vs. Perceived Risk of Occasional Marijuana Use



Alcohol and Marijuana Availability to Teens

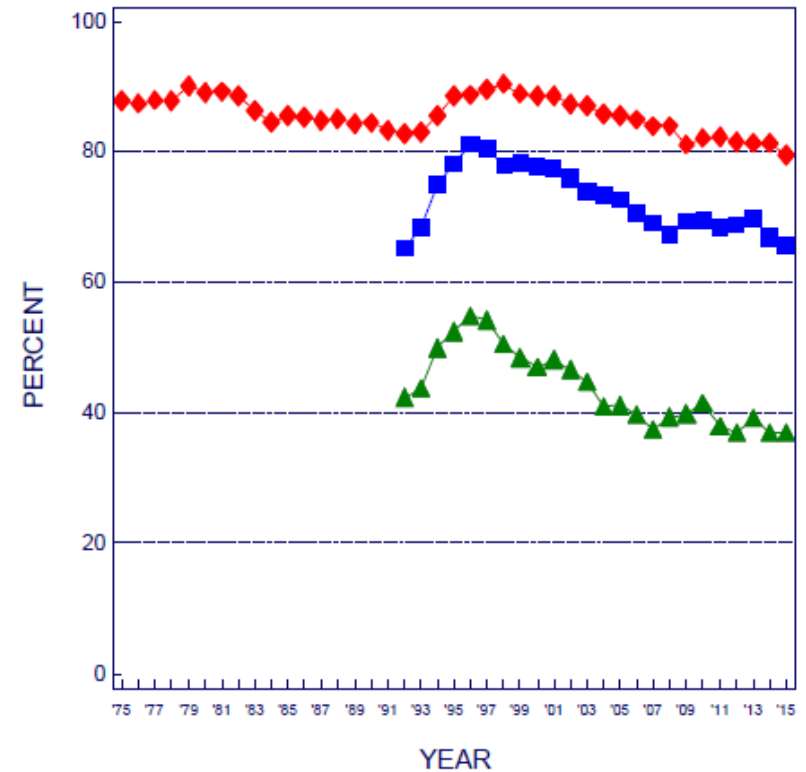
Alcohol

% saying "fairly easy" or "very easy" to get

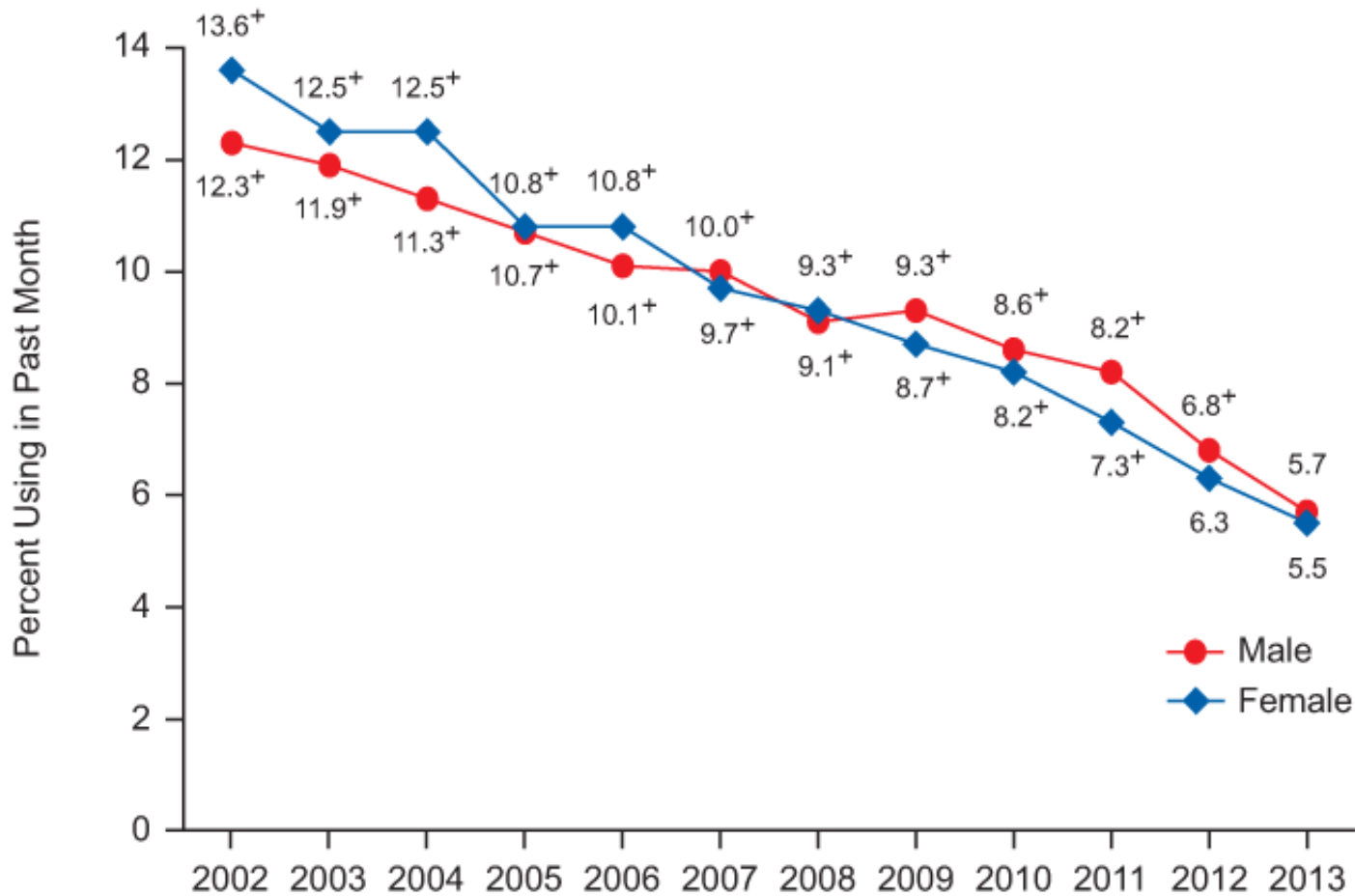


Marijuana

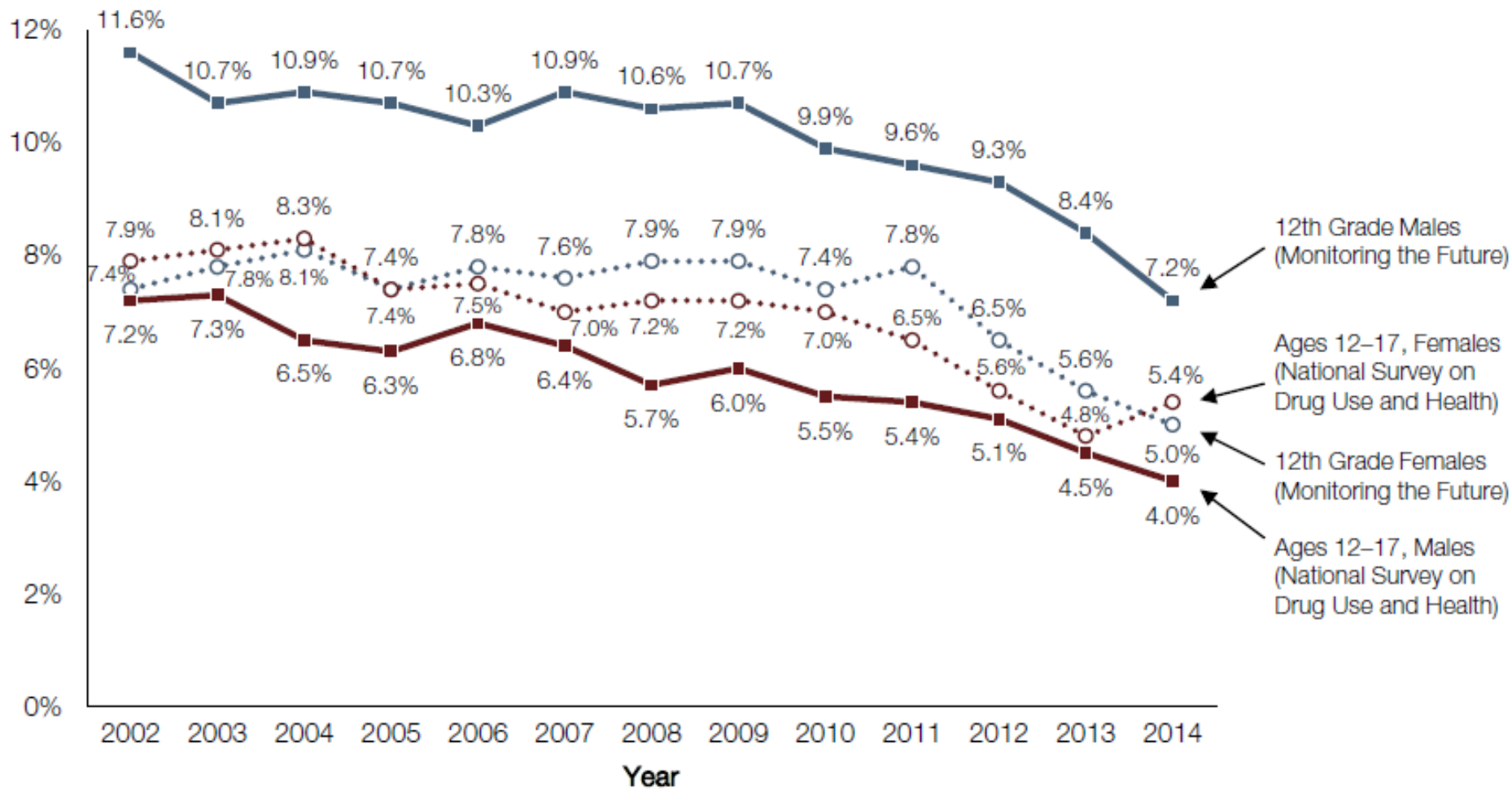
% saying "fairly easy" or "very easy" to get



Past Month Cigarette Use among Youth Aged 12-17



Past Year Nonmedical Use of Pain Relievers Among Adolescents (2002–2014)

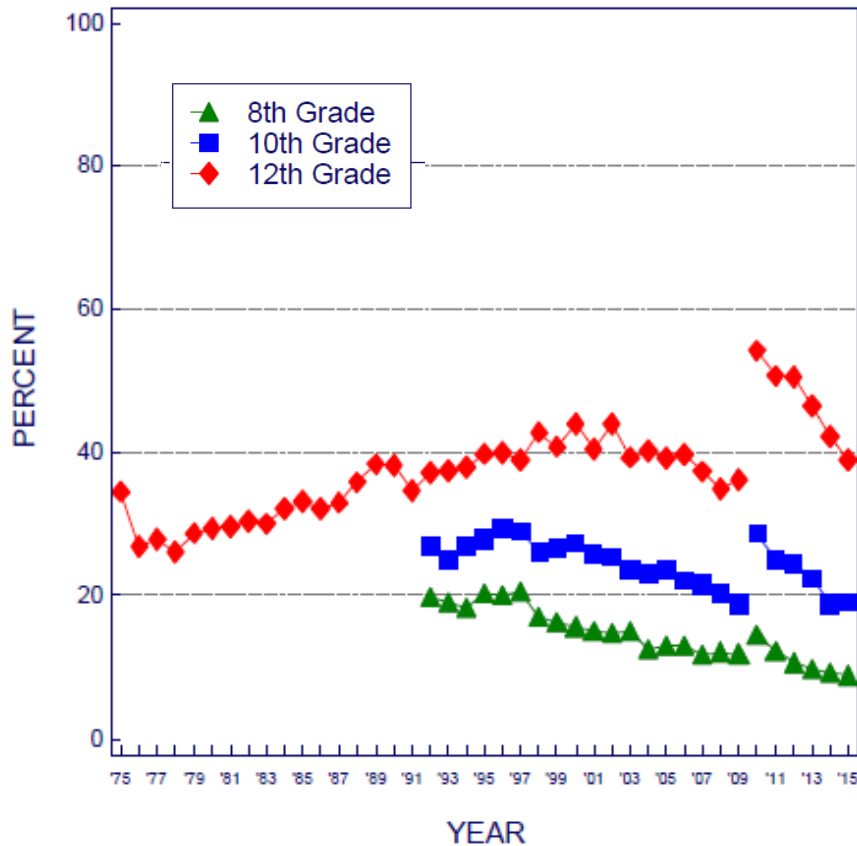


NSDUH 2002–2014
MTF 2002–2014

Prescription Drug Availability to Teens

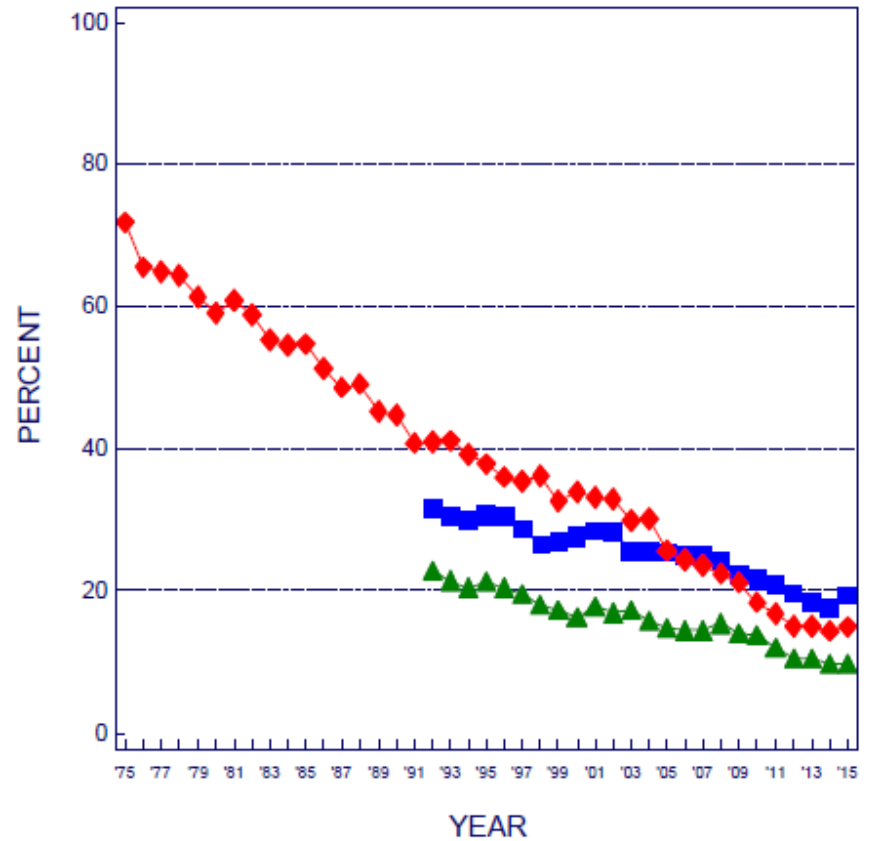
Prescription Opioids

% saying "fairly easy" or "very easy" to get

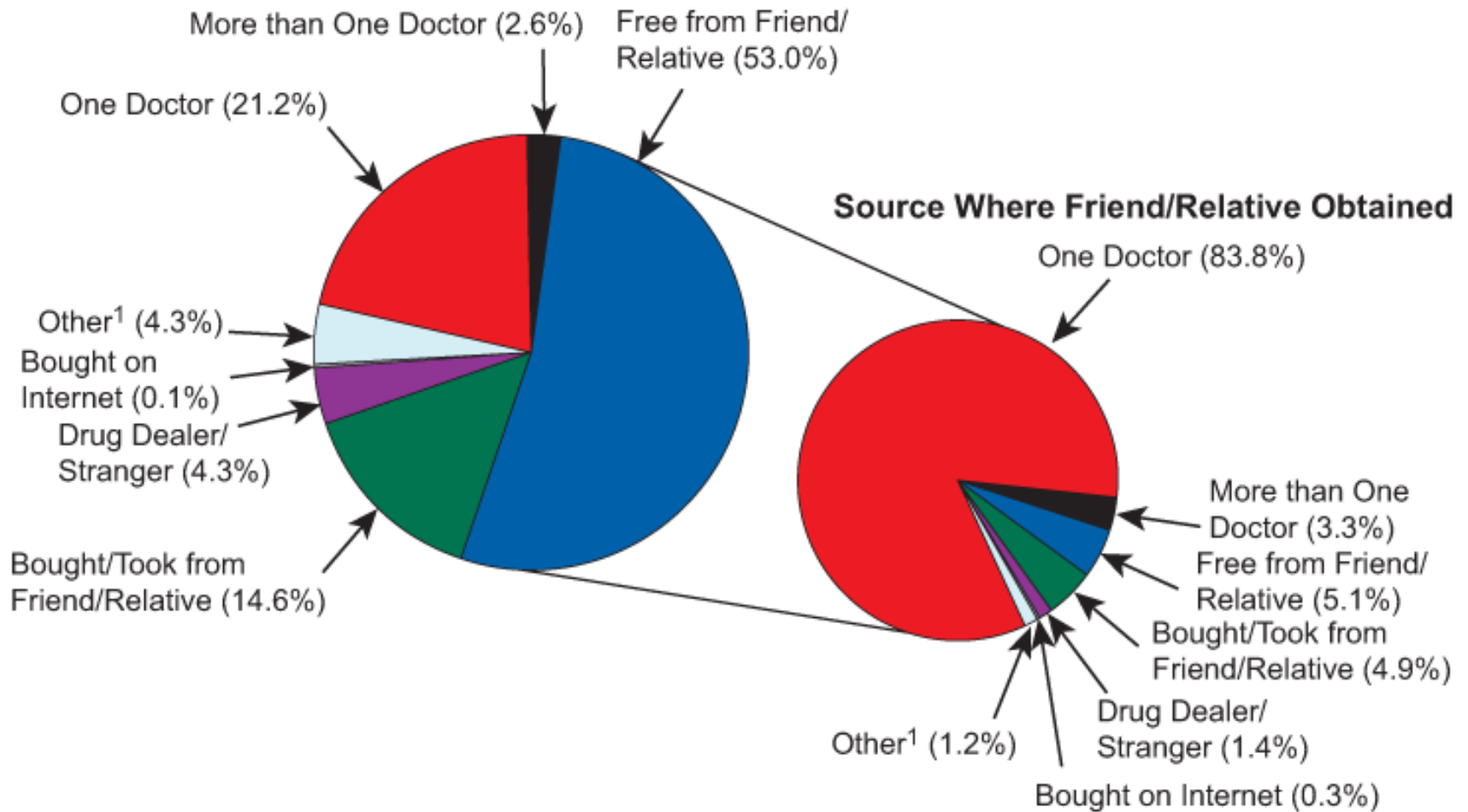


Prescription Benzodiazepines

% saying "fairly easy" or "very easy" to get

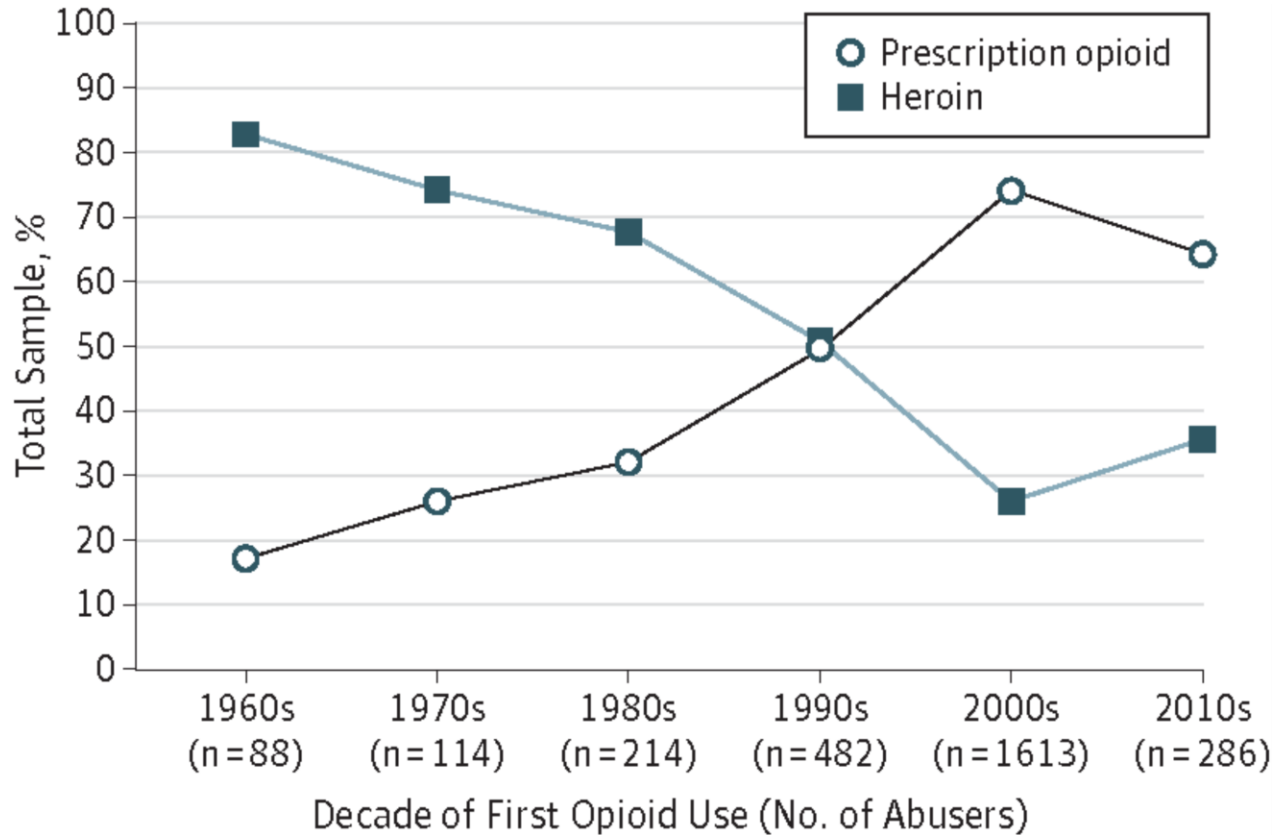


Where Prescription Opioids Used Non-Medically Were Obtained



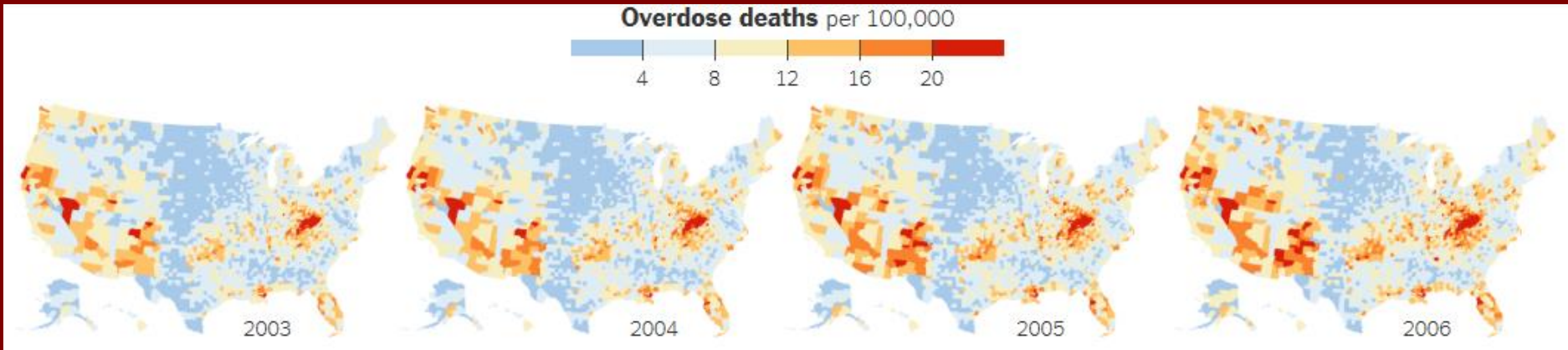
Shifting Pattern of Heroin vs. Prescription Opioid

Percentage of Heroin-Addicted Treatment Admissions that Used Heroin or Prescription Opioid as First Opioid



- 1960s: >80% started with heroin
- 2000s: 75% started with prescription opioids
- 2010-2013: Increasing initiation with heroin

