The Science of Drug Addiction: Implications for Treatment

Susan R B Weiss, Ph.D.
Acting Director
Office of Science Policy and Communications
National Institute on Drug Abuse
National Institutes of Health
Department of Health and Human Services

Addiction Medicine: Improving Clinical, Teaching, and Research Skills
May 2012

Estimated Economic Cost to Society Due to Substance Abuse and Addiction:

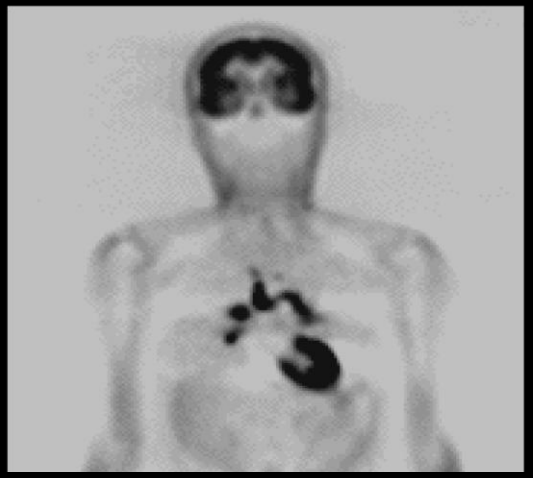
Tobacco:	**$193 billion/year**
Alcohol:	**$235 billion/year**
Illegal drugs:	**$181 billion/year**
Total:	**$609 billion/year**

Source: ONDCP, 2004; CDC, 2007; Rehm et al., 2009 Lancet 373:2223-33

NIDA

ADDICTION

MEDICAL



Neurotoxicity
Aids
Cancer
Mental illness

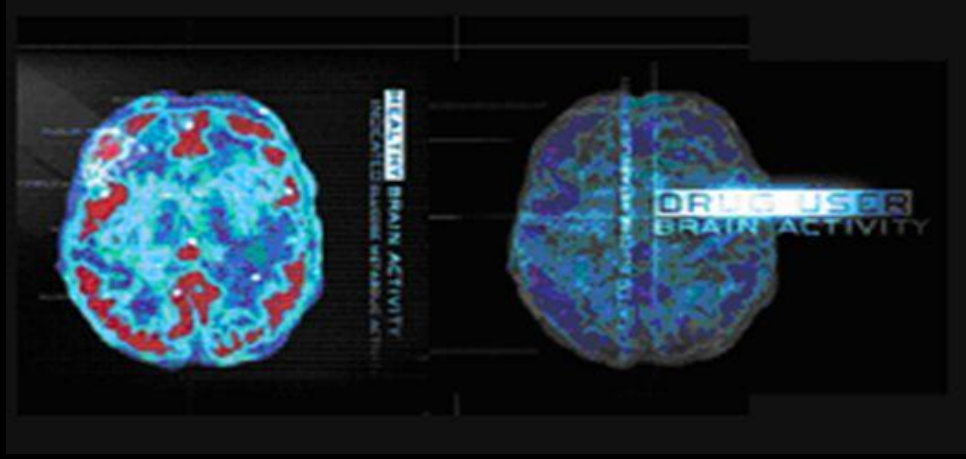
SOCIAL

Homelessness
Crime
Violence

ECONOMIC

Health care
Productivity
Accidents

What is Addiction? Addiction is A Brain Disease



- that develops over time
- that starts as voluntary drug use
- that leads to uncontrollable drug craving and use
- that changes brain structure and function
- that interferes with a persons functioning in family and society
- that leads to serious medical consequences

No one wants to be a drug addict- they want to say "no" but they can't- it's not a moral failing or a result of "weak will"- it's a compulsive behavioral disorder

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