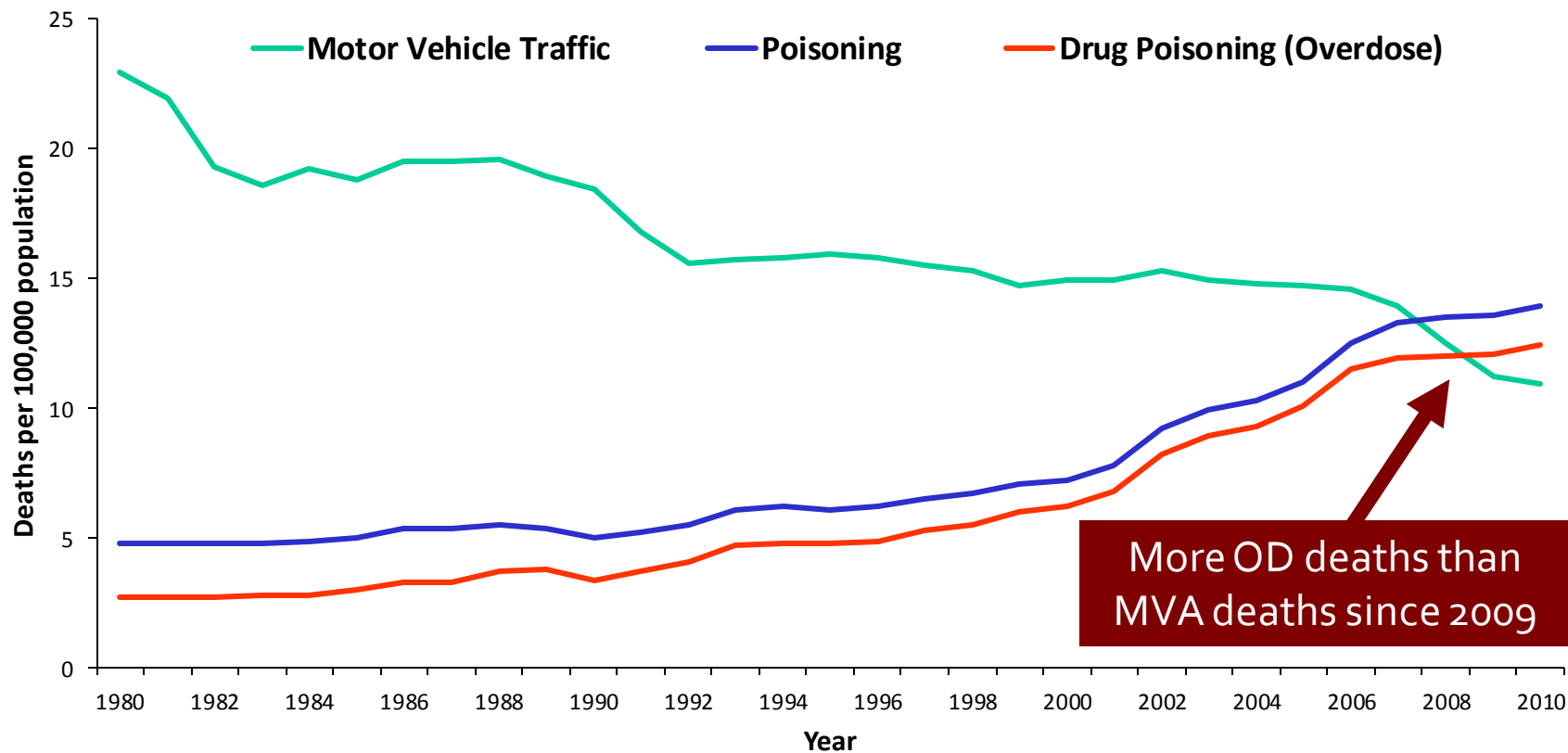
Opioid Overdose Deaths



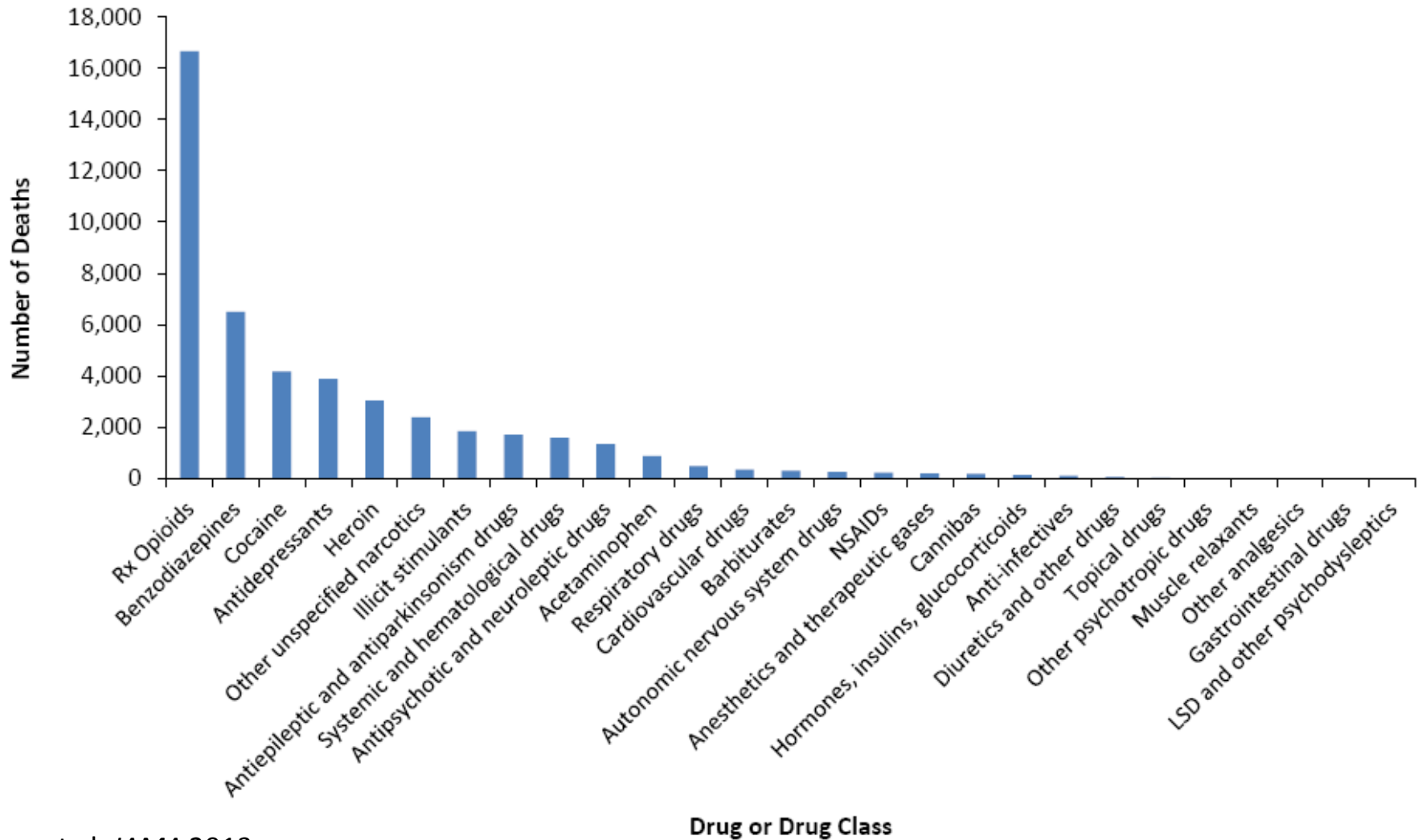
Opioids killed > 28,000 people in 2014

~50% opioid overdose deaths involve a prescription opioid

Drug Overdose Death Rates More Than Tripled Since 1990



Prescription Opioids: Primary Driver of Overdose Deaths



Jones, et al. *JAMA* 2013
CDC/NCHS NVSS MCOD 2010

Opioid Overdose Trends



CDC/NCHS National Vital Statistics System NCHS Data Brief, No. 190, March 2015

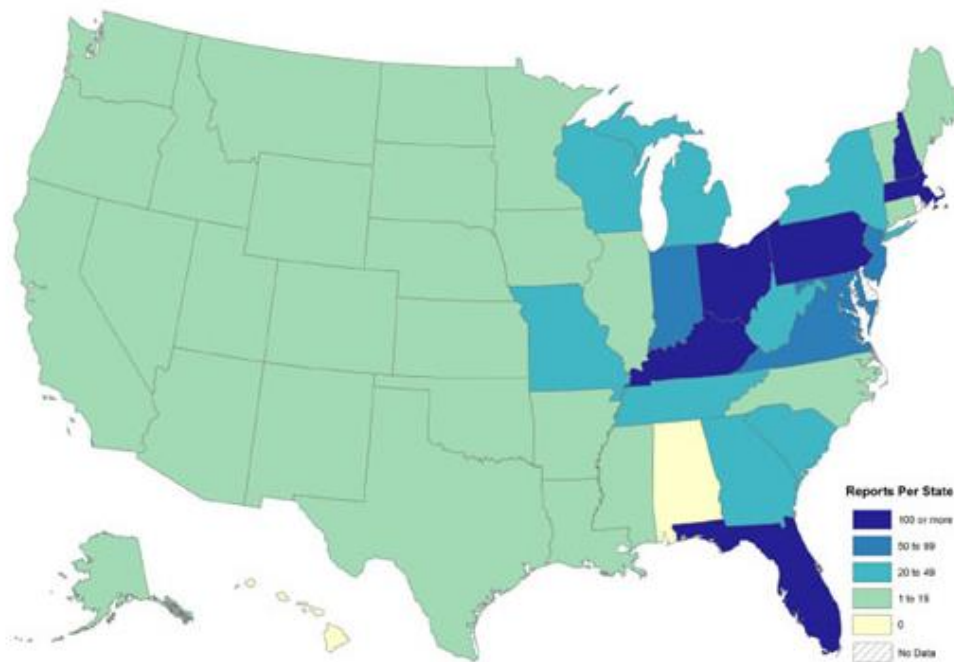
Dart RC et al. *N Engl J Med.* 2015

Larochelle et al. *JAMA Intern Med.* 2015

Illegally-made fentanyl use is on the rise

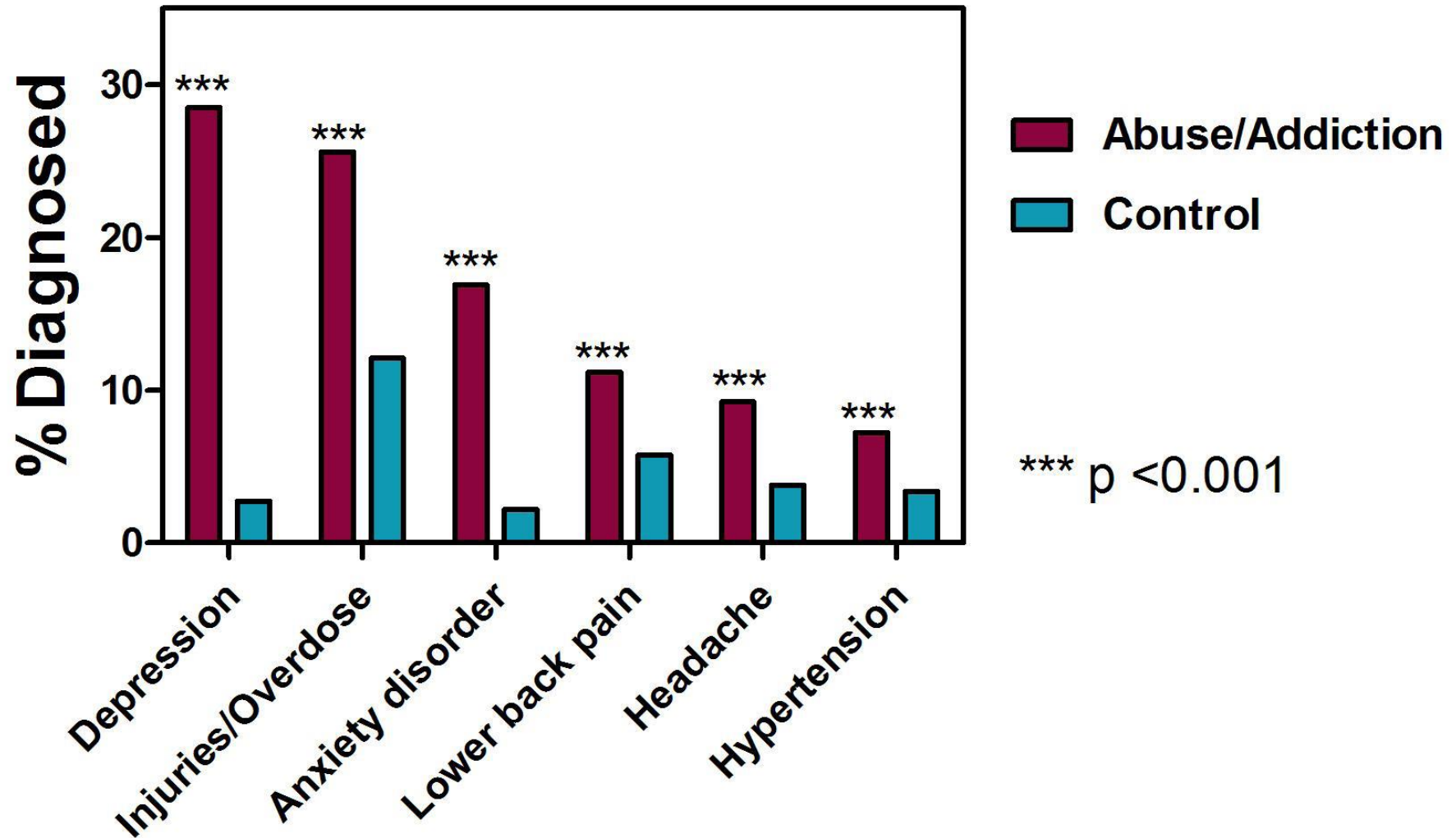
Fentanyl reports in NFLIS, by State

July – December 2014

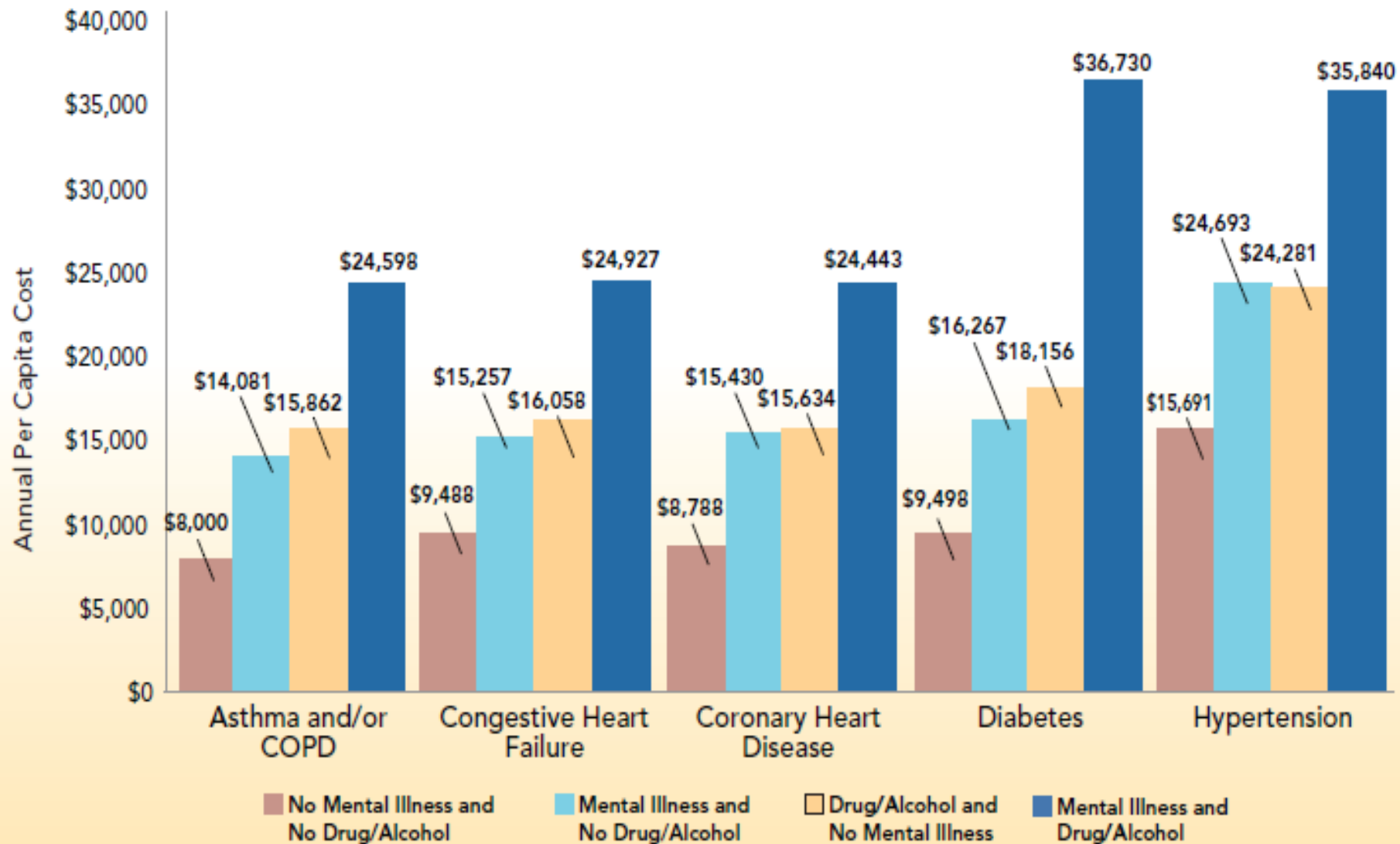


- OD deaths involving illegally made, non-pharmaceutical fentanyl, increased by 80% from 2013 to 2014
- ~ 5,500 people died from fentanyl OD in 2014
- National Forensic Laboratory Information System (NFLIS), confiscations, or seizures, of fentanyl increased by nearly 7x from 2012 to 2014

Why focus on drug use in medical settings?



Substance Use Complicates other Chronic Diseases



Why do people take drugs?

To feel good

To have novel:
Feelings
Sensations
Experiences
AND
To share them

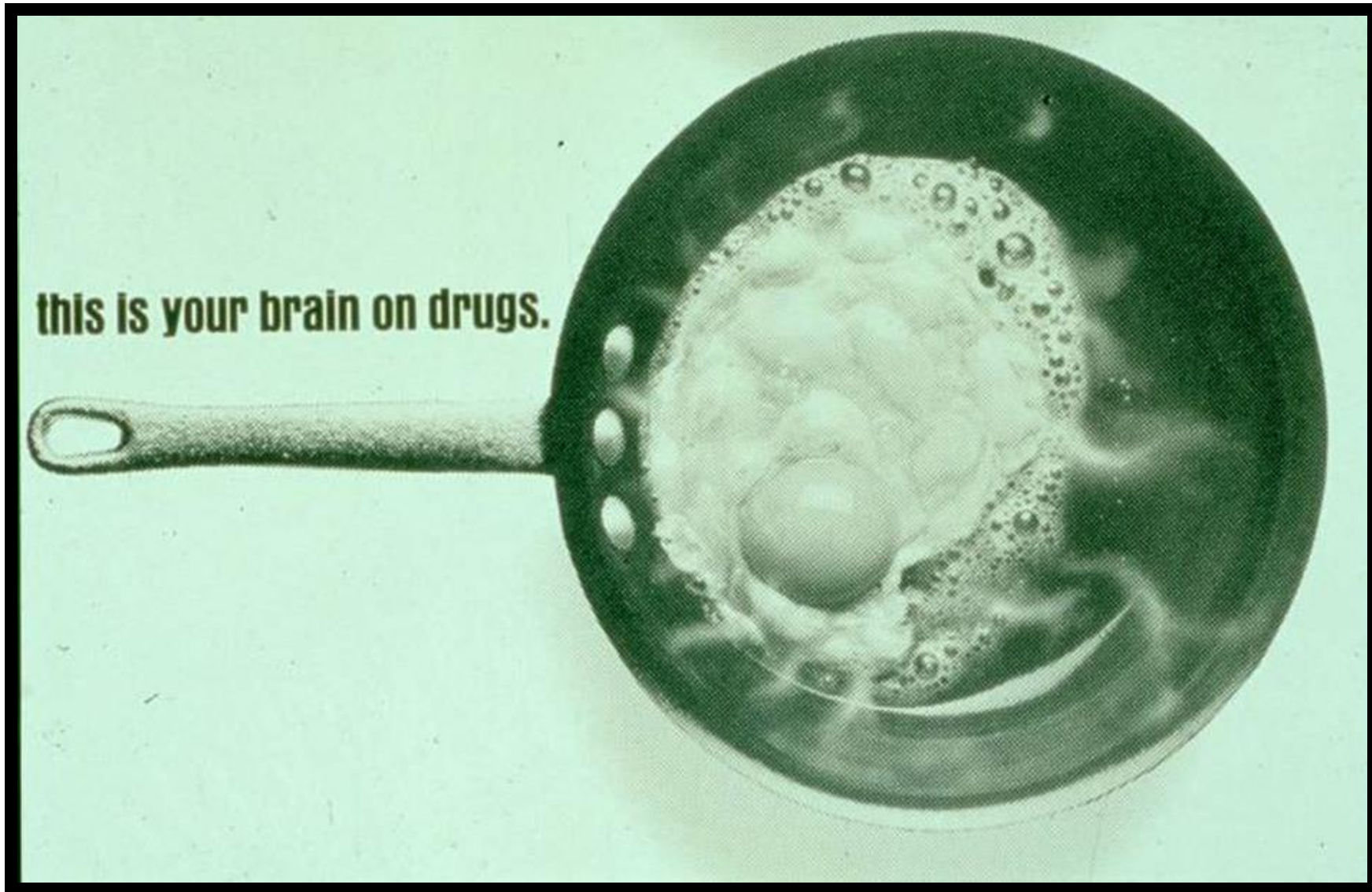


To feel better

To lessen:
Anxiety
Worries
Fears
Depression
Hopelessness
Withdrawal

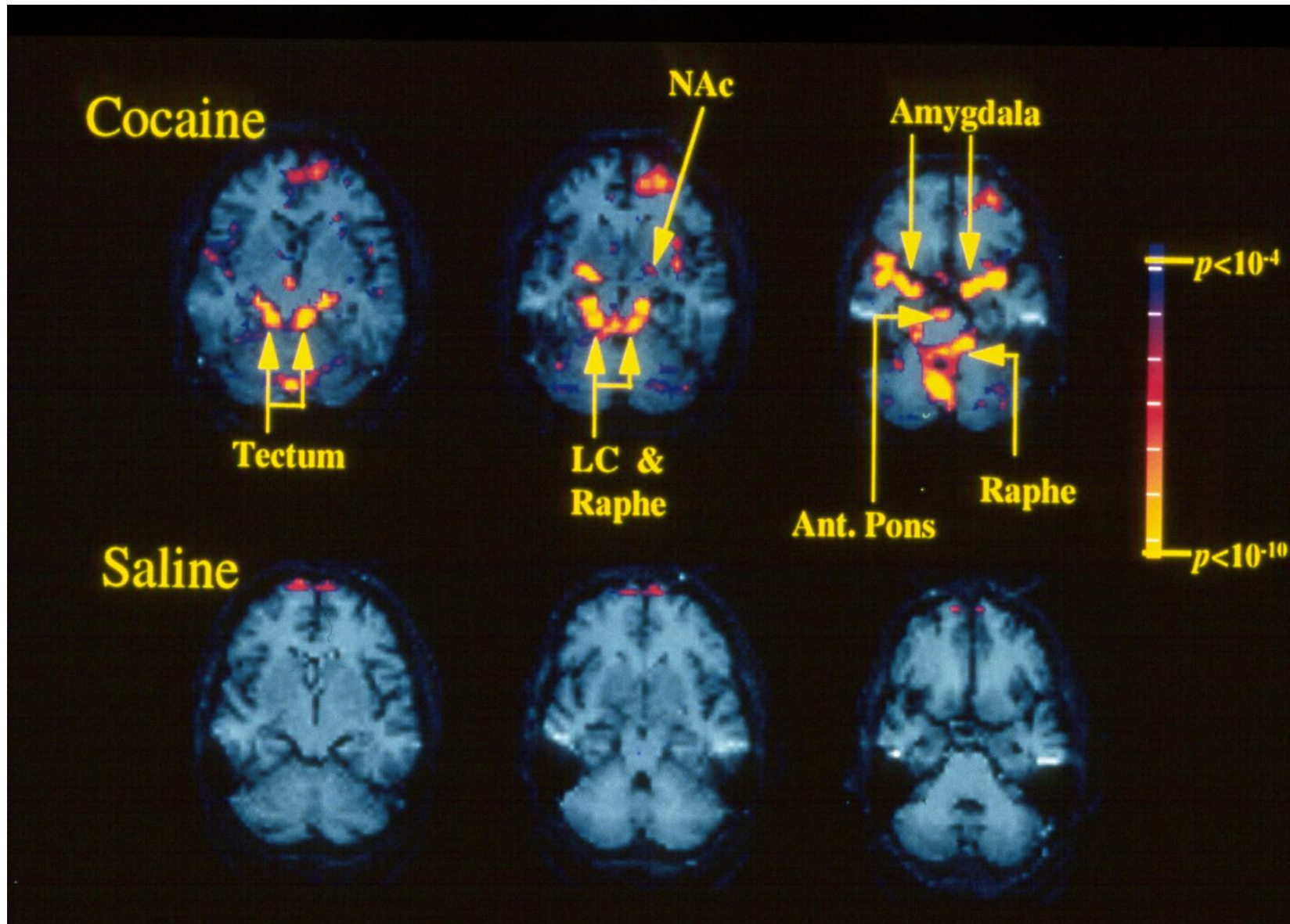


Drawings courtesy of Vivian Felsen



**Campaign by Partnership for a Drug-Free America
launched in 1987**

Your Brain on Drugs

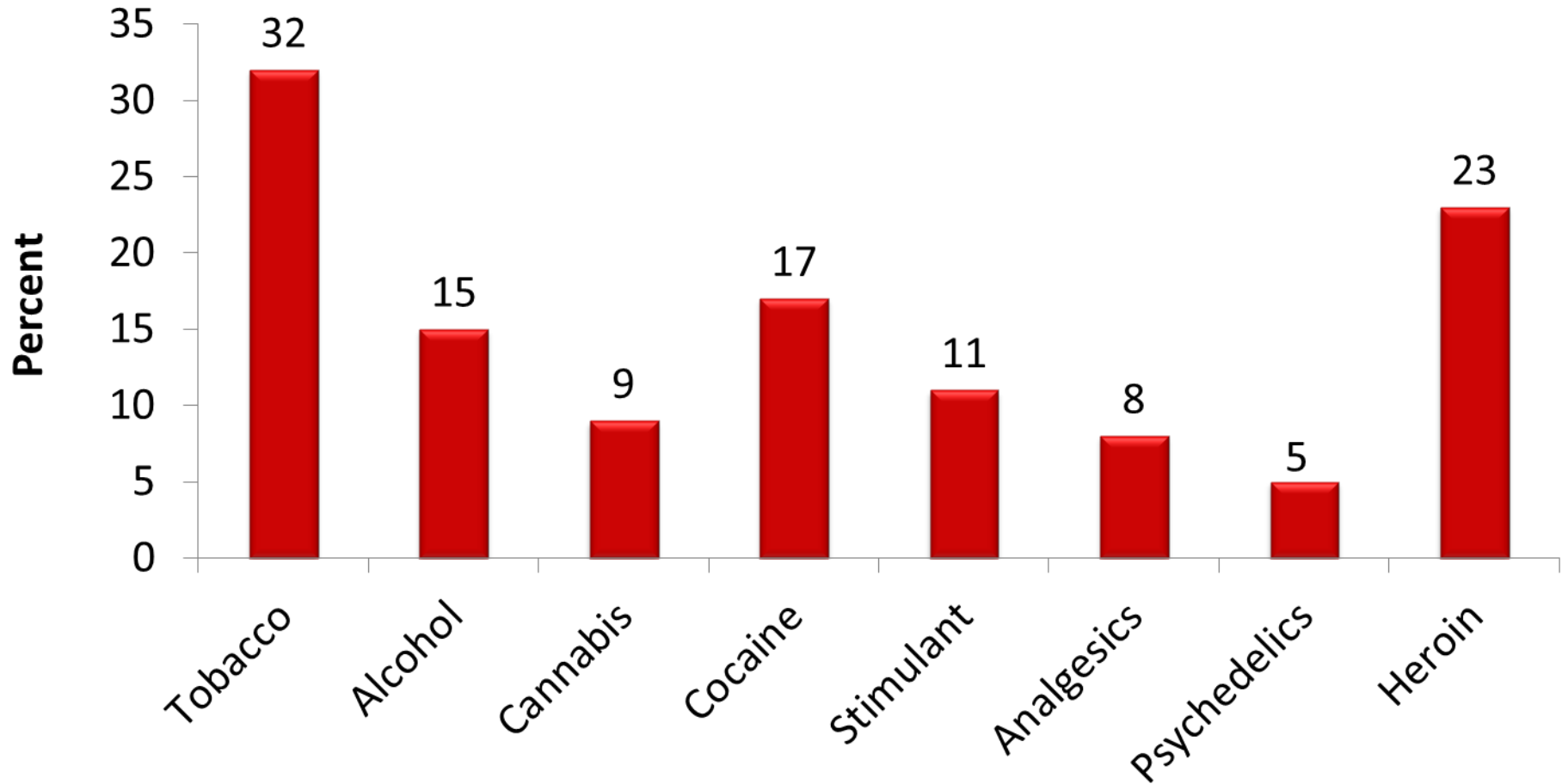


What have we
learned about
vulnerability?

Why do some
people become
addicted while
others do not?

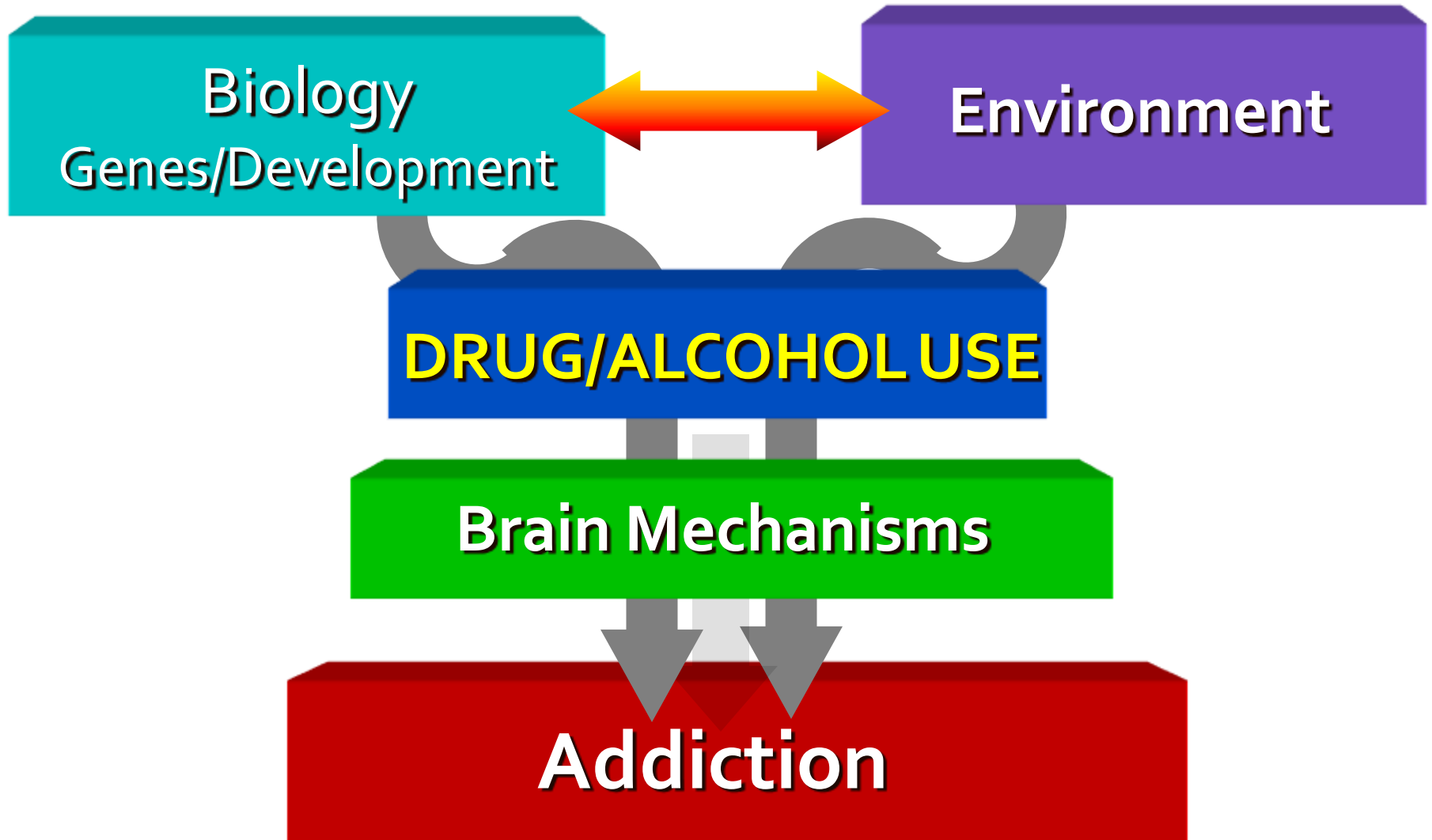


Addiction Prevalence Varies by Substance



Estimated Prevalence of Dependence Among Users

Development of Addiction Involve Multiple Factors



Heritability

Trait	Heritability
Type II DM	0.3 ¹
Type I DM	0.7 ²
Hypertension	0.3 - 0.5 ³
Peanut allergy	0.8 ⁴
Cataract (age-related)	0.5 ⁵
Alcoholism	0.6 ⁶
Nicotine	0.5 – 0.6 ⁷
Cocaine and stimulants	0.4 – 0.8 ⁸
Heroin and opiates	0.5 ⁹
Marijuana	0.3 – 0.8 ¹⁰

¹Poulsen et al., Diabetologia 1999

²Kyvik et al., BMJ 1995

³Corvol & Jeunemaitre, Endocrine Rev 1997

⁴Sicherer et al., J Allergy Clin Immunol 2000

⁵Hammond et al., N Engl J Med 2000

⁶Goate & Edenberg, Curr Opin Genet Dev.1998

⁷Sabol et al., Health Psych. 1999

⁸⁻¹⁰Tsuang et al. 1996; Am J Med Genet. 1996

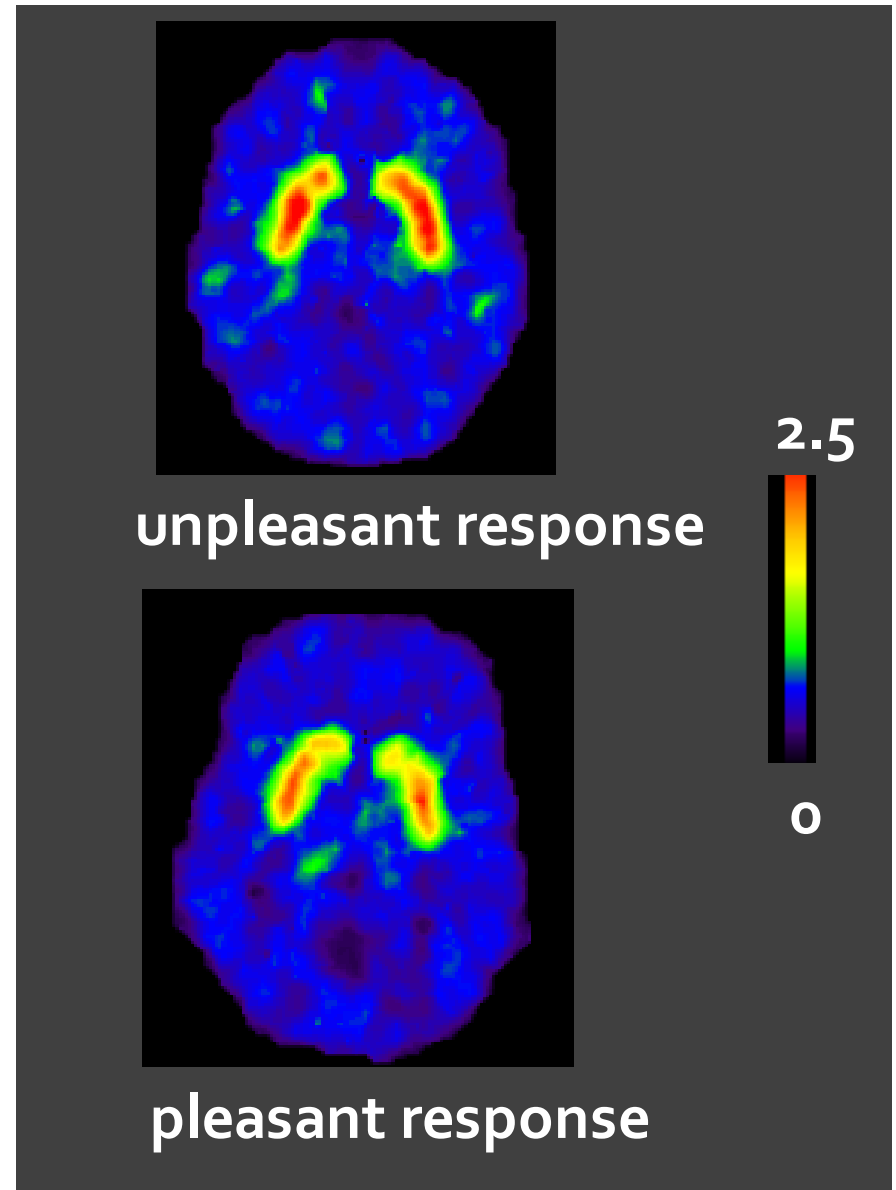
Susceptibility to Addiction Results from Interaction of Many Genes

- **FAAH** - associated with drug dependence
- **OPRM1** - associated with opiates and alcoholism
- **CYP2A6, CYP2B6** - associated with smoking and smoking cessation
- **ALDH2** - associated with protection against alcoholism
- **DBH** (Dopamine beta-hydroxylase) – cocaine-induced paranoia
- **DRD2, DRD4** (Dopamine receptors) - reward, craving
- **NrCAM, neurexins** (Cell adhesions genes) - assoc with drug abuse and addiction
- **Prodynorphin gene** - associated with protection against cocaine dependence
- **Nicotinic alpha 7 promoter** – assoc. with decreased expression of its message in different brains regions and with sensory gating defects in schizophrenics
- **Alpha 5 and beta 3** (nicotinic receptors) – assoc. with nicotine dependence
- **5HT1B** (serotonin receptor) - associated with conduct disorder and alcoholism

DA Receptor Levels and Response to MP

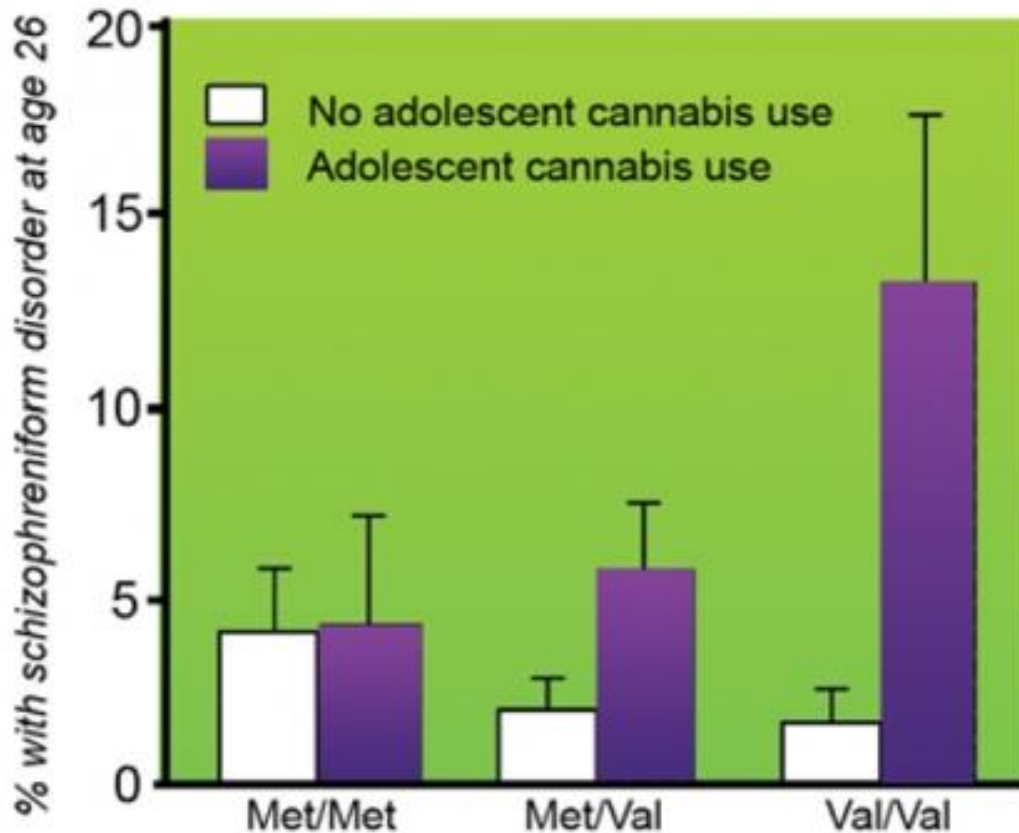
- Striatal DA D2 receptors levels predicted reinforcing responses to psychostimulant methylphenidate (MP) in nondrug-abusing subjects (n=7)
- Subjects with low receptor levels found MP pleasant while those with high levels found MP unpleasant
- Striatal DA D2 receptors modulate reinforcing responses to stimulants in humans and may underlie predisposition for drug self-administration

Volkow ND et al. Synapse. 2002

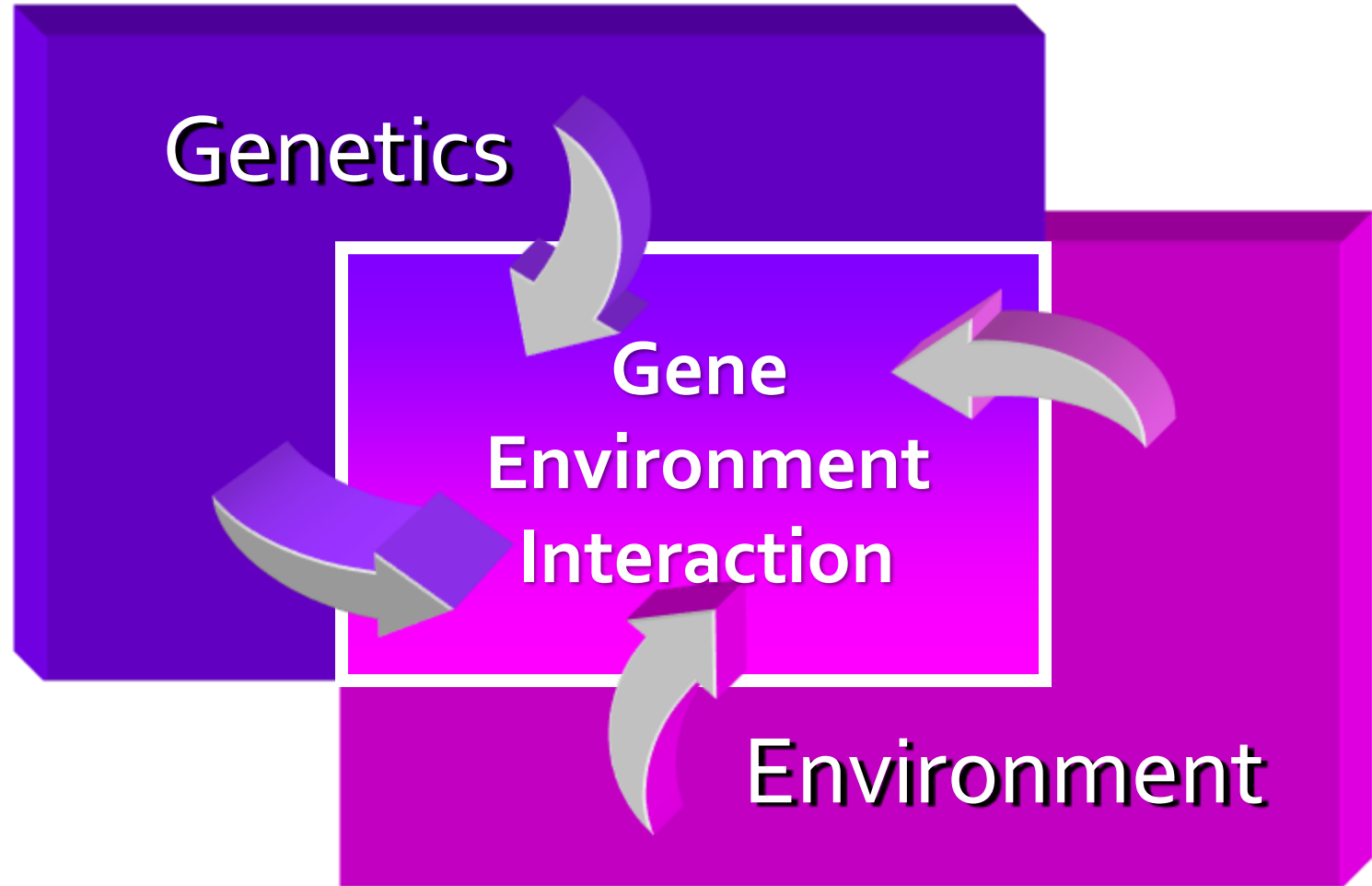


Genetic Variability and Effects of Drugs

Genetic variation in COMT influences the harmful effects of abused drugs



- Longitudinal birth cohort n=1,037 followed from 3y to adulthood
- Functional polymorphism in catechol-O-methyltransferase (COMT) gene
- COMT valine allele more likely to develop psychotic symptoms and schizophreniform disorder if used cannabis



What Environmental Factors Contribute to Addiction?

Drug availability

Peers who use drugs

Family Problems

Early physical or sexual abuse

Stress in general

Effects of a Social Stressor on Brain Dopamine D2 Receptors and Propensity to Administer Drugs

Individually Housed

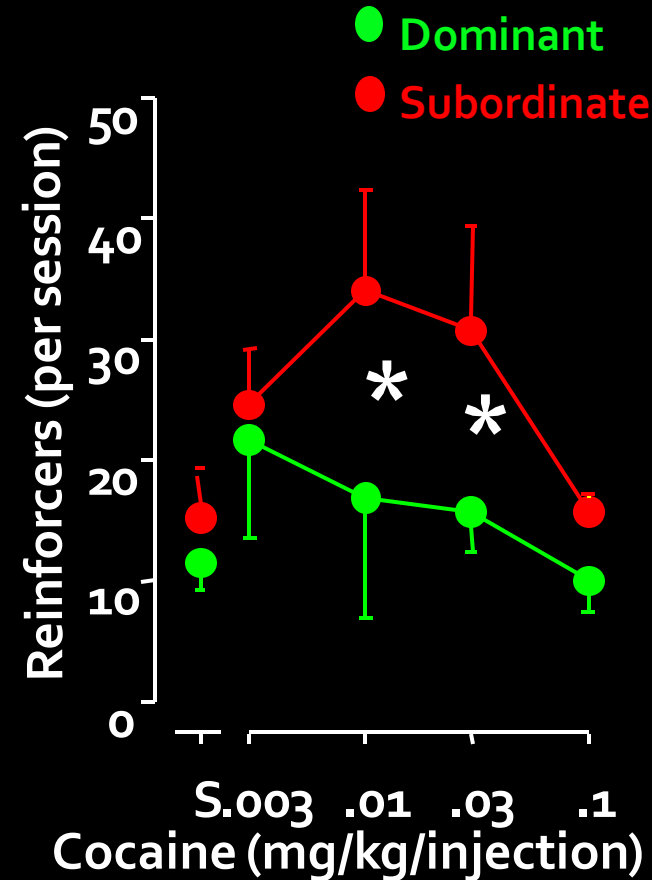
Group Housed

*Becomes Dominant
No longer stressed*



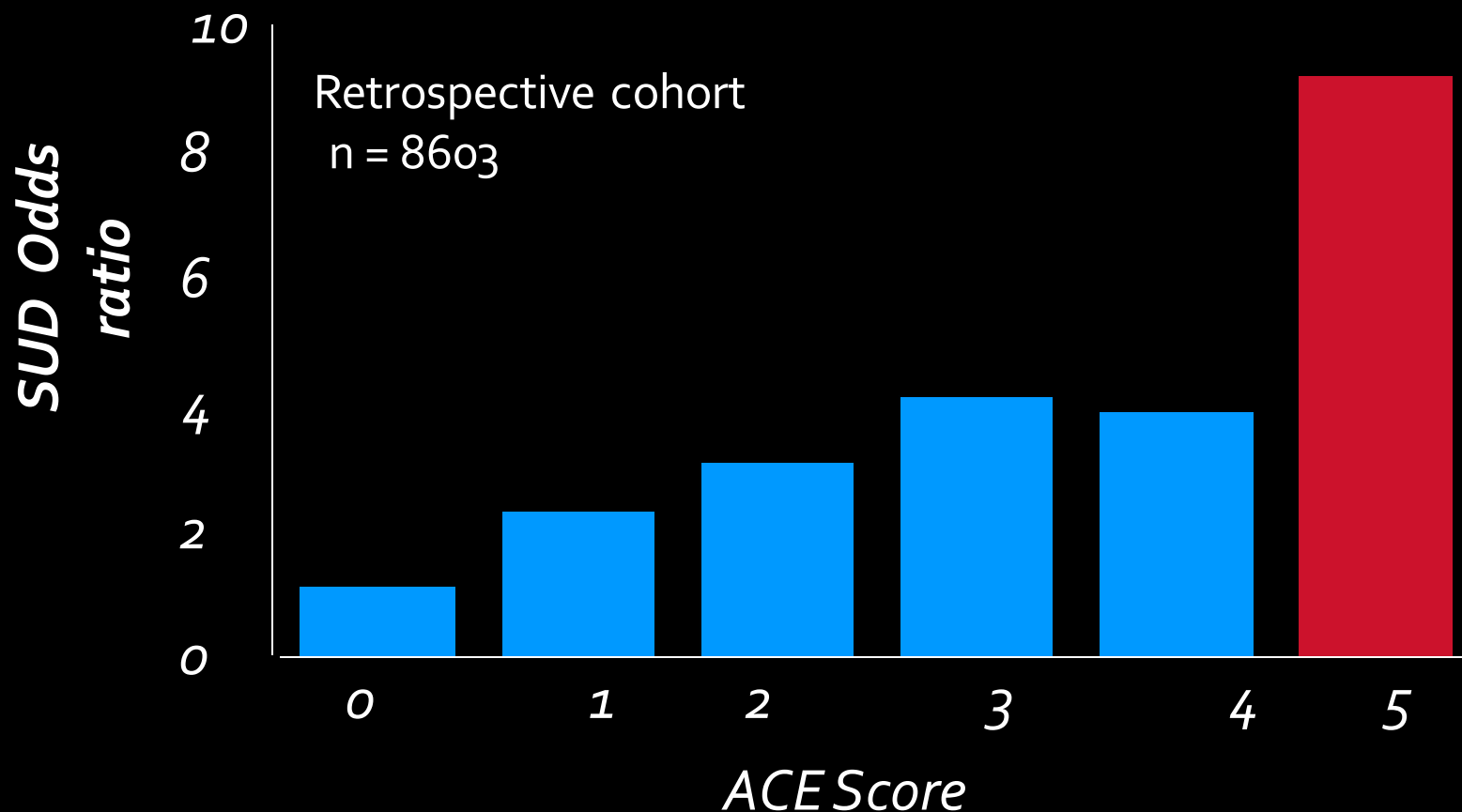
Social Setting Can Change Neurobiology

*Becomes Subordinate
Stress remains*



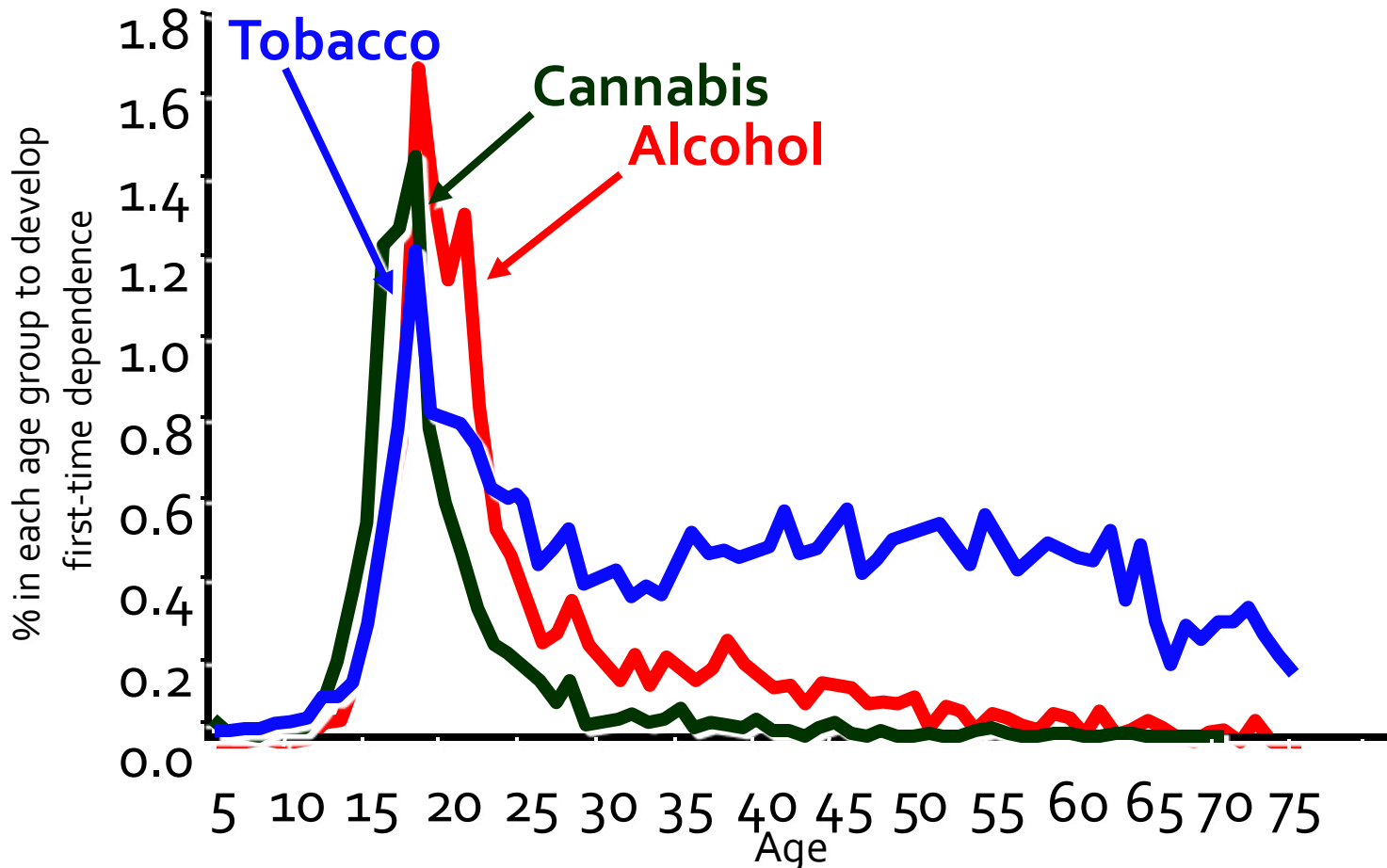
Morgan, D. et al. *Nature Neuroscience*, 2002.

Adverse Childhood Experiences (ACE) and Illicit Drug Use



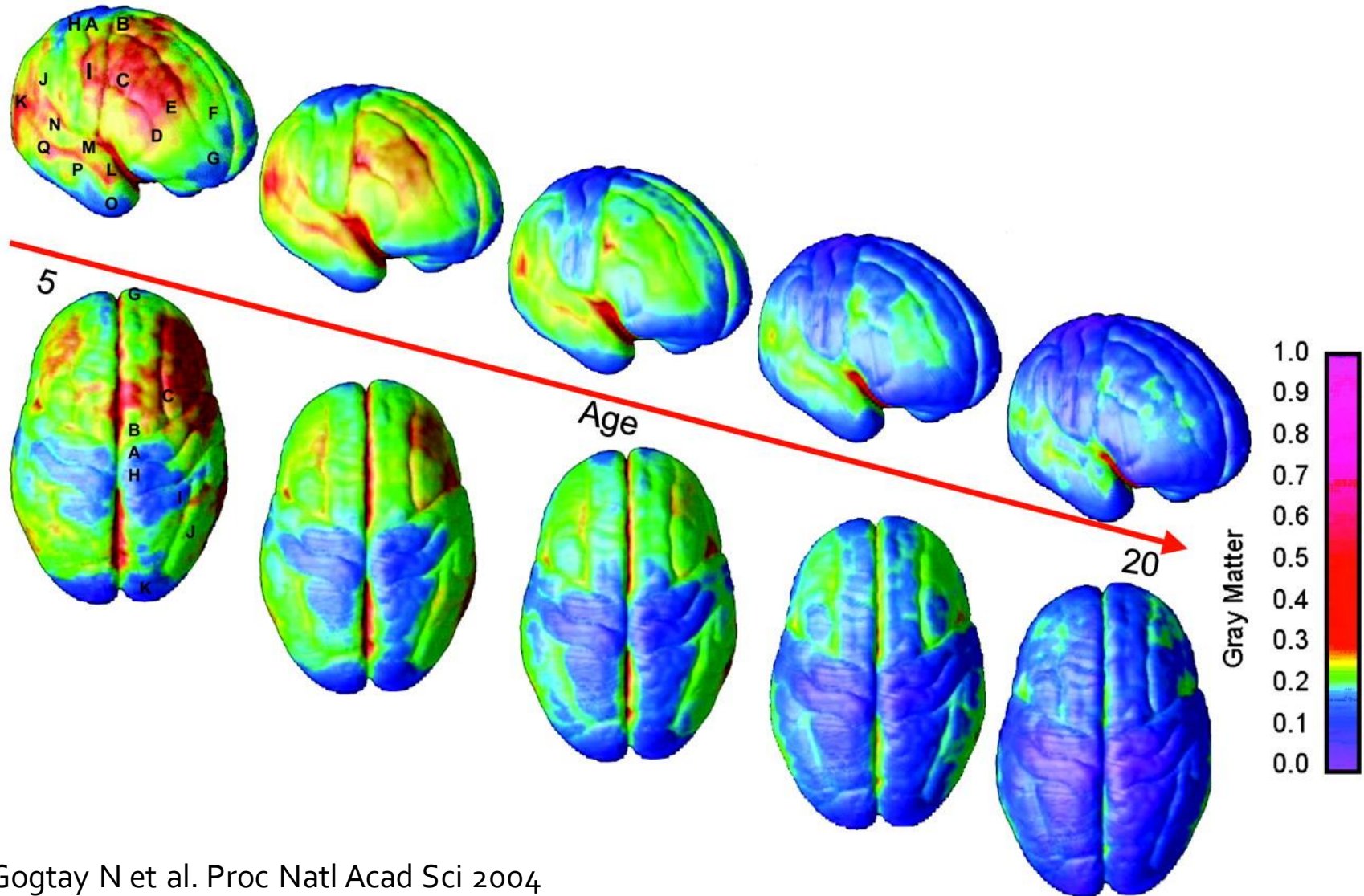
ACE assoc w/ 1/2 - 2/3 of serious problems with drug use

Addiction Is a Developmental Disease starts in Childhood and Adolescence

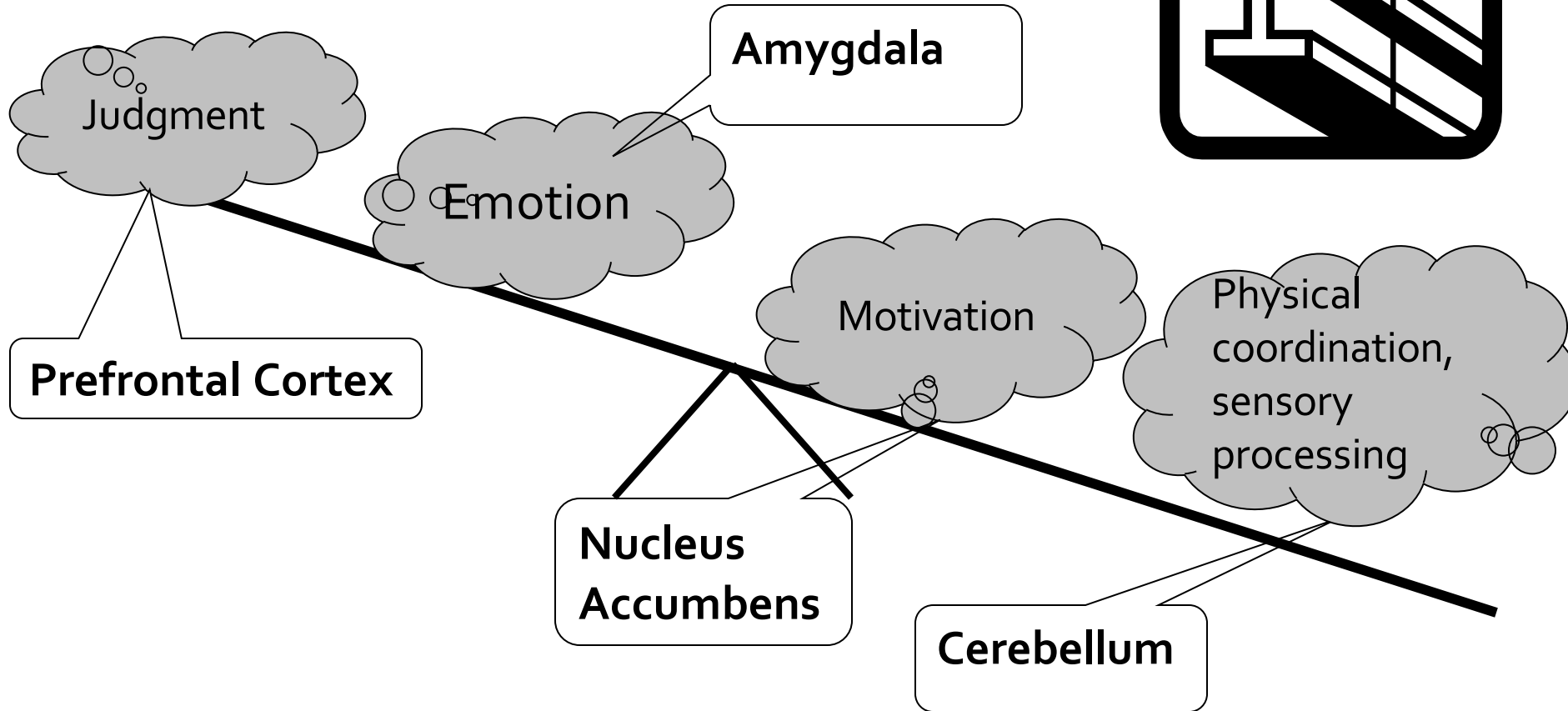
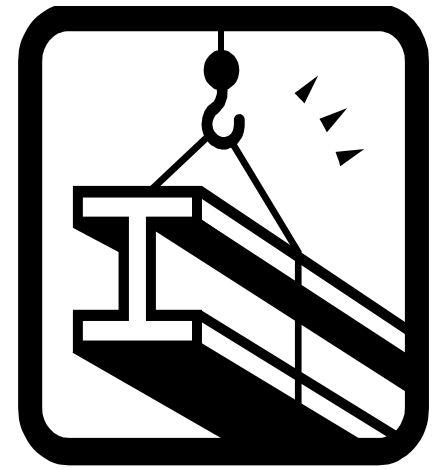


Age at tobacco, at alcohol and at cannabis dependence, as per DSM IV

Sequence of Gray Matter Maturation



Maturation starts at the back of the brain ...and moves to the front



Notice: Judgment is last to develop!

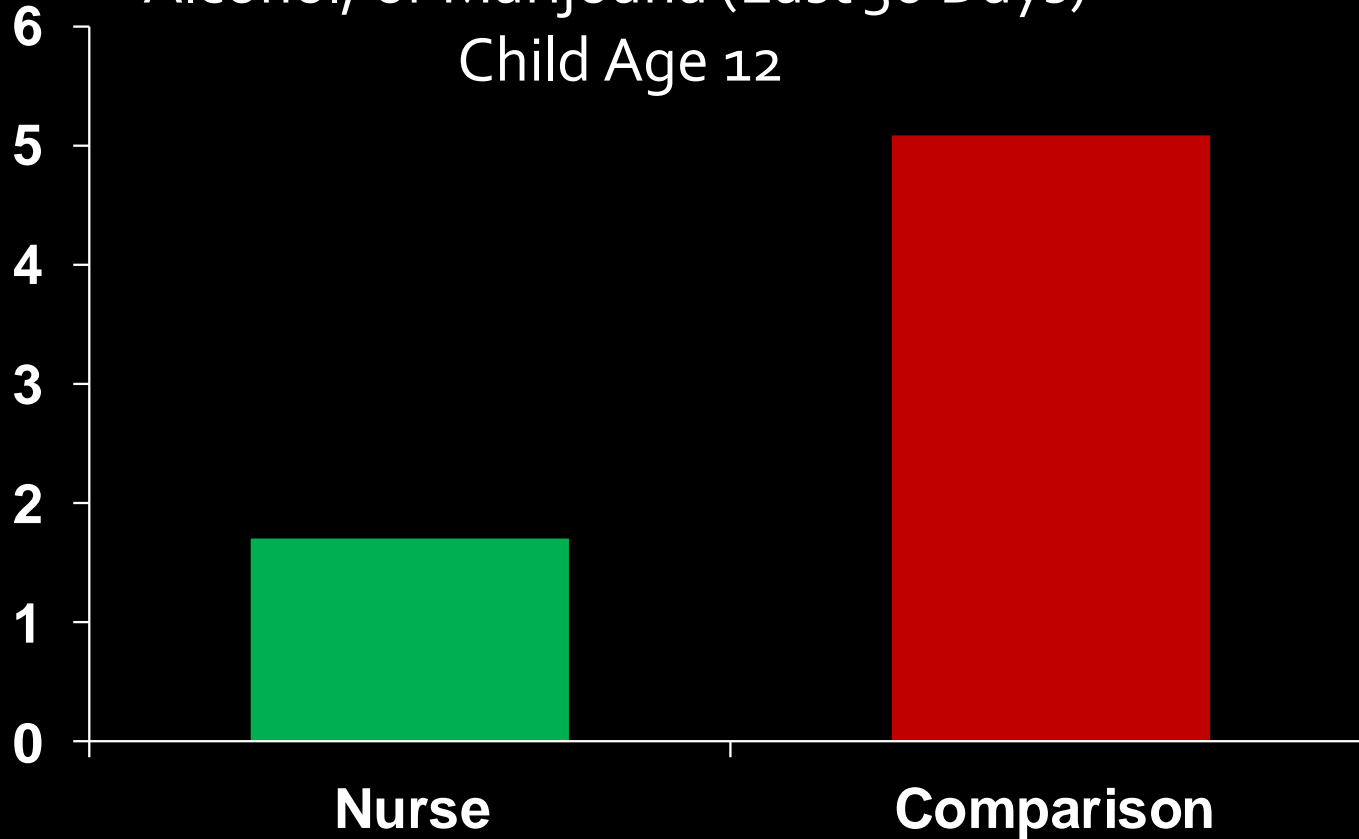
The Adolescent Brain

- Brain develops till mid/late 20s!
- Pre-frontal cortex last to develop
- Exposure to drugs during adolescence could have profound effects on brain development & plasticity
- Age of drug use onset is predictor of later life drug problems
- 15% of those who start drinking by age 14 develop problems as adults (vs 2% who wait till age 21)

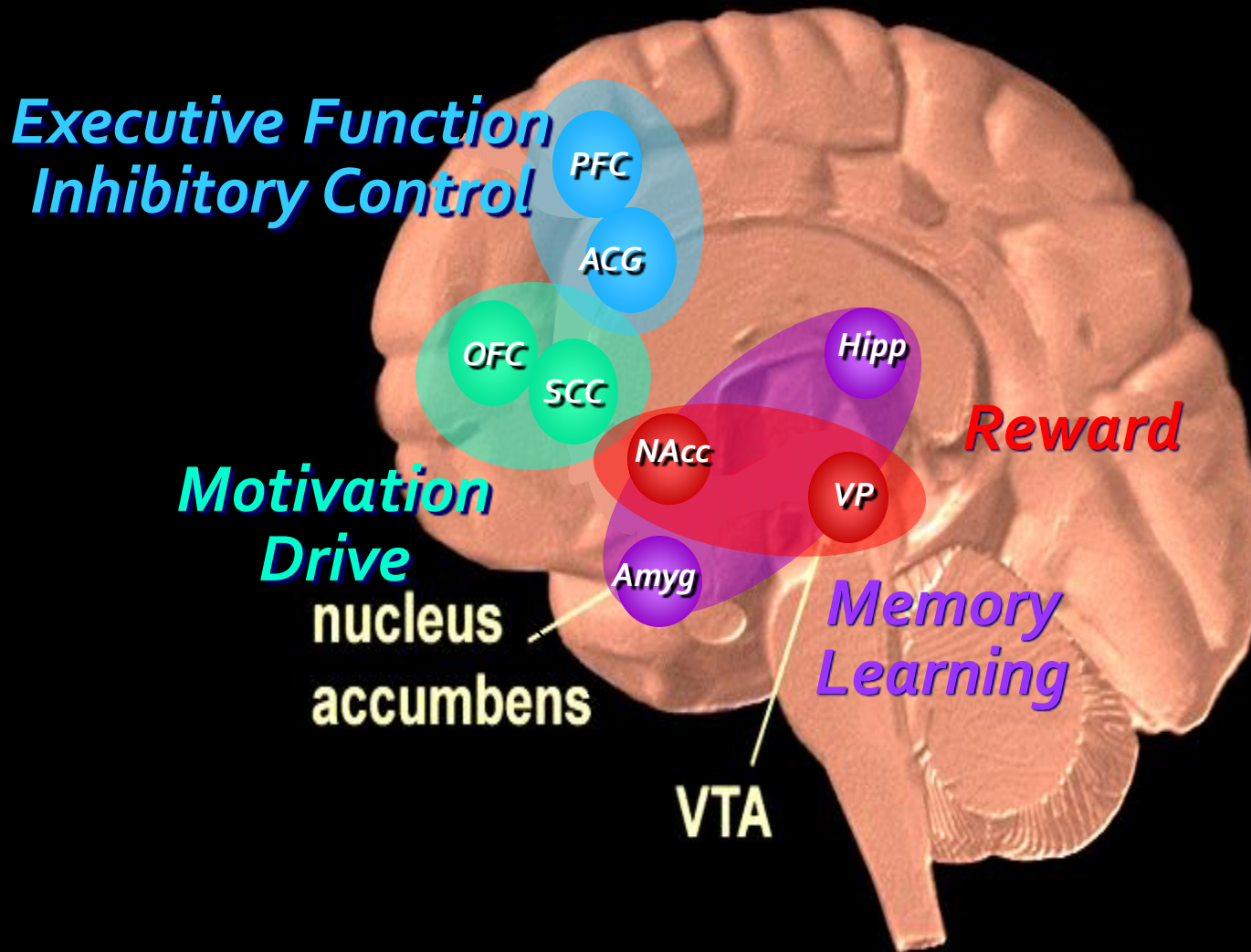
Nurse Home Visiting Program (prenatal-age 2)

n=743

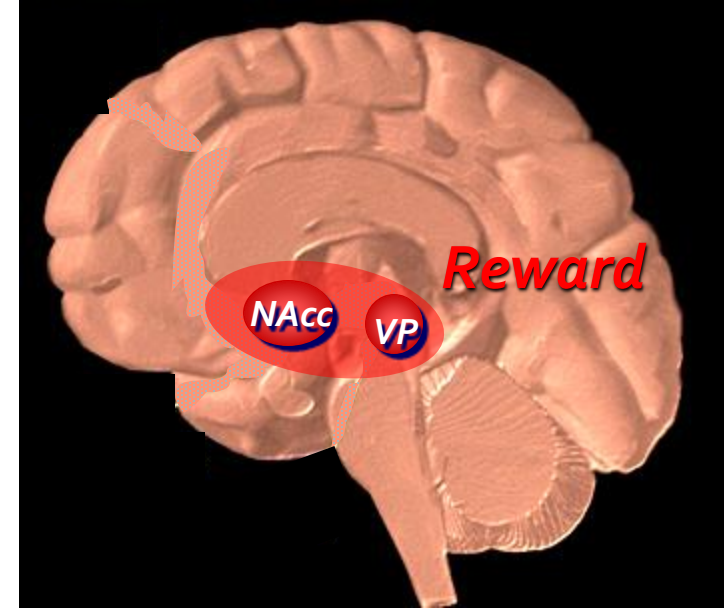
Percent of Children Who Used Tobacco,
Alcohol, or Marijuana (Last 30 Days)
Child Age 12



Neuronal Circuits Involved In Substance Use and Addiction

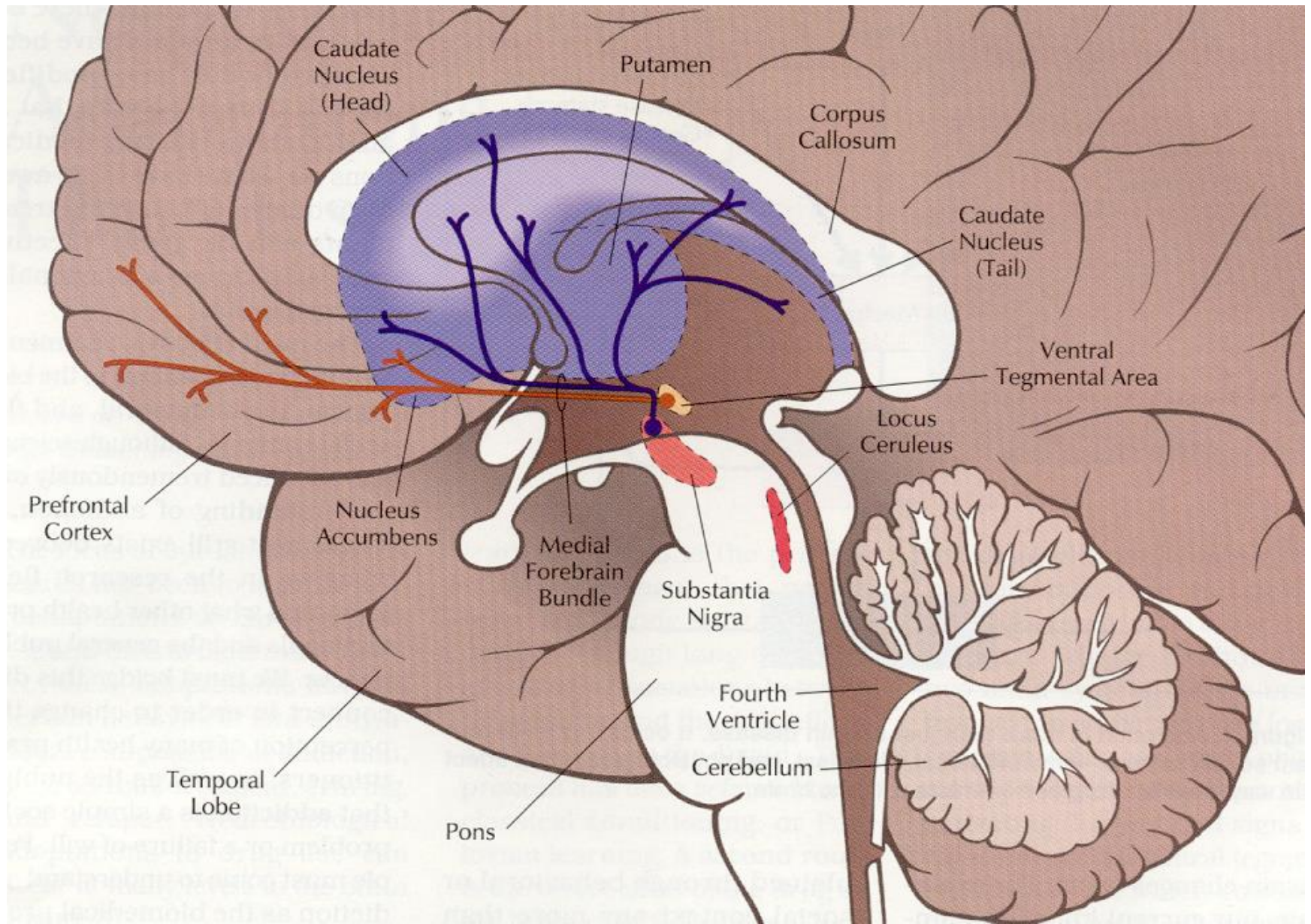


1. Reward Circuit

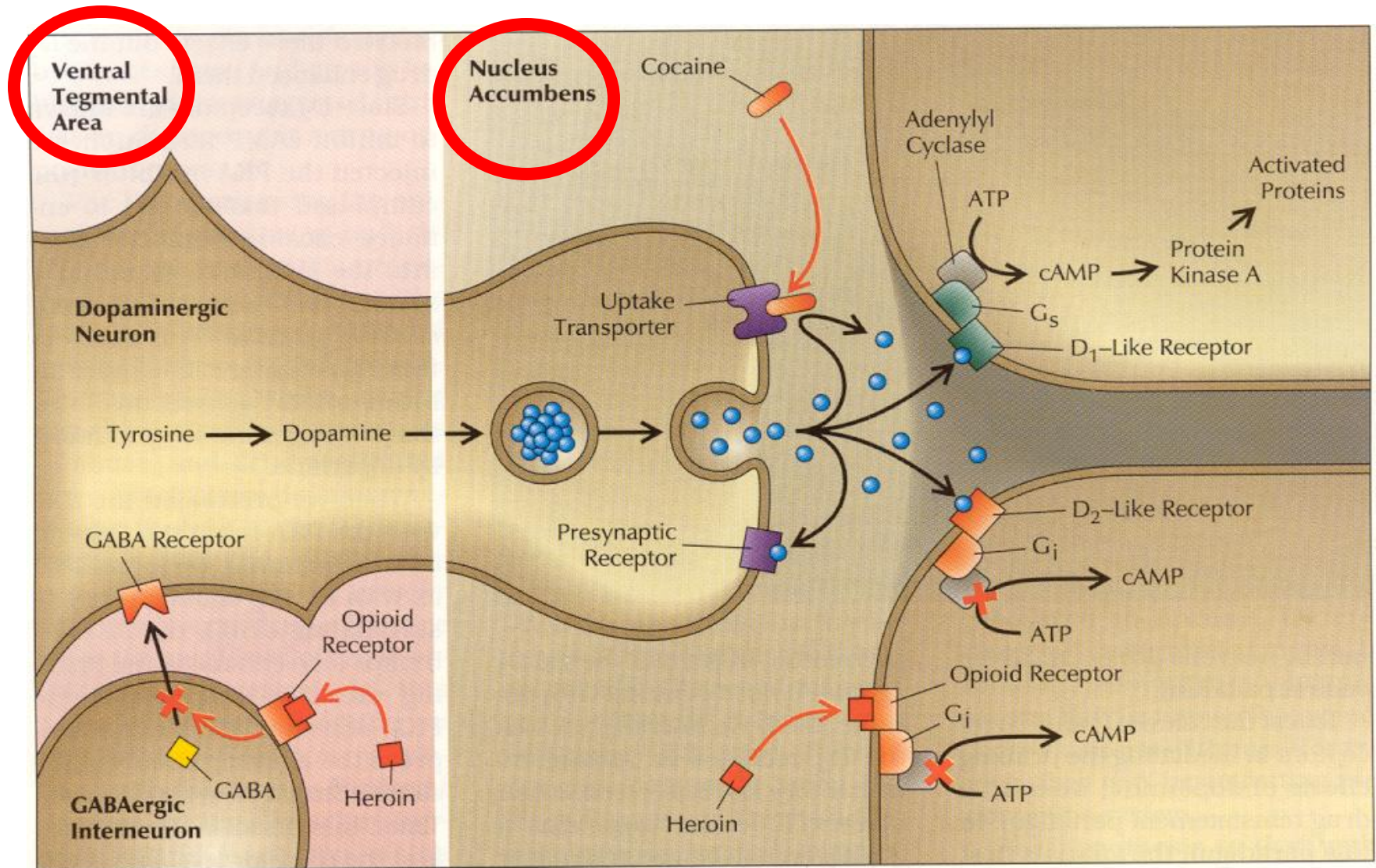


Drugs of Abuse Engage Systems in the Motivation Pathways of the Brain

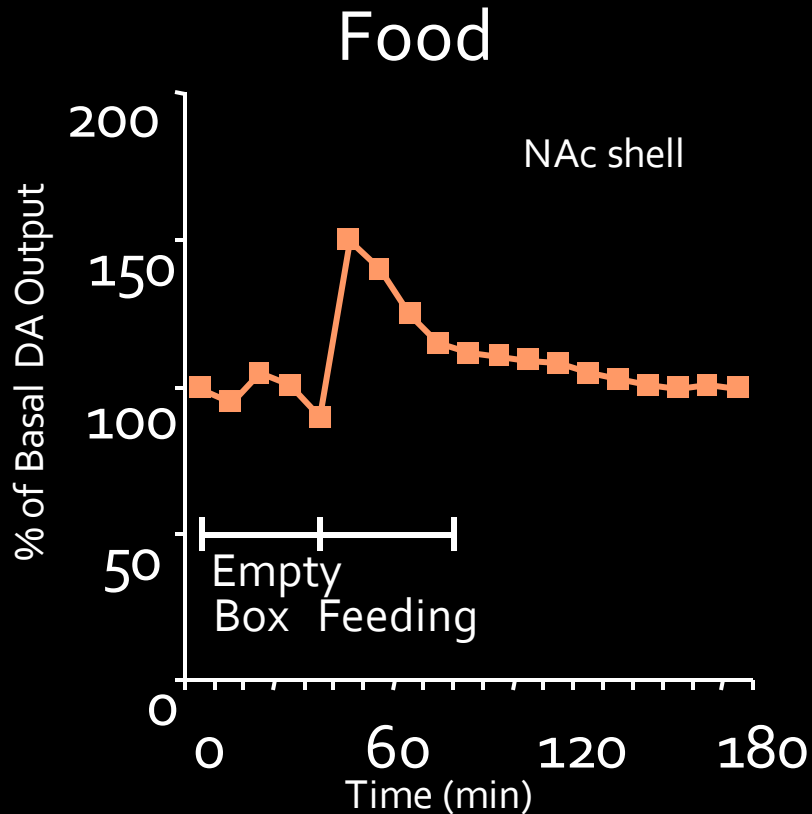
The Reward Pathway



The Reward Pathway

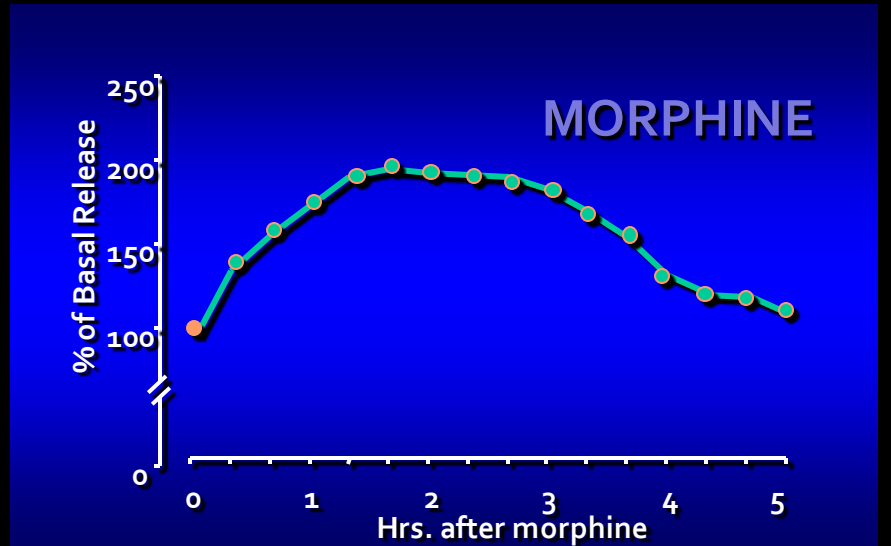
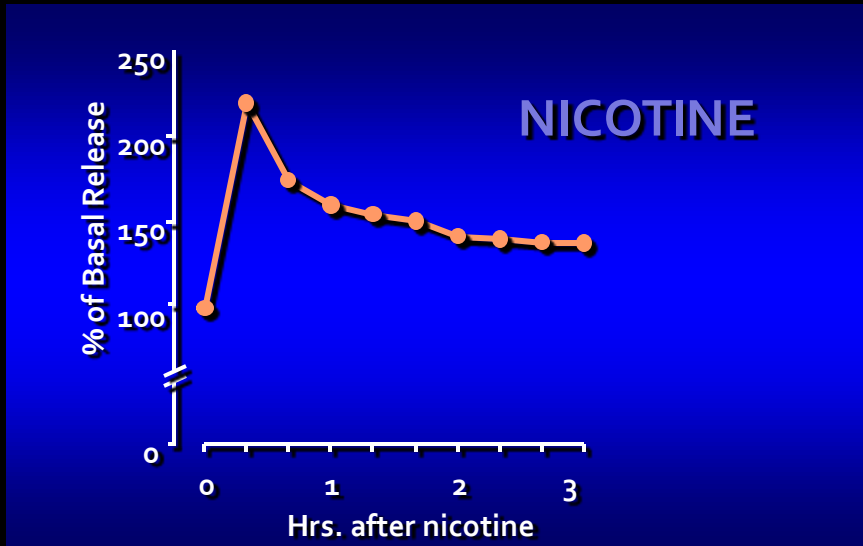
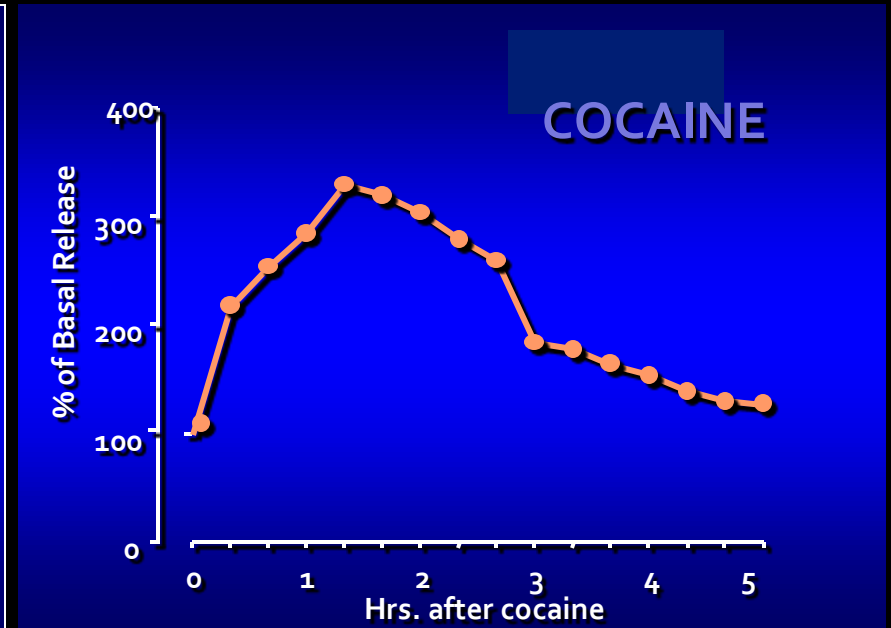
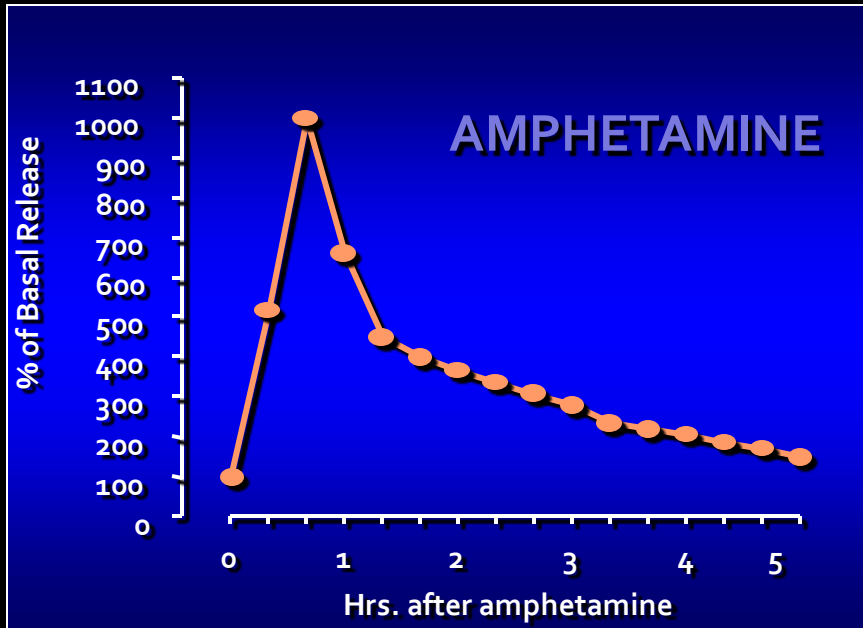


Natural Rewards Elevate Dopamine Levels

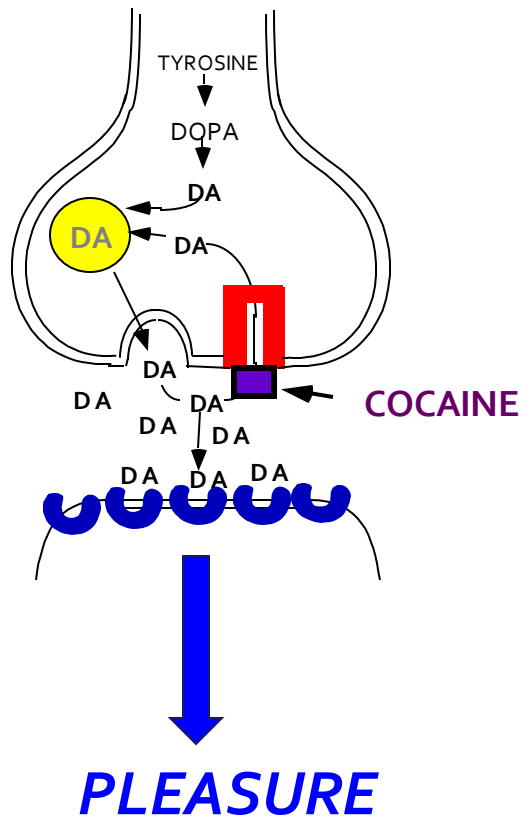


Di Chiara et al., Neuroscience, 1999
Fiorino and Phillips, J. Neuroscience, 1997

Drugs Elevated Dopamine More/Longer



Repeated Drug Use Changes the Brain *Weakens the Brain Dopamine System*



Dopamine Receptors Lower in Addiction

Volkow et al., Neuro Learn Mem 2002



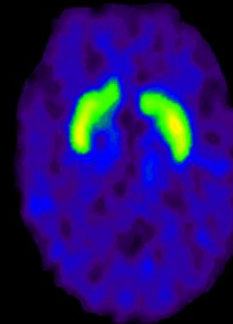
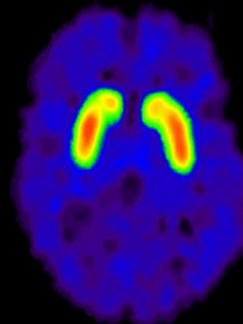
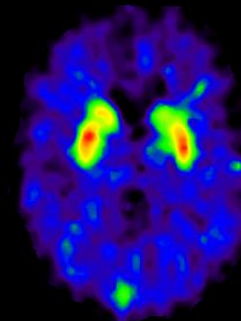
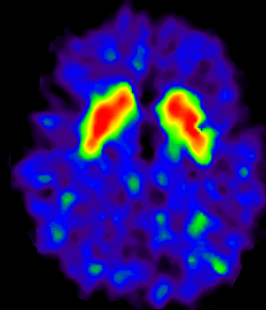
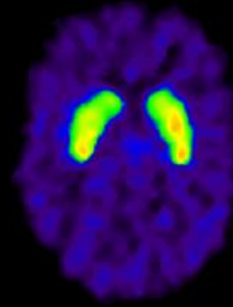
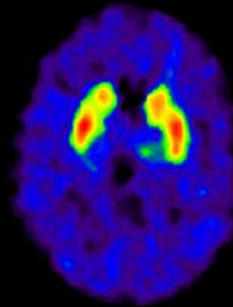
Cocaine



Alcohol



Heroin

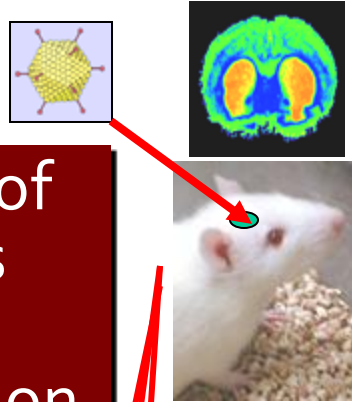


DA D2 Receptor Availability

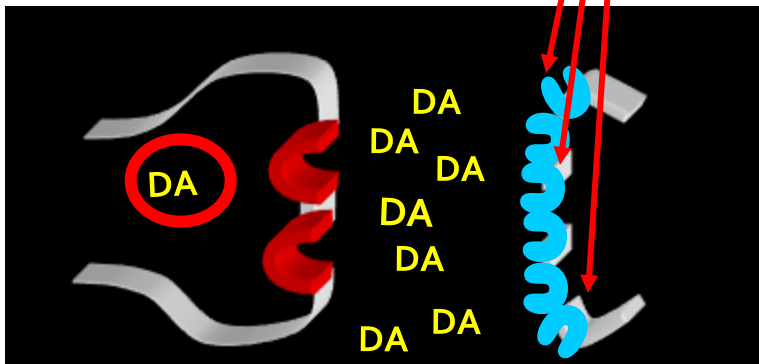
Control

Addicted

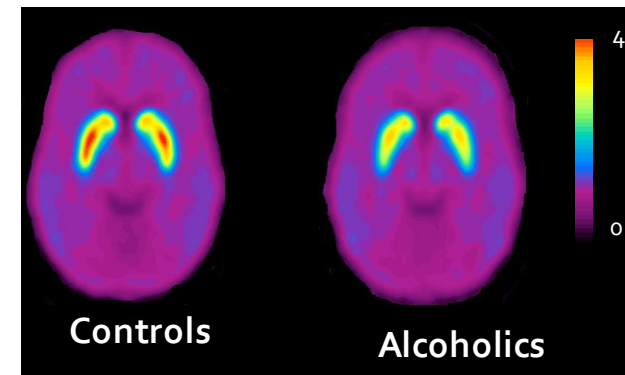
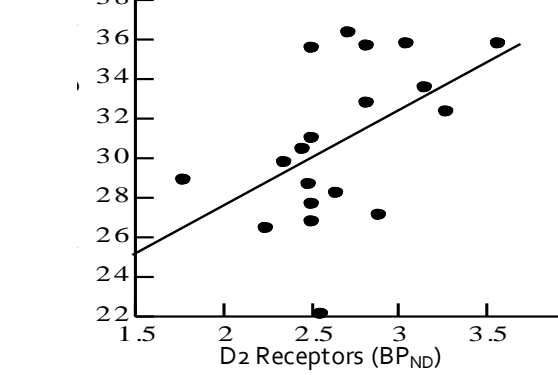
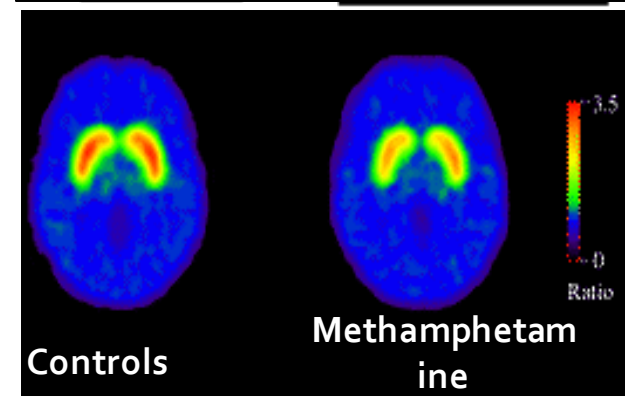
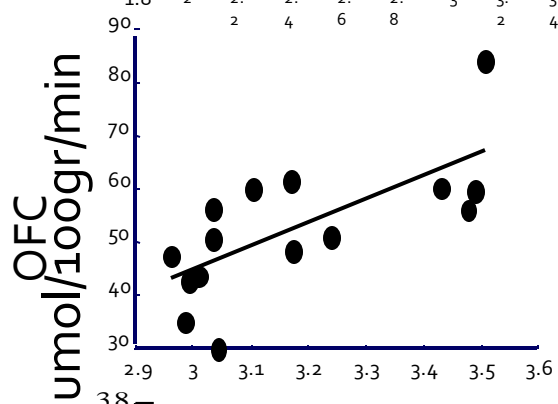
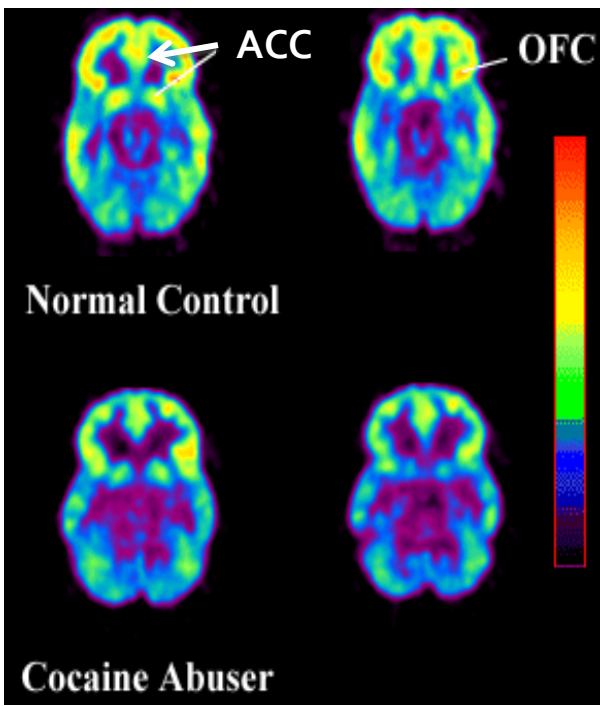
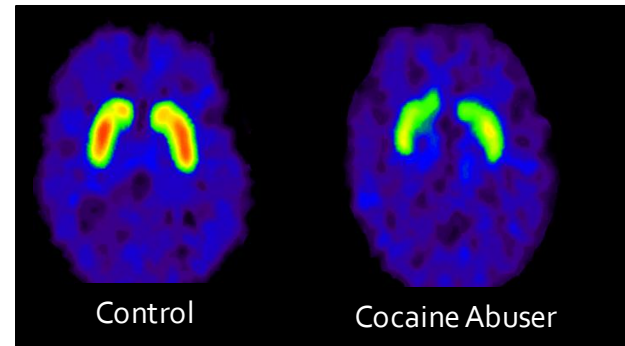
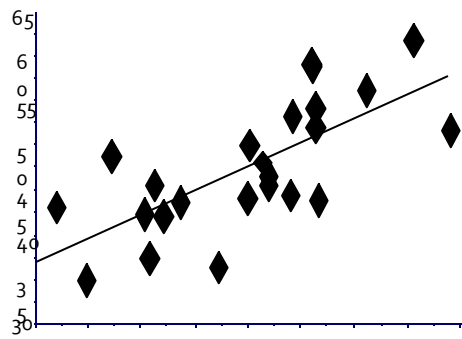
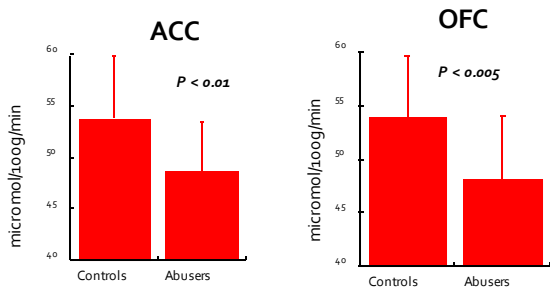
Effects of Tx with an Adenovirus Carrying a DA D2 Receptor Gene into NAc in DA D2 Receptors



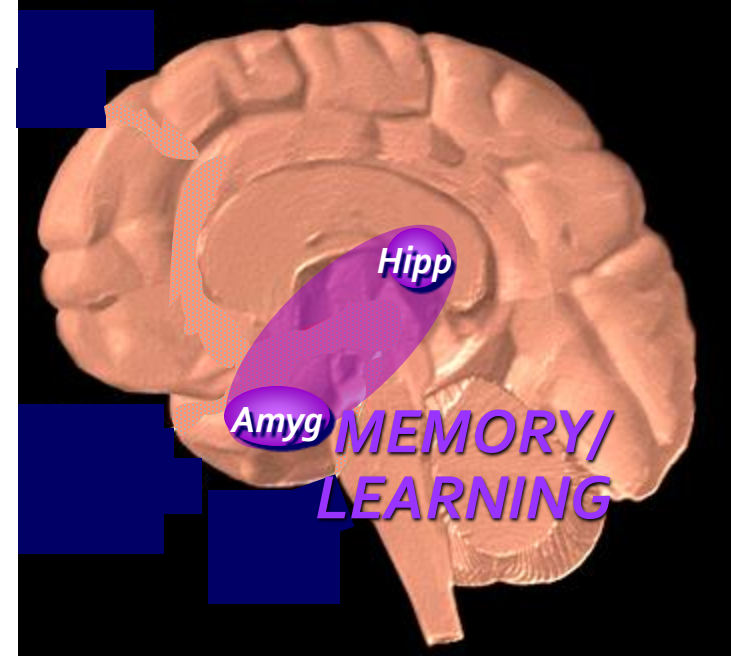
Overexpression of DA D2 receptors reduces alcohol self-administration



Relationship Between Brain Glucose Metabolism and Striatal D2 Receptors

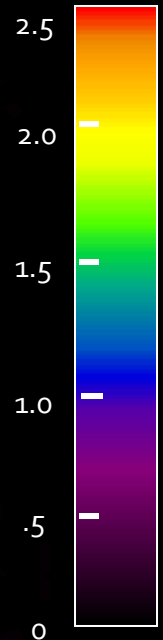
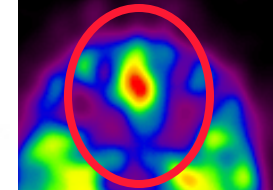
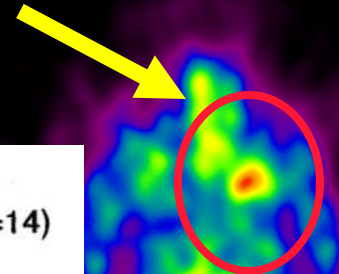
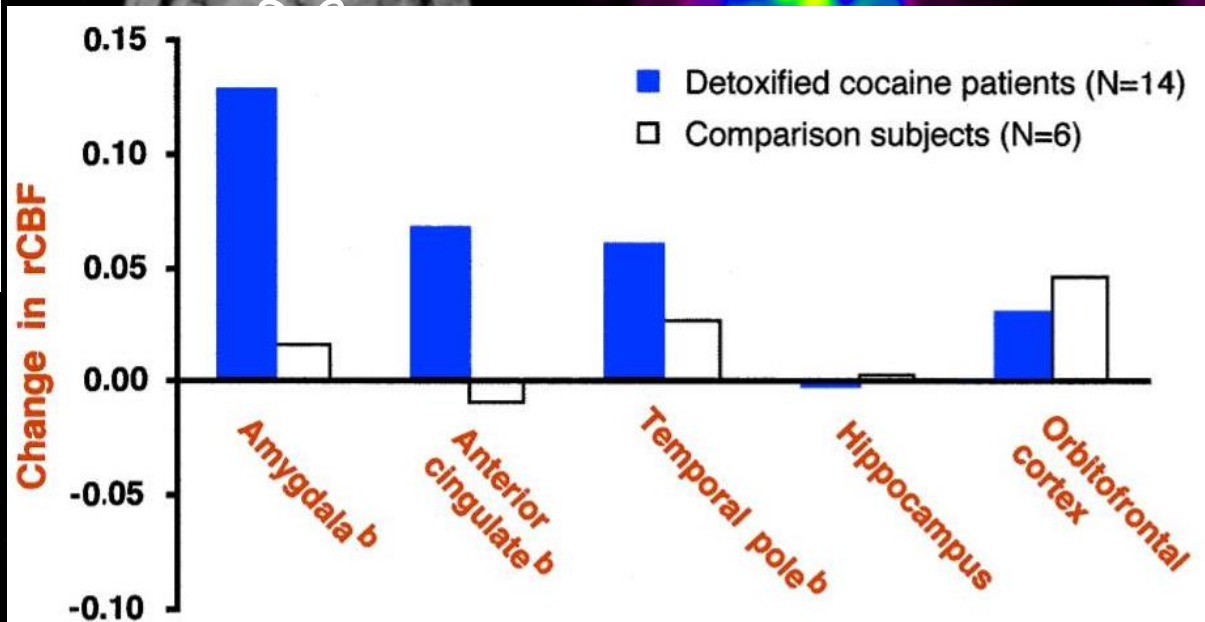
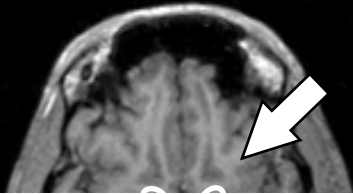


2. *Memory circuit*



Conditioned Association

Amygdala

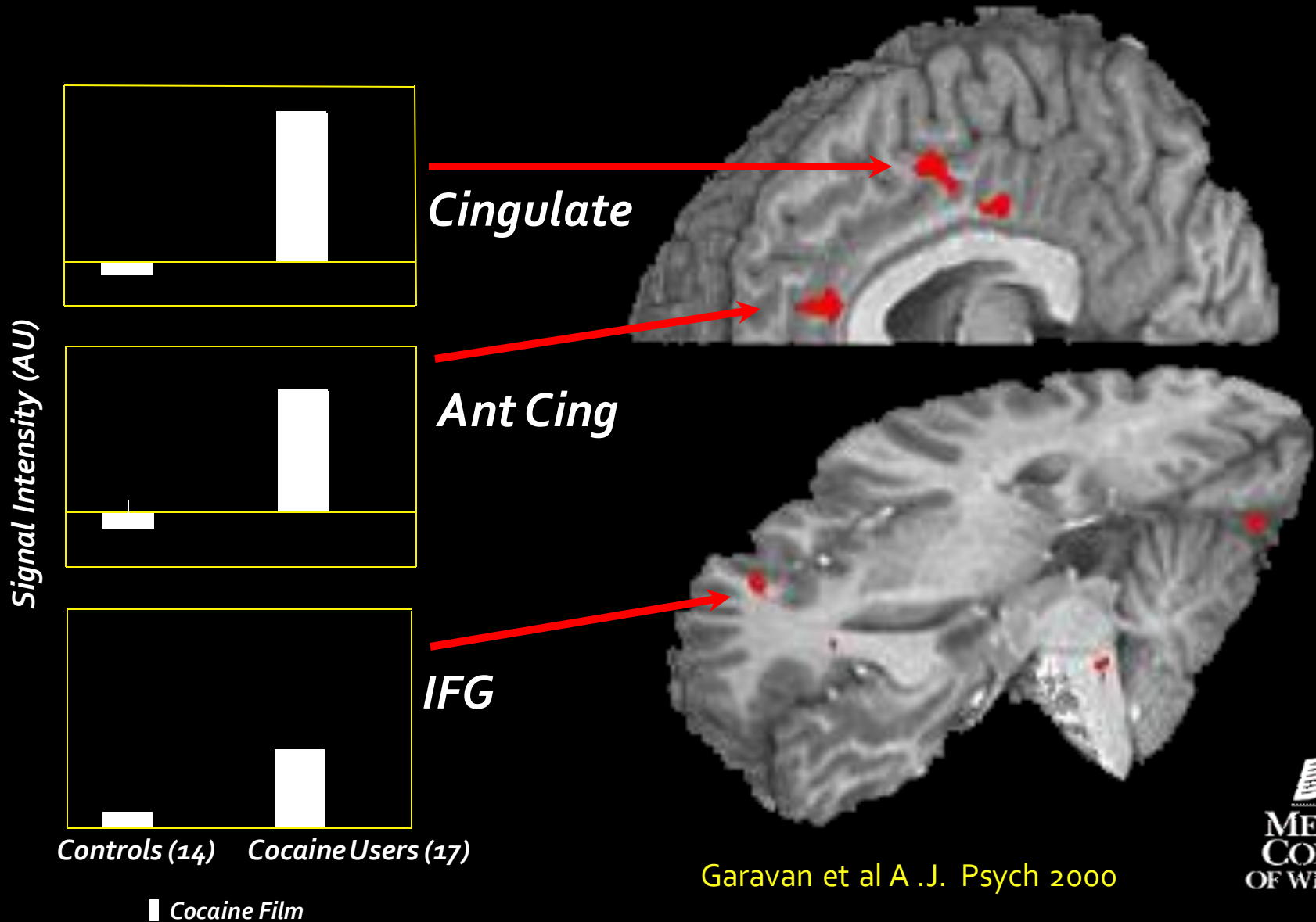


Nature Video

Cocaine Video

Cocaine Craving:

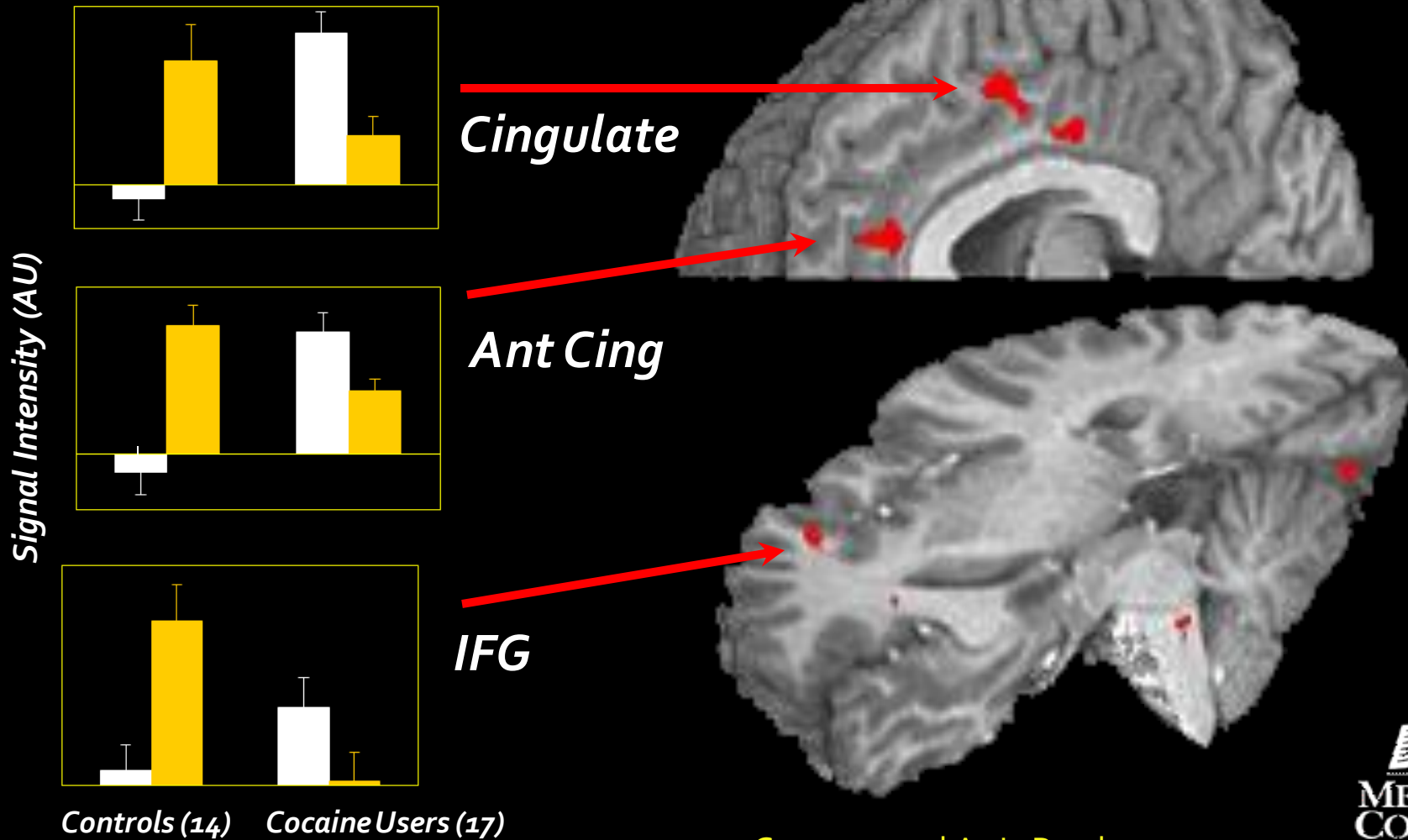
Population (Cocaine Users, Controls) x Film (cocaine)



Garavan et al A .J. Psych 2000

Cocaine Craving:

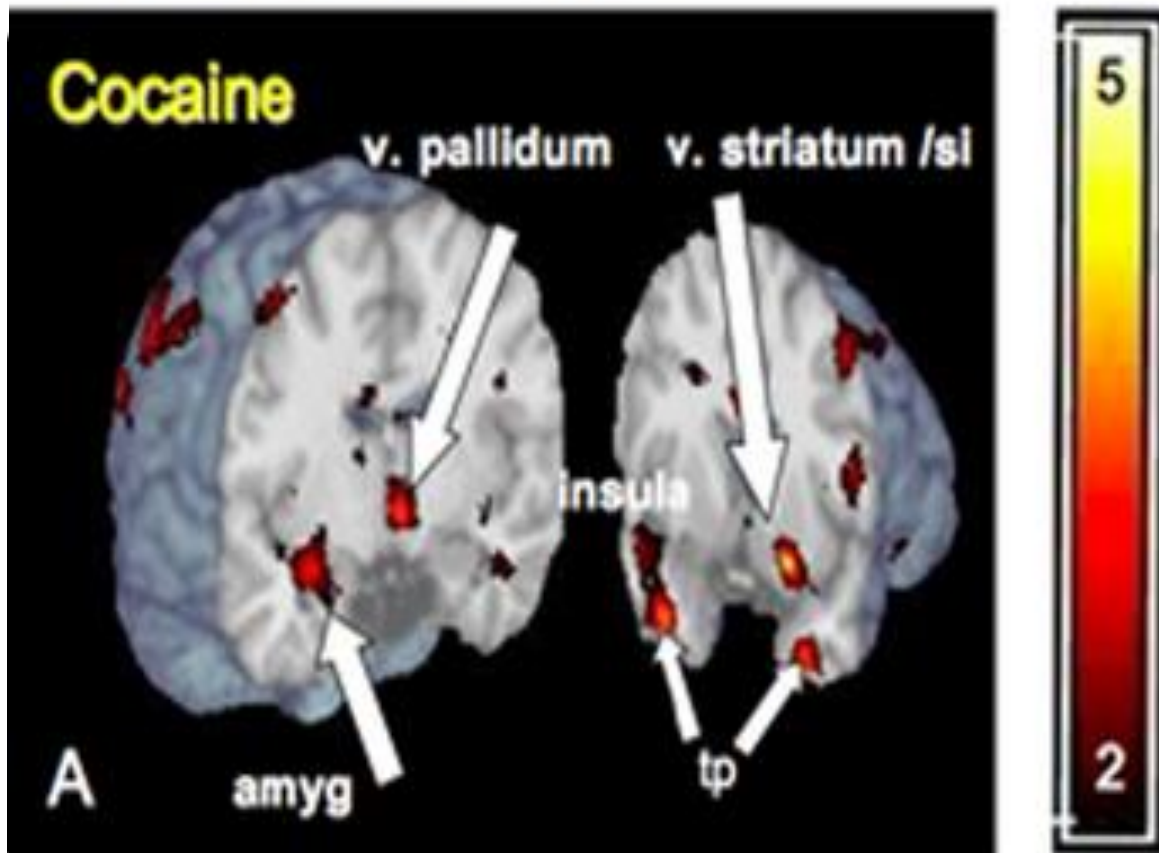
Population (Cocaine Users, Controls) x Film (cocaine, erotic)



Garavan et al A .J. Psych 2000

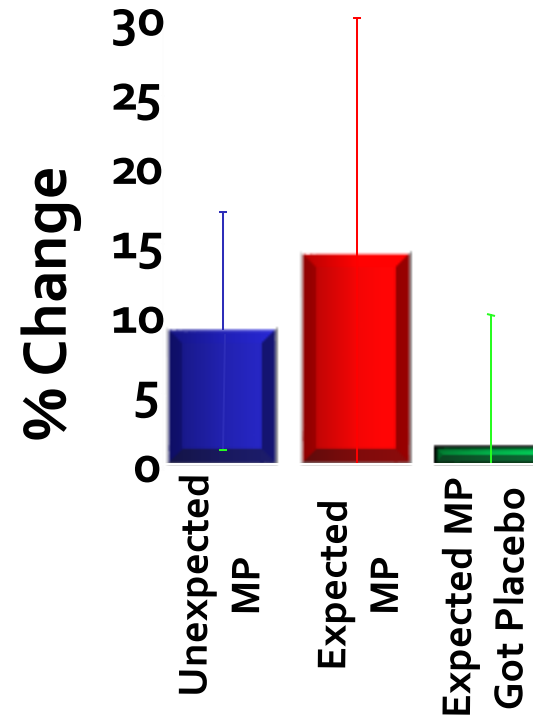
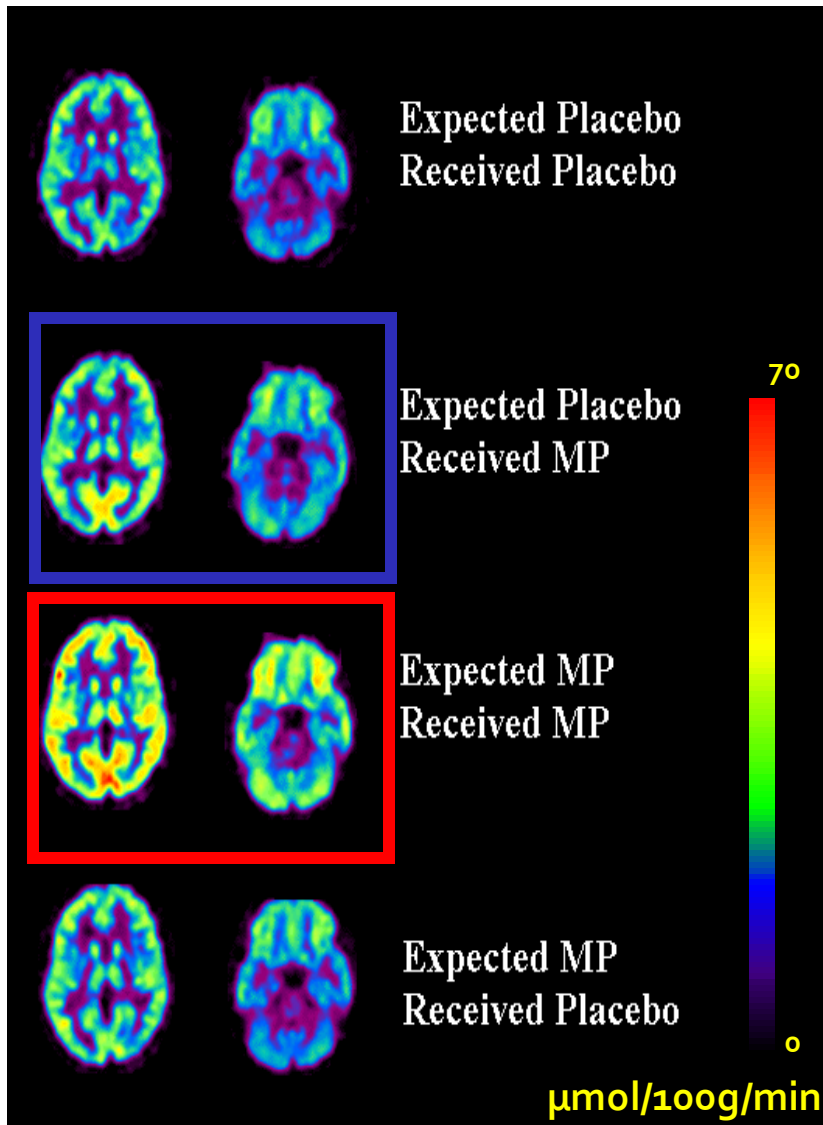
Even Unconscious Cues Can Elicit Brain Responses

Activations



Brain Regions Activated by 33 millisecond Cocaine Cues (*too fast for conscious recognition*)

Glucose Metabolism Was Greatly Increased By the *Expectation* of the Drug

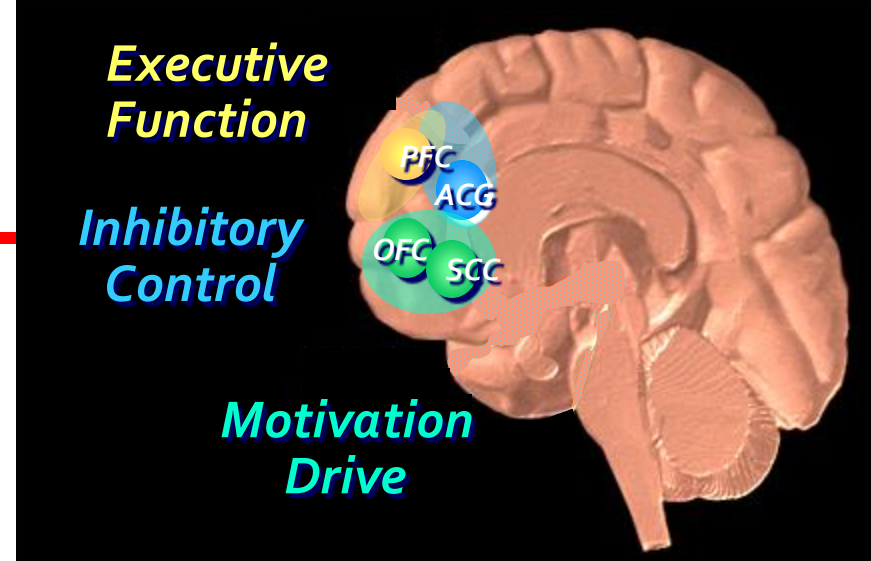


Increases in Metabolism Were About 50% Larger When MP Was Expected Than Unexpected

Memories Appear to be a Critical Part of Addiction

“People, places and things...”

3. *Motivation & Executive Control Circuits*



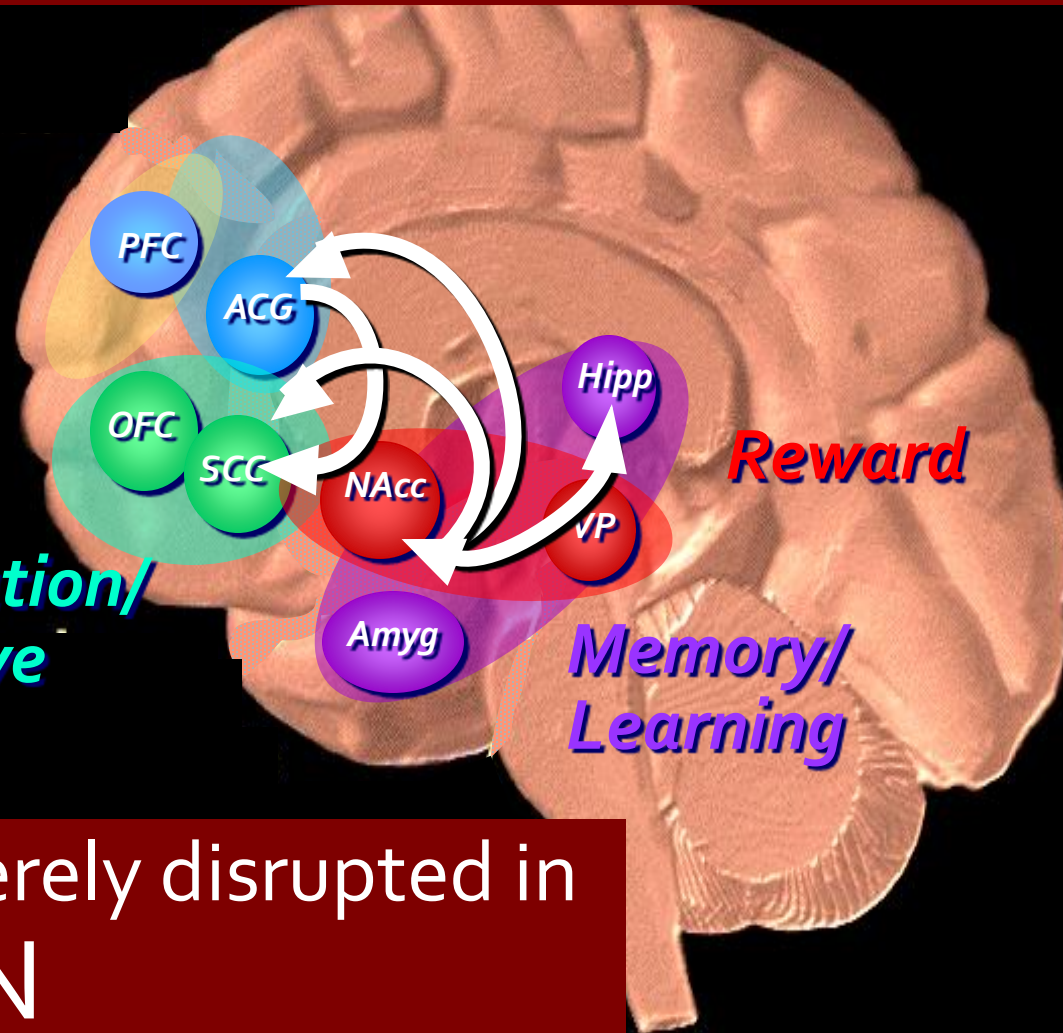
Dopamine is also associated with motivation and executive function via regulation of frontal activity.

Fine balance in connections that normally exists between reward, motivation/drive, learning/memory and inhibitory control...

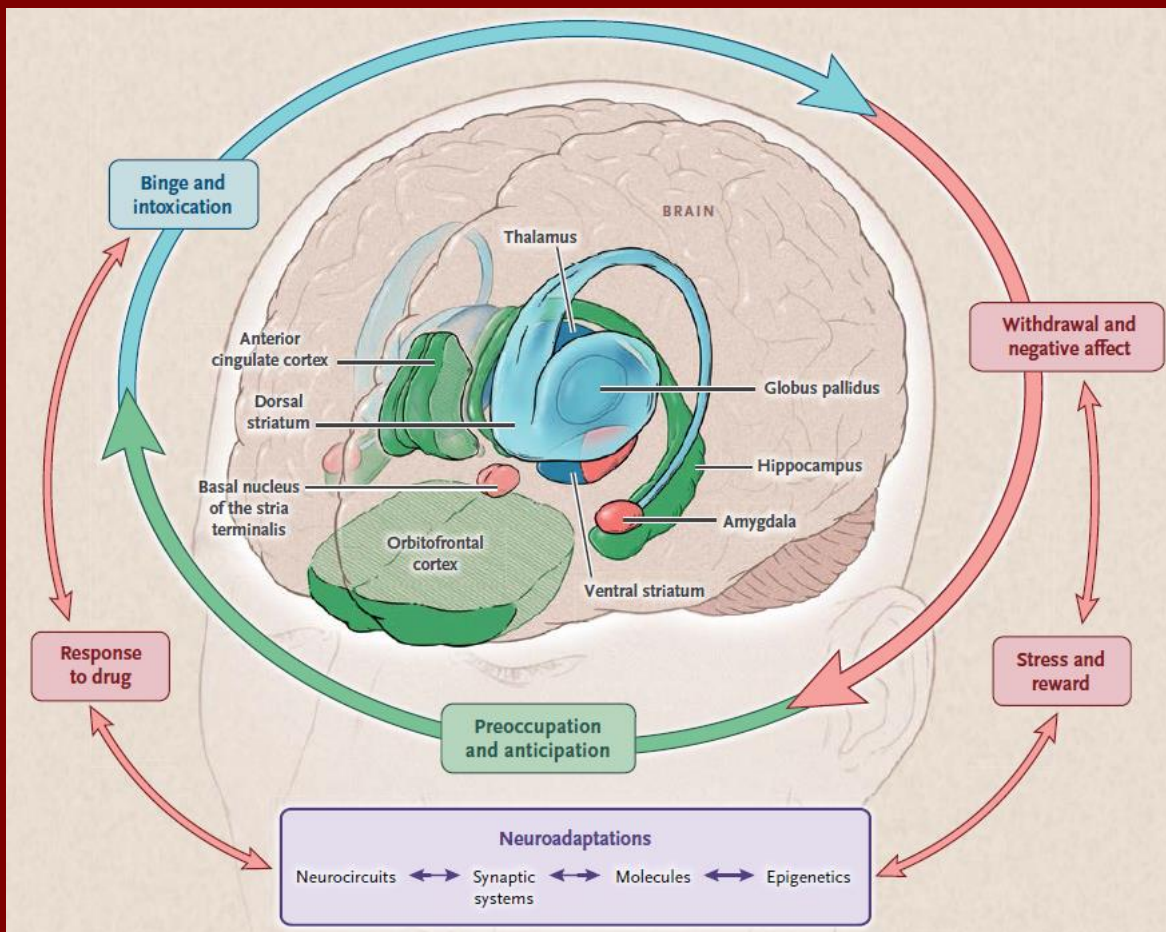
Executive Function

Inhibitory Control

Motivation/ Drive



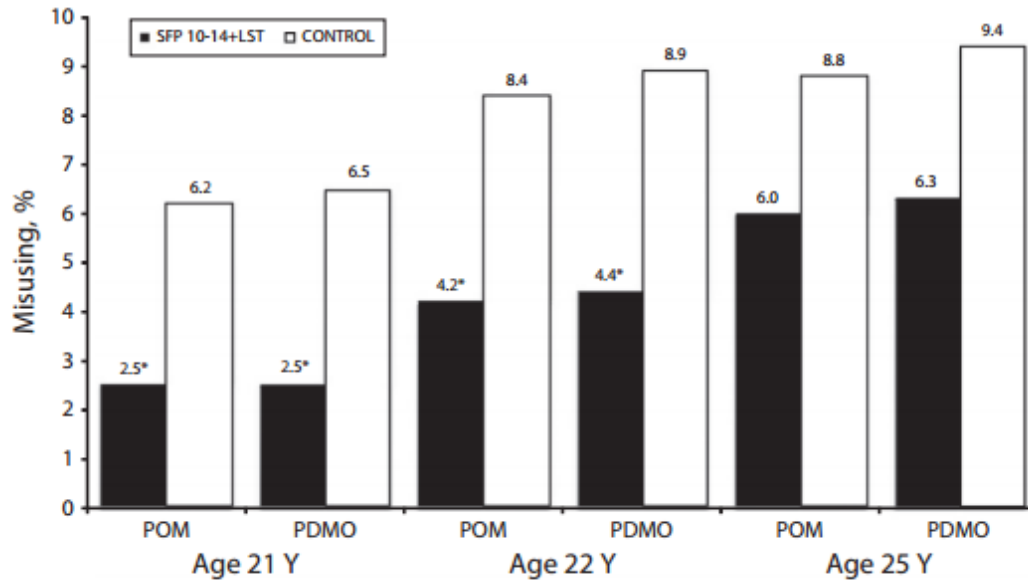
...becomes severely disrupted in
ADDICTION



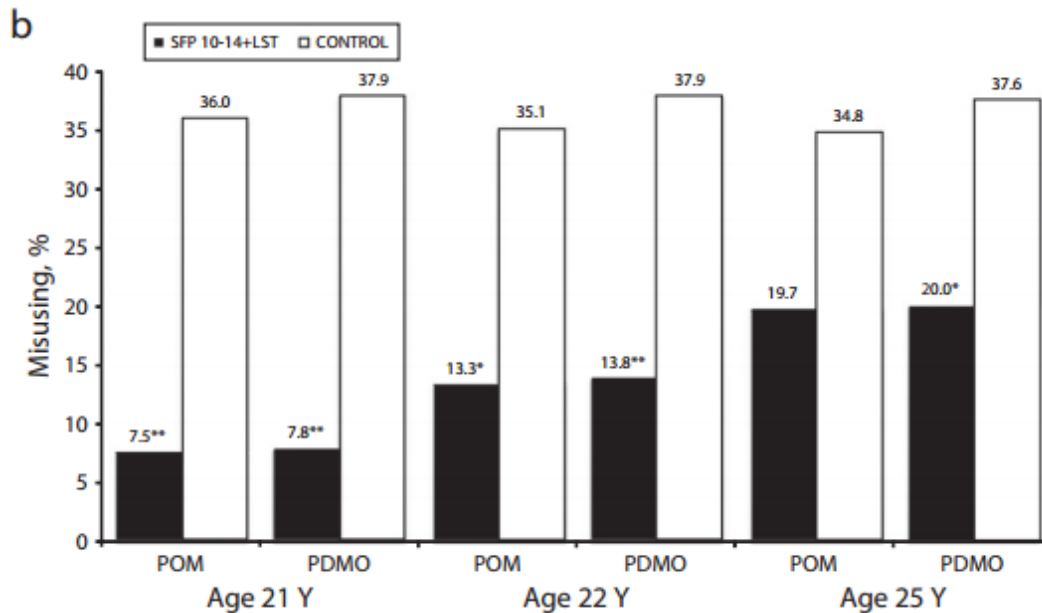
- Desensitized reward circuits → dampened pleasure
- Conditioned responses & stress reactivity → cravings and negative emotions
- Weakened executive function decision making, inhibitory control & self regulation → relapse

Stage of Addiction	Shifting Drivers Resulting from Neuroadaptations		
Binge and intoxication	Feeling euphoric	→ Feeling good	→ Escaping dysphoria
Withdrawal and negative affect	Feeling reduced energy	→ Feeling reduced excitement	→ Feeling depressed, anxious, restless
Preoccupation and anticipation	Looking forward	→ Desiring drug	→ Obsessing and planning to get drug

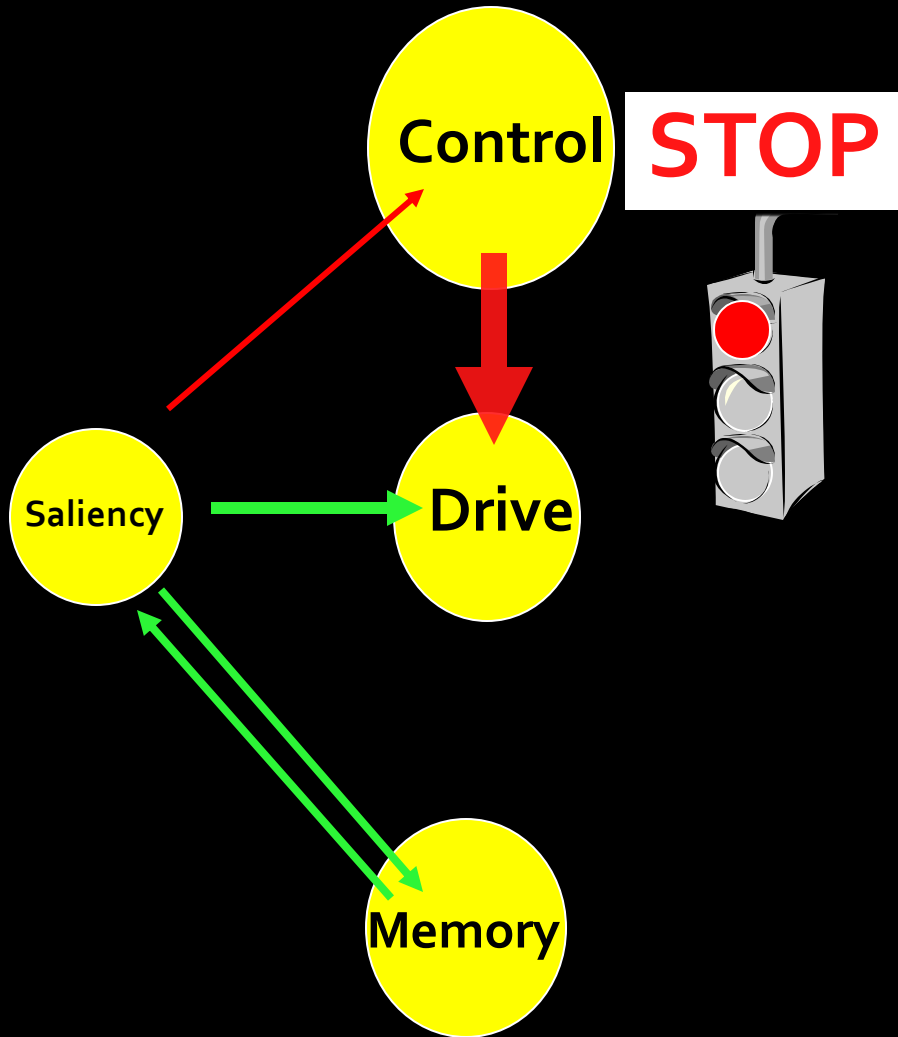
Prescription Drug Abuse Prevention



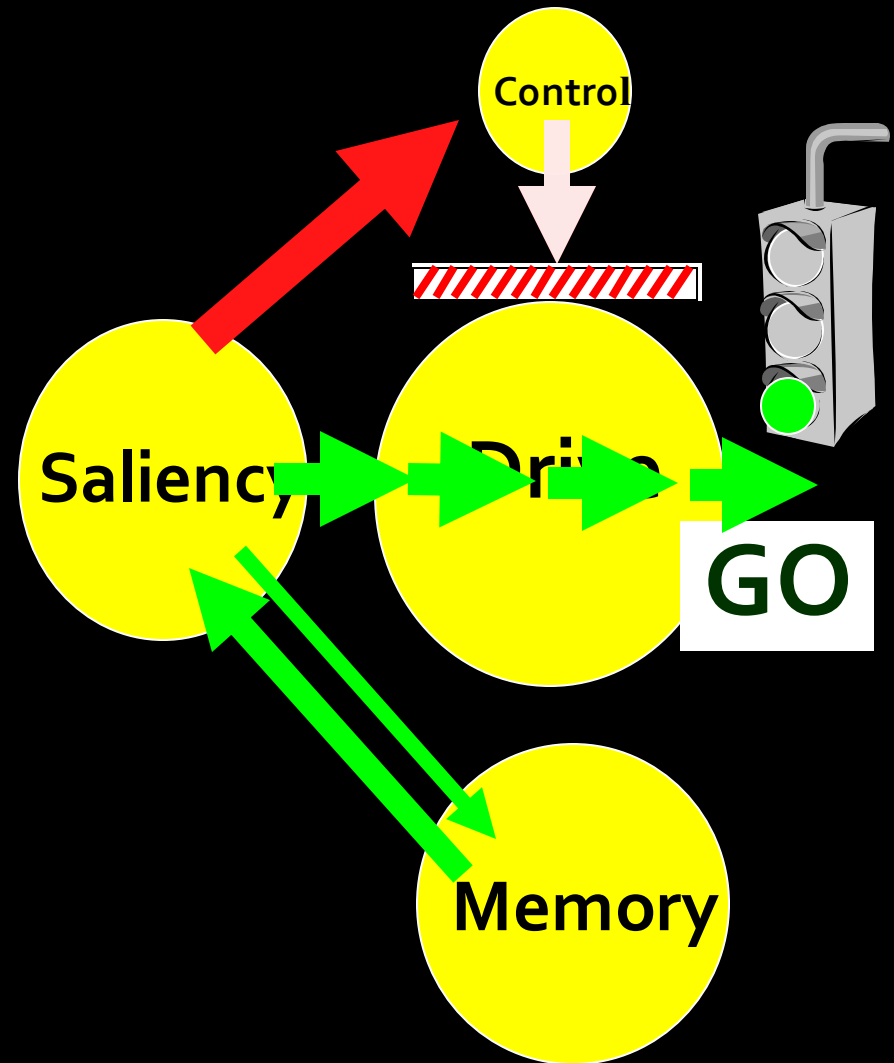
Three studies suggest the impact of universal prevention on prescription drug abuse.



Non Addicted Brain

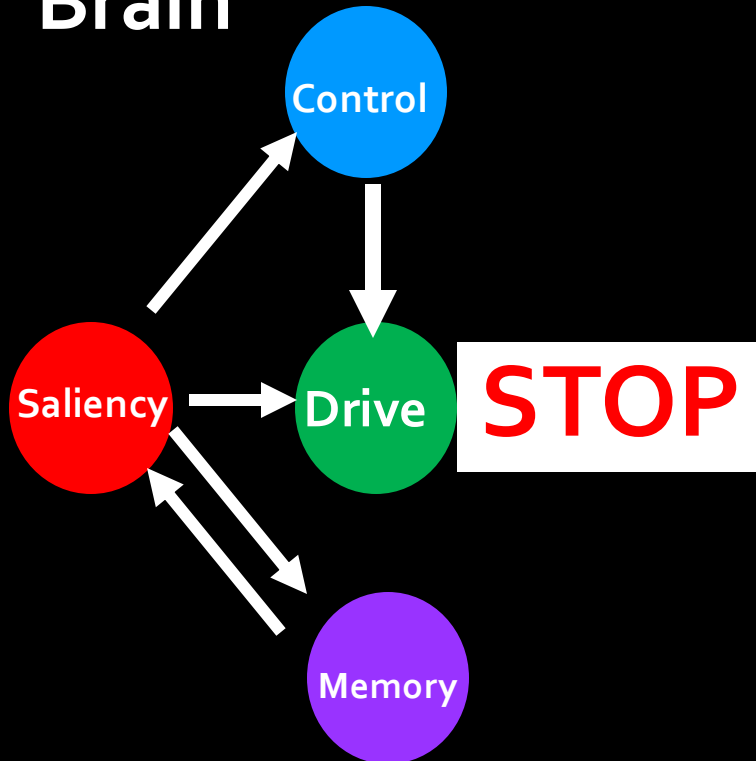


Addicted Brain



Behavioral Treatments

Non-Addicted Brain



Interfere with drug's reinforcing effects

Executive function/
Inhibitory control

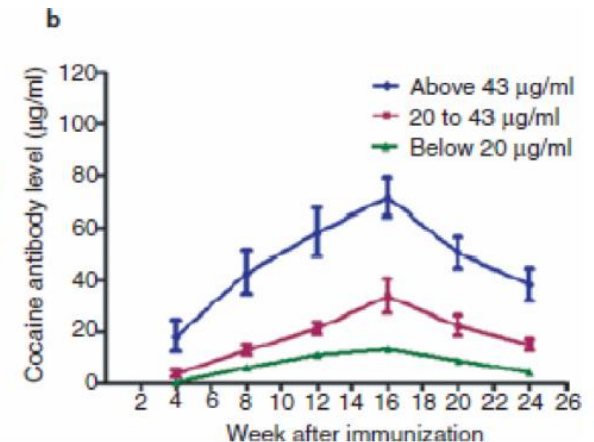
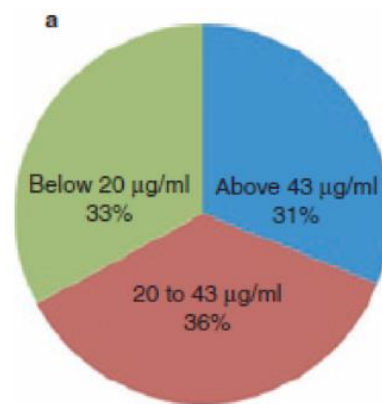
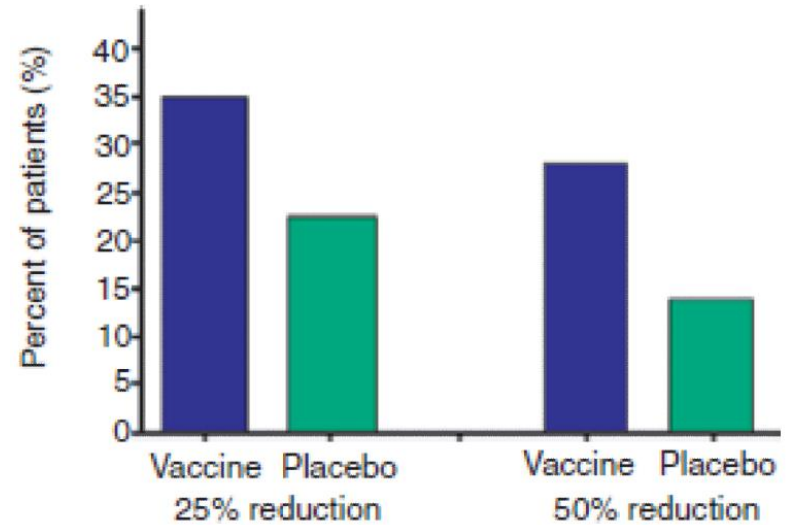
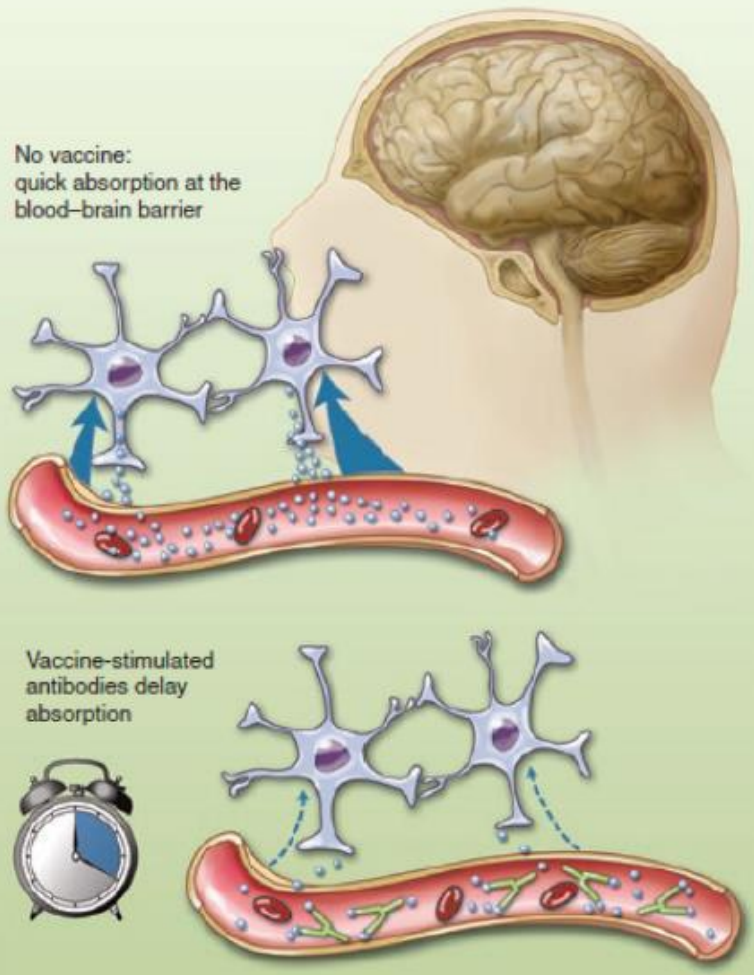
Strengthen prefrontal-striatal communication

Interfere with conditioned memories

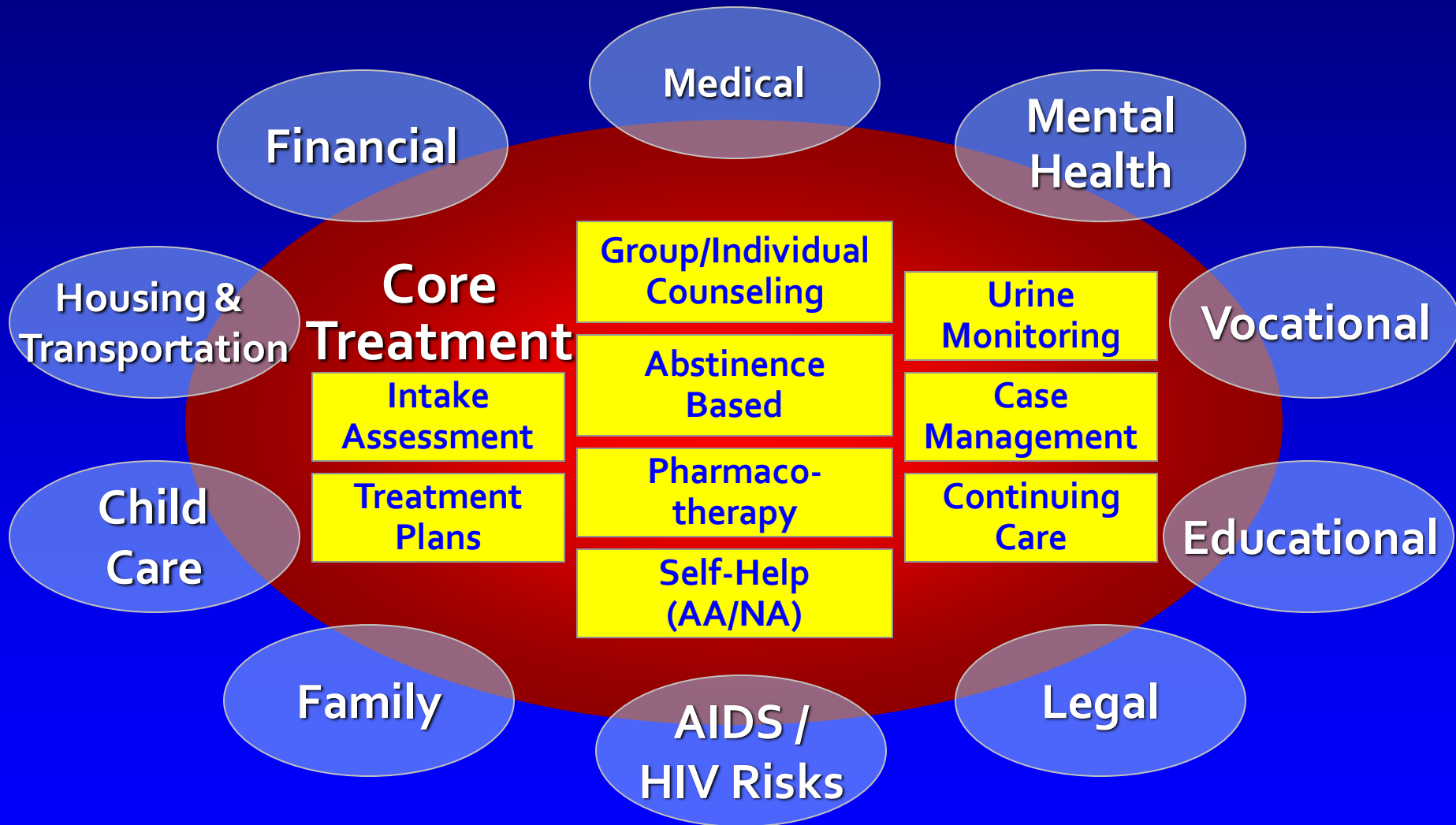
Teach new memories

Counteract stress responses that lead to relapse

Vaccines for Addiction



Addiction Treatment Core Components and Comprehensive Services



Receipt of SUD Services Lags Behind other Chronic Disorders

Any Mental
Illness
45.9 million



39.2 % receiving
treatment

Substance
Use Disorder
23.1 million



11.2 % receiving
treatment

Diabetes
25.8 million



84 % receiving
treatment

Heart Disease
81.1 million



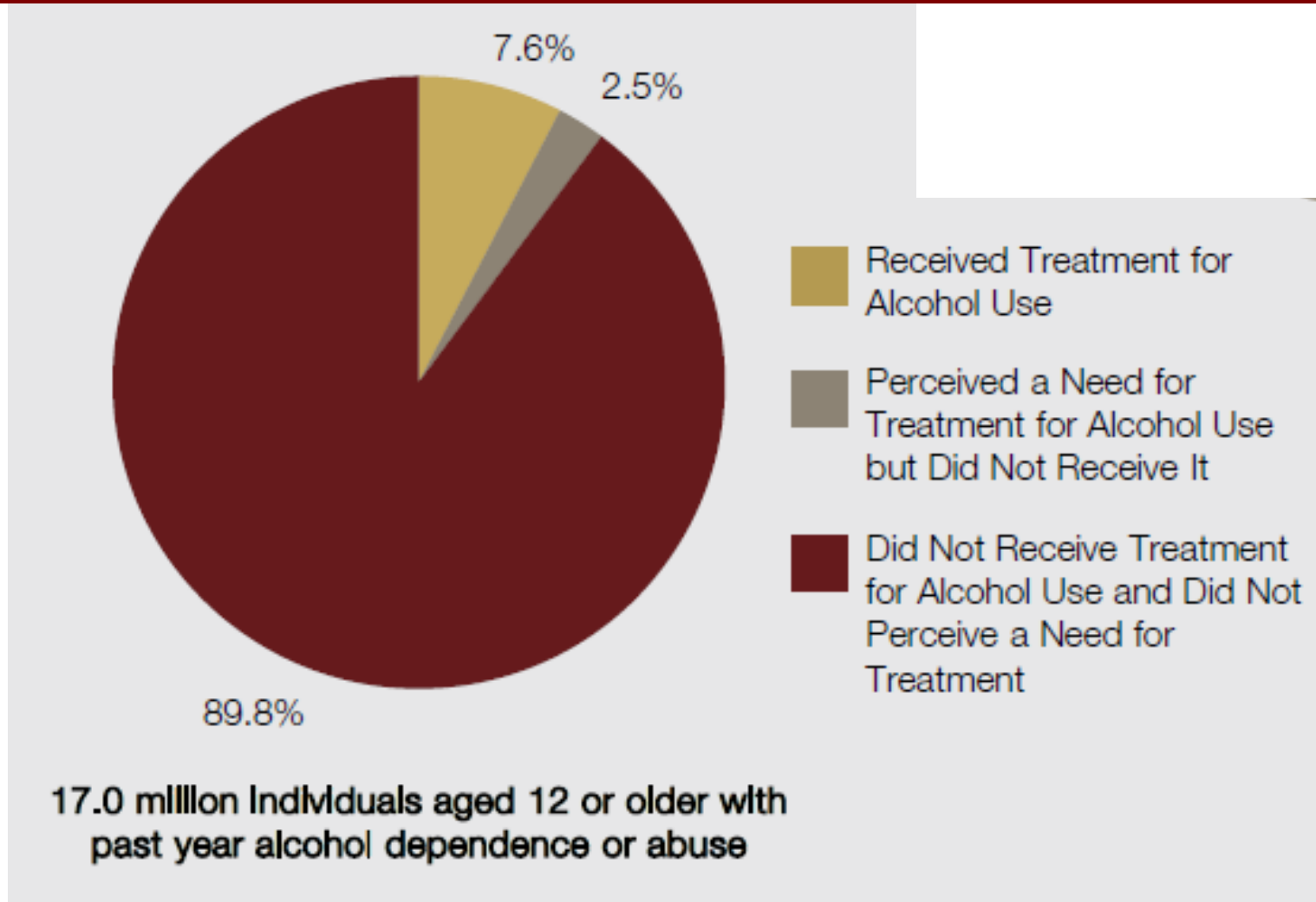
74.6 % receiving
screenings

Hypertension
74.5 million

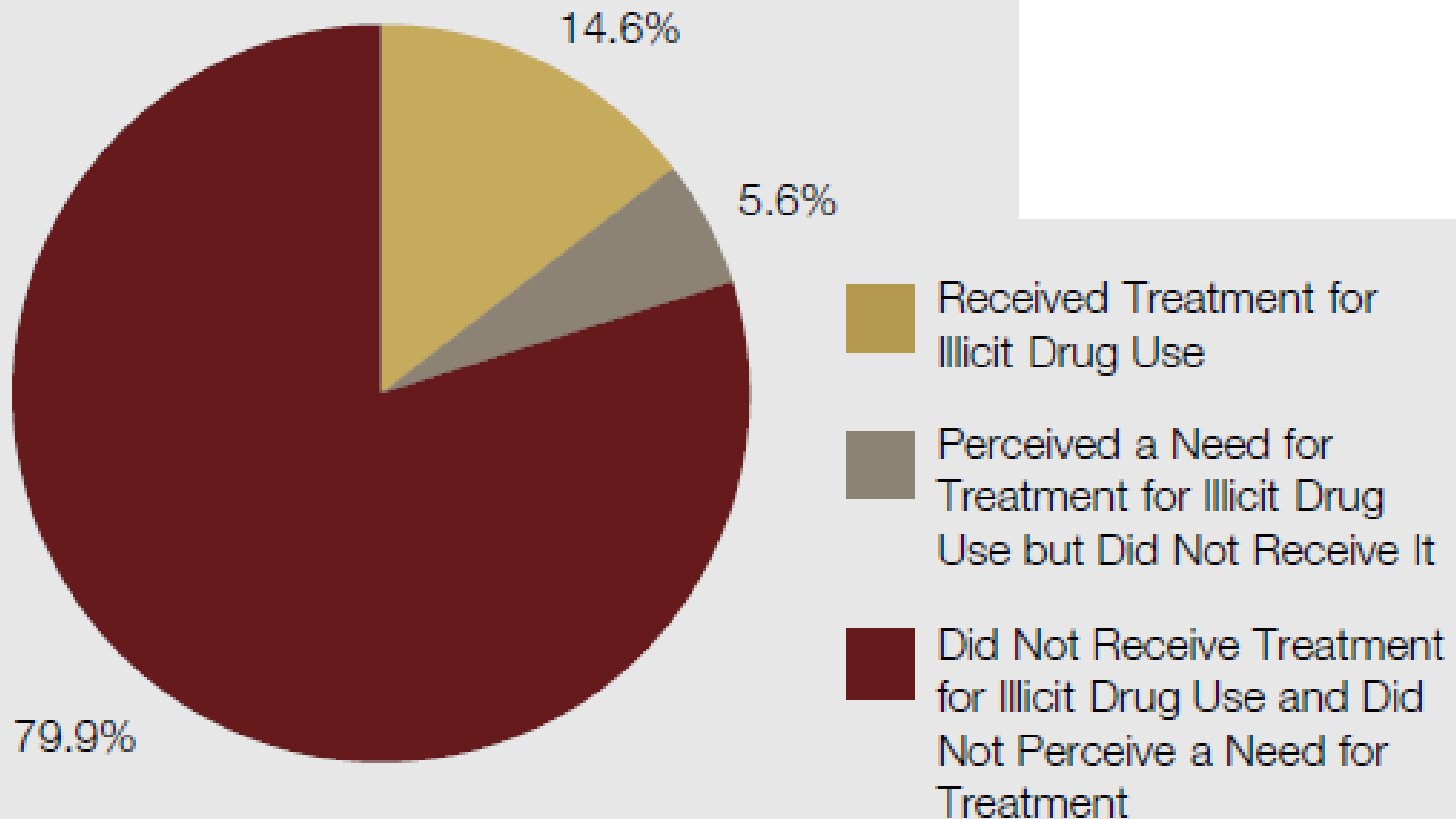


70.4 % receiving
treatment

Perception of Treatment Need Among Adults with Alcohol Use Disorders (2014)

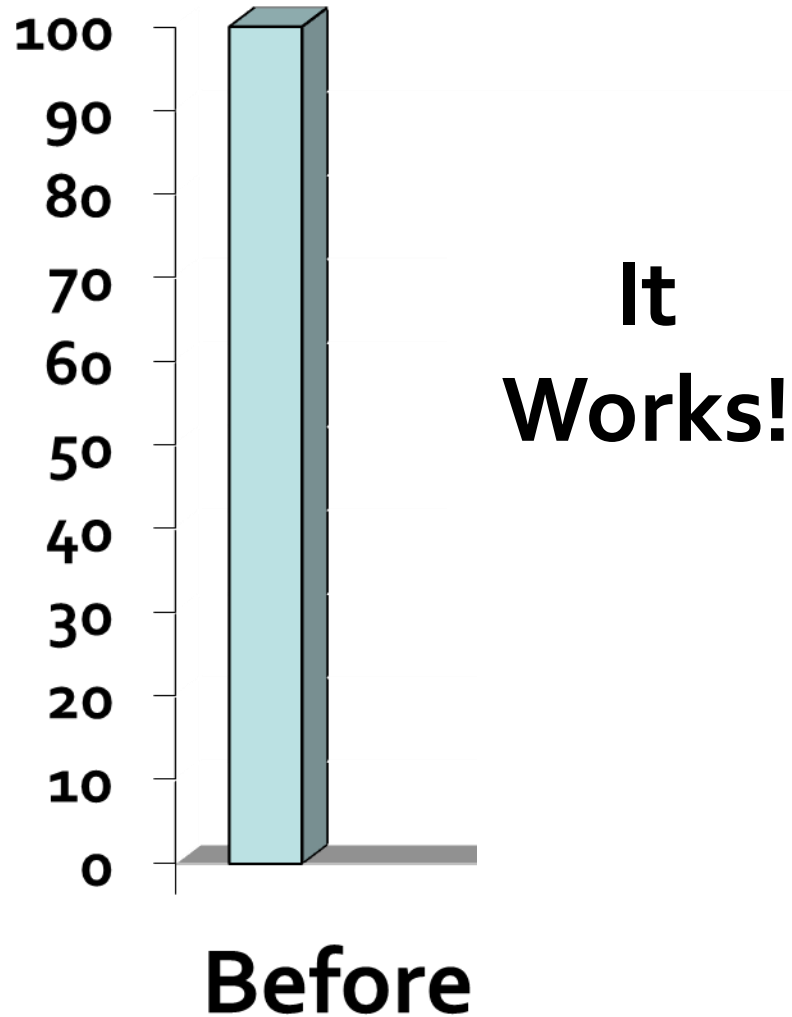


Perception of Treatment Need Among Adults with Drug Use Disorders (2014)

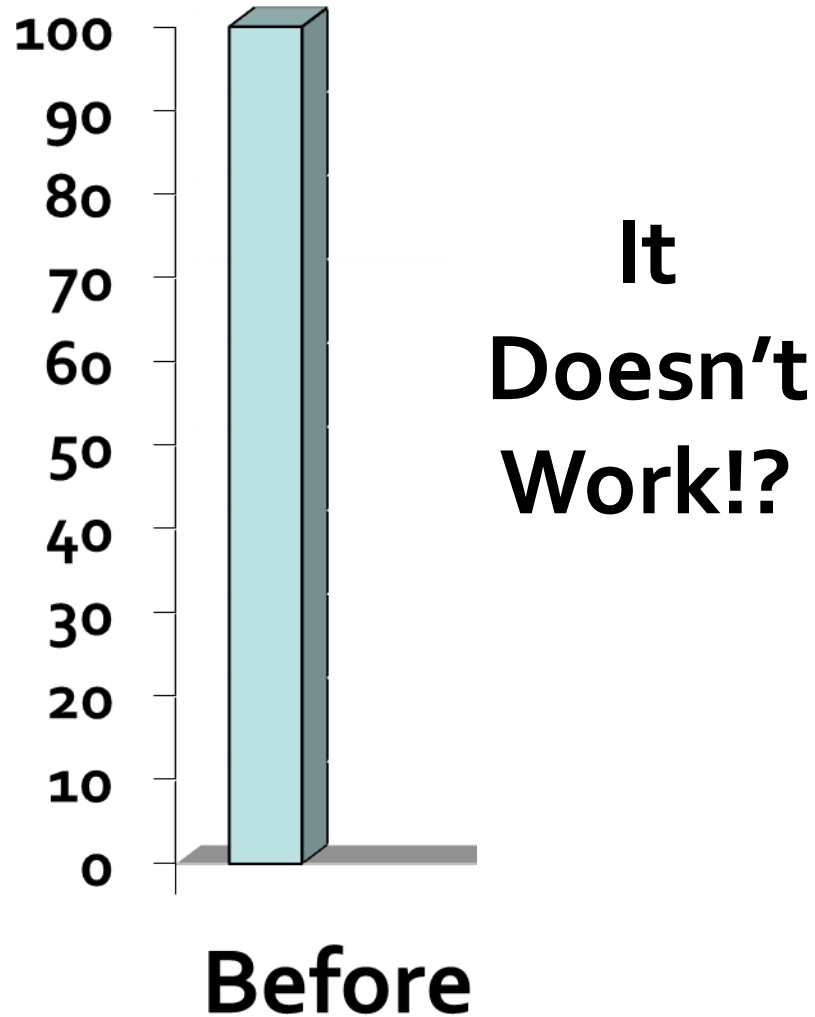


7.1 million individuals aged 12 or older with past year illicit drug dependence or abuse

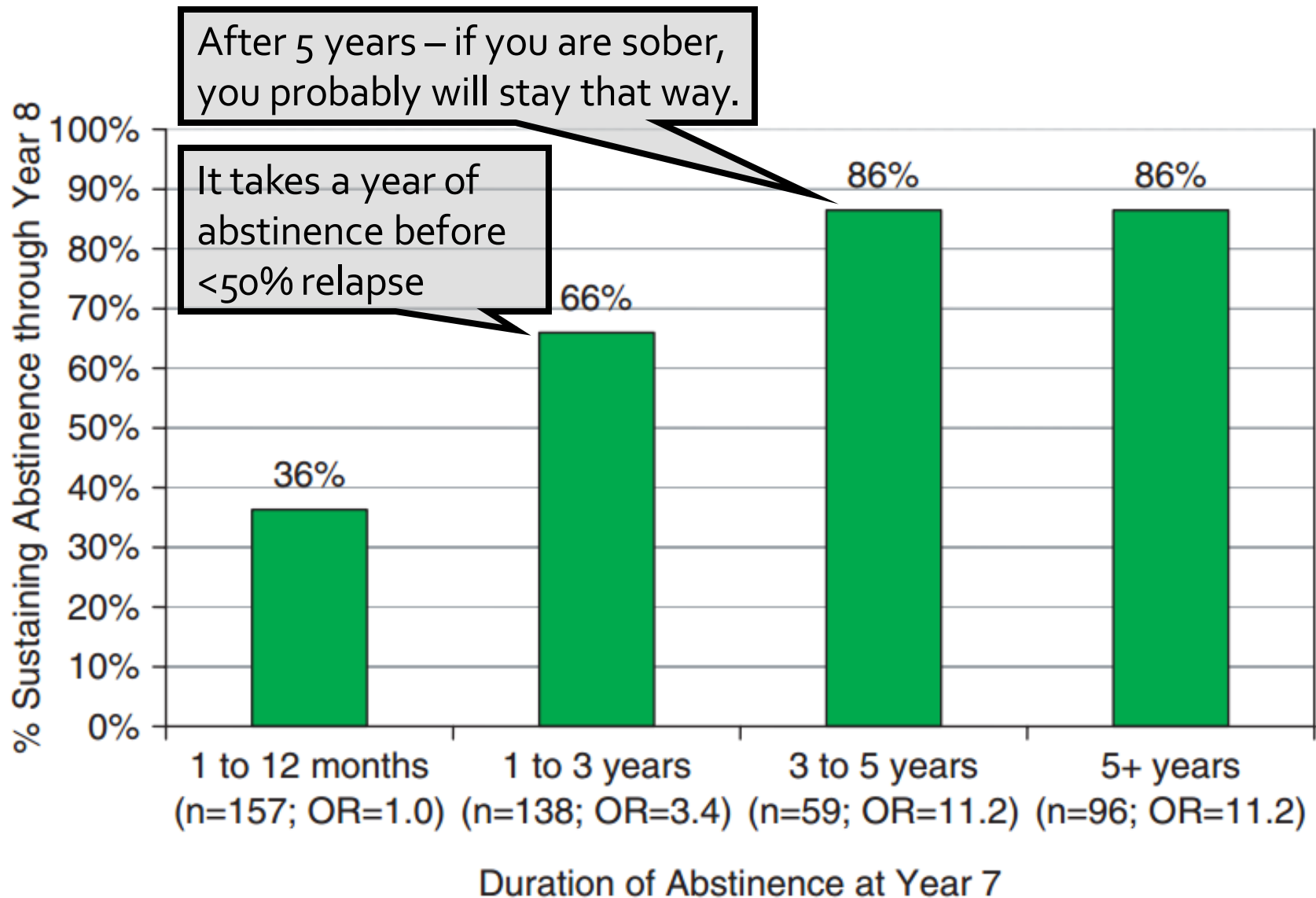
Evaluating Hypertension Treatment



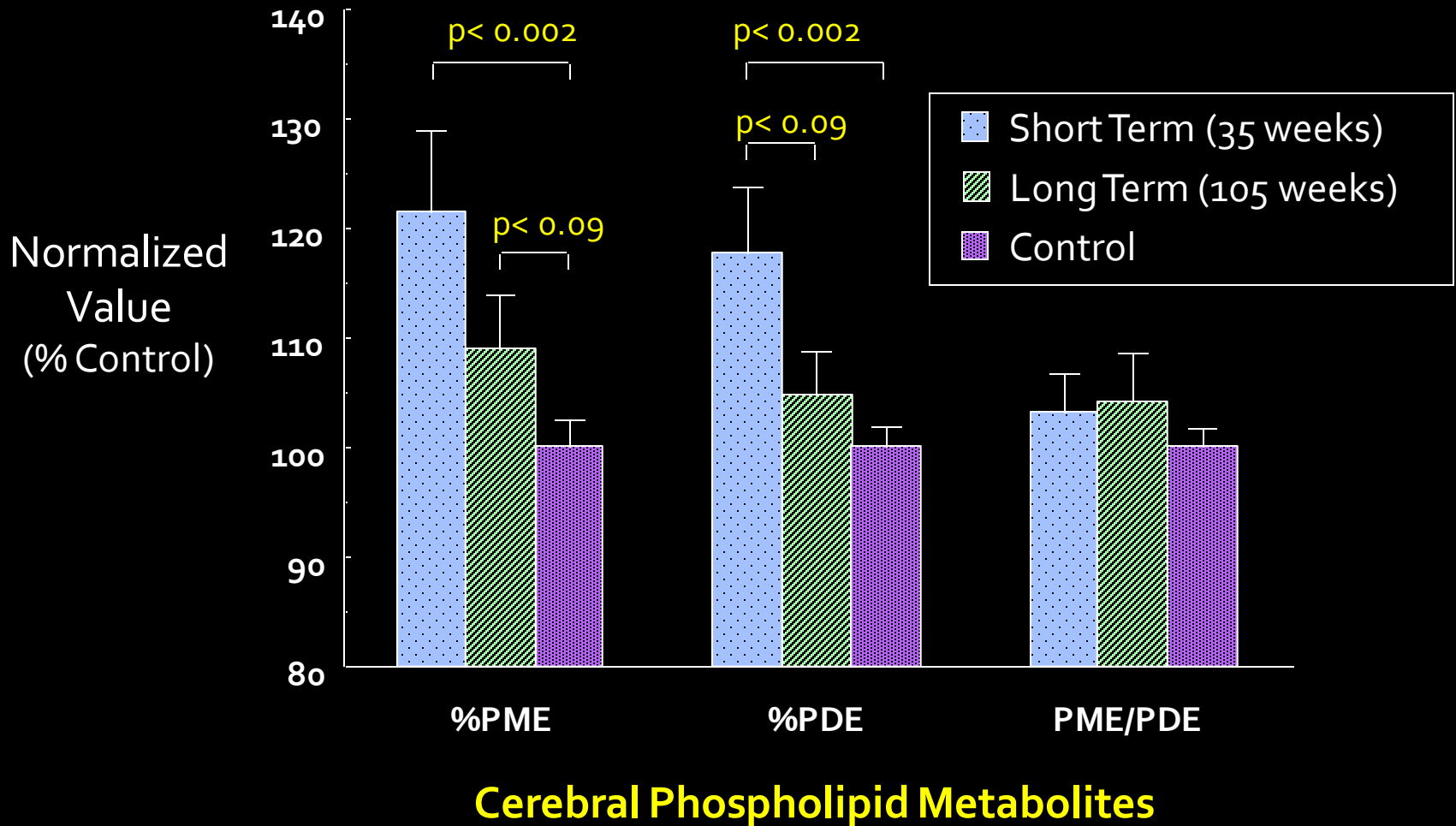
Evaluating Addiction Treatment



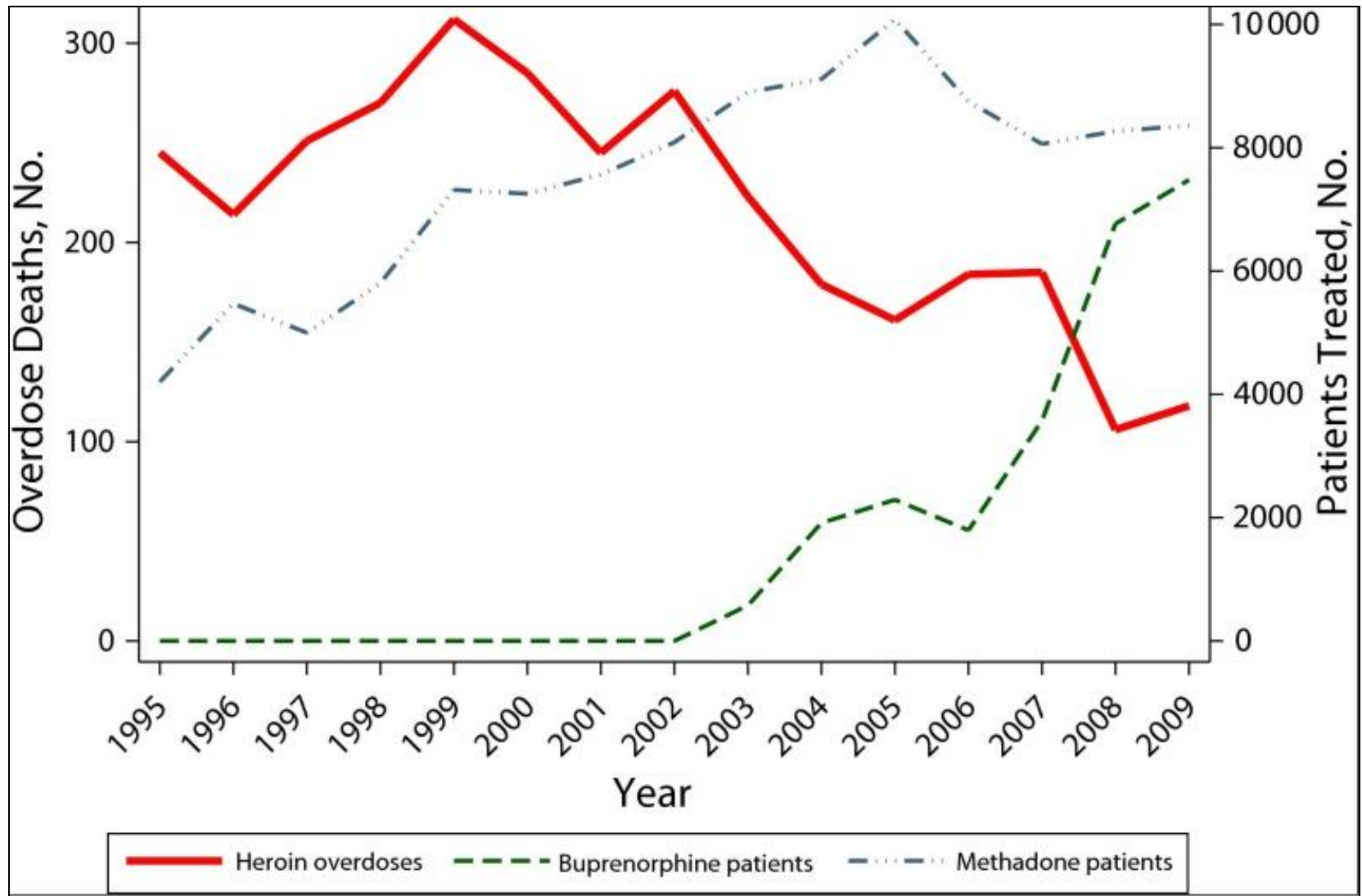
Longitudinal Trends in Recovery (Pathways $N=1326$)



Methadone Maintenance Improved Brain Neurochemistry



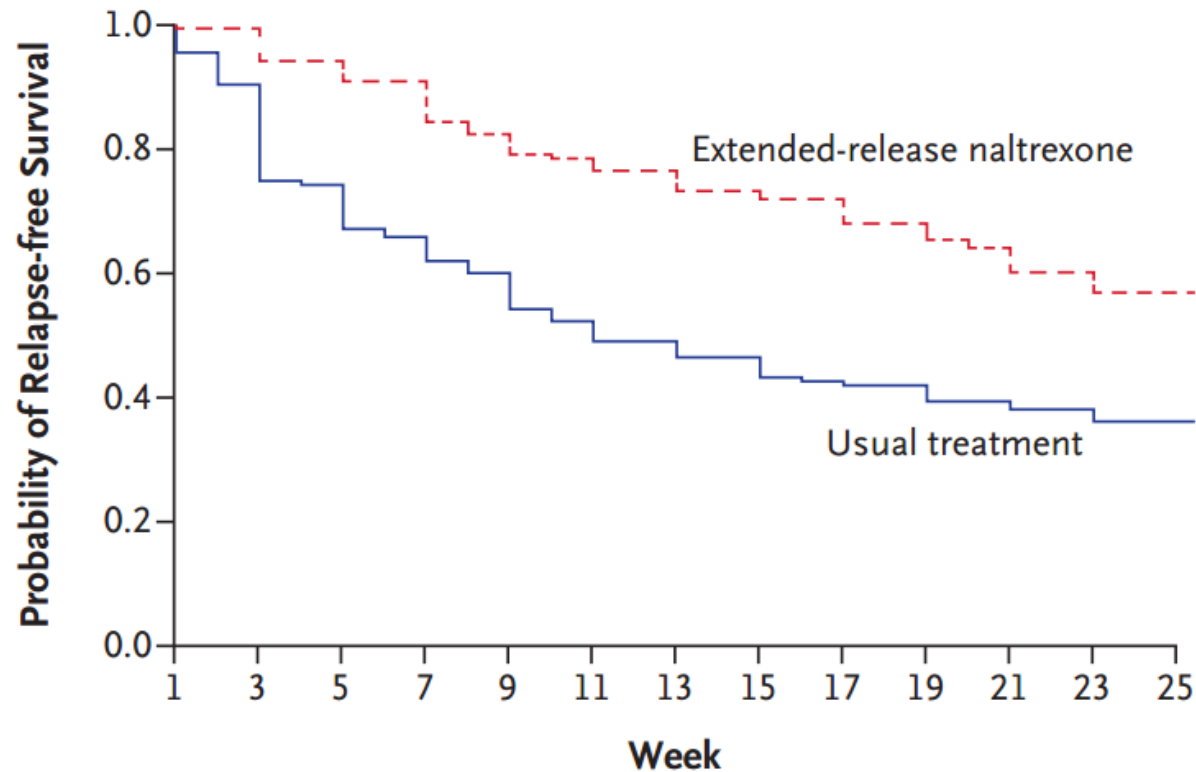
Medical Treatment May Reduce Deaths



ED–Initiated Buprenorphine/Naloxone Treatment for Opioid Dependence

- RCT n=329 opioid-dependent patients treated in an urban teaching hospital ED
 - 104 → referral
 - 111 → brief intervention and referral
 - 114 → buprenorphine treatment
- Buprenorphine treatment increased engagement in outpatient addiction treatment services, reduced self-reported illicit opioid use, decreased inpatient addiction treatment services

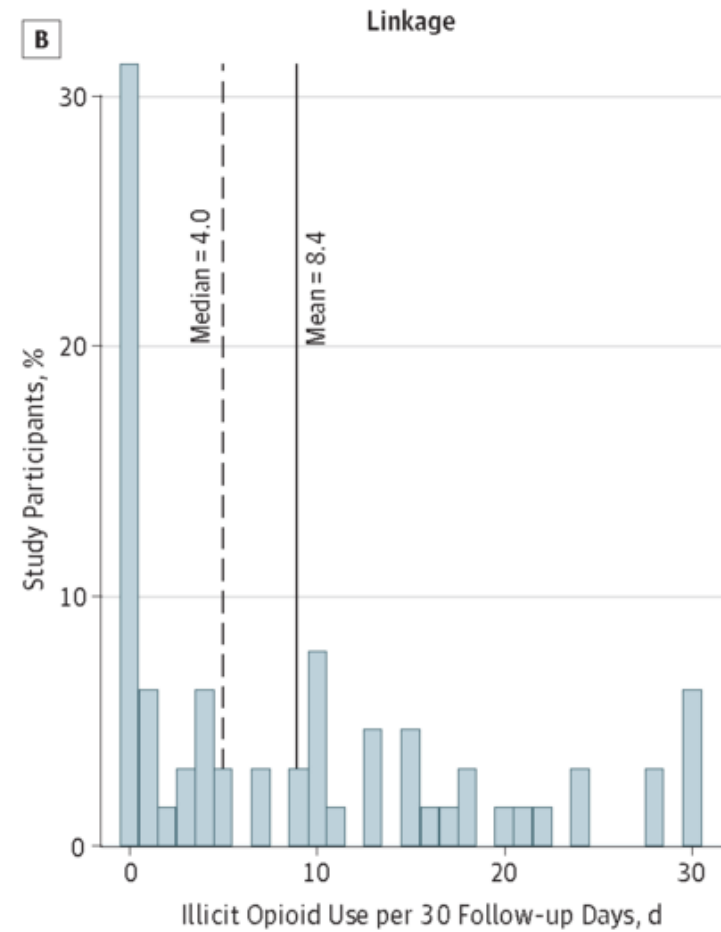
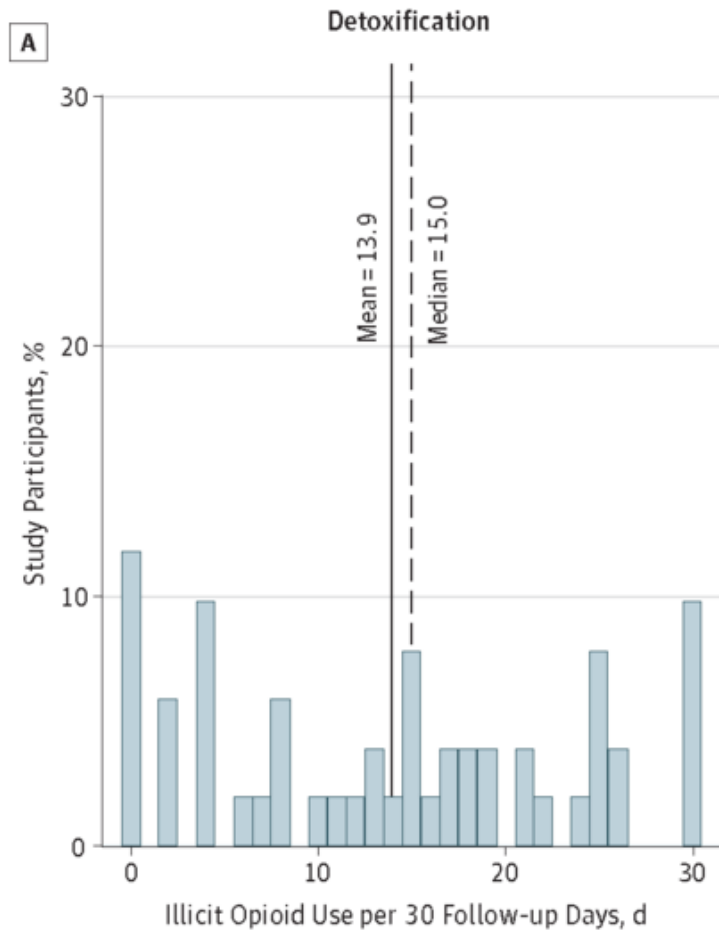
Extended-Release Naltrexone to Prevent Opioid Relapse in Criminal Justice Offenders



No. at Risk

Extended-release naltrexone	153	144	139	129	121	117	112	110	104	100	92	87	87
Usual treatment	155	116	104	96	84	76	72	67	65	61	59	56	56

Buprenorphine Treatment for Hospitalized, Opioid-Dependent Patients



Addiction is Like Many Other Diseases

- Addiction is preventable
- Addiction is treatable
- Recovery is possible

The Language We Use...

Friedmann and Schwartz *Addiction Science & Clinical Practice* 2012, **7**:10
<http://www.ascjournal.org/content/7/1/10>



ADDICTION SCIENCE &
CLINICAL PRACTICE

COMMENTARY

Open Access

Just call it “treatment”

Peter D Friedmann^{1*} and Robert P Schwartz²



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Editorial

Stop Talking ‘Dirty’: Clinicians, Language, and Quality of Care for the Leading Cause of Preventable Death in the United States

John F. Kelly, PhD^a, Sarah E. Wakeman, MD^b, Richard Saitz, MD^c

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EDITORIAL

Confronting Inadvertent Stigma and Pejorative Language in Addiction Scholarship: A Recognition and Response

Lauren M. Broyles, PhD, RN,^{1,2,3} Ingrid A. Binswanger, MD, MPH,^{4,5} Jennifer A. Jenkins, MPH,¹
Deborah S. Finnell, DNS, PMHNP,⁶ Babalola Faseru, MD, MPH,^{7,8,9} Alan Cavaioia, PhD,¹⁰
Marianne Pugatch, MSW,^{11,12,13,14} and Adam J. Gordon, MD, MPH^{1,2,3}

New Legislation...

The Mental Health Parity and Addiction Equity Act of 2008 (MHPAEA)

Requires medical insurance plans to provide same coverage for SUD and other mental illnesses that is provided for other illnesses

TREAT Act Legislation Proposes Increasing Buprenorphine Prescribing Cap

by ASAM Staff | August 12, 2014

On July 23, Massachusetts Senator Edward Markey introduced The Recovery Enhancement for Addiction Treatment Act (TREAT Act). This bill, cosponsored by four other Senators, would lift the buprenorphine prescribing limit for addiction physician specialists and non-specialist providers that satisfy additional training requirements

COMPREHENSIVE ADDICTION AND RECOVERY ACT (CARA)

ASK YOUR SENATOR OR REPRESENTATIVE TO SUPPORT THE COMPREHENSIVE ADDICTION AND RECOVERY ACT (CARA) OF 2015

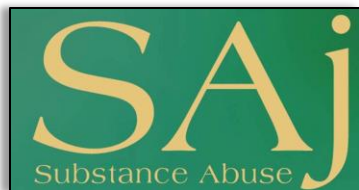
If you are interested in learning more...



- **ASAM** (American Society of Addiction Medicine)
 - founded in 1954, a professional society representing over 3,700 physicians in the field of addiction medicine dedicated to increasing access and improving the quality of addiction treatment, educating physicians and the public and promoting the appropriate role of physicians in the care of patients with addiction.



- **AMERSA** (Association for Medical Education and Research in Substance Abuse)
 - founded in 1976, a professional organization whose mission is to improve health and well-being through interdisciplinary leadership in substance use education, research, clinical care and policy. ~300 members



If you are interested in a career...

The Addiction Medicine Foundation

40

Addiction Medicine Fellowship Programs

Accredited by

The Addiction Medicine Foundation

2016-2017

The
Addiction
Medicine
Foundation

Advancing
Medical
Practice in
Addiction
Prevention
and Treatment



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**American Board of Medical Specialties Officially Recognizes
Addiction Medicine as a Subspecialty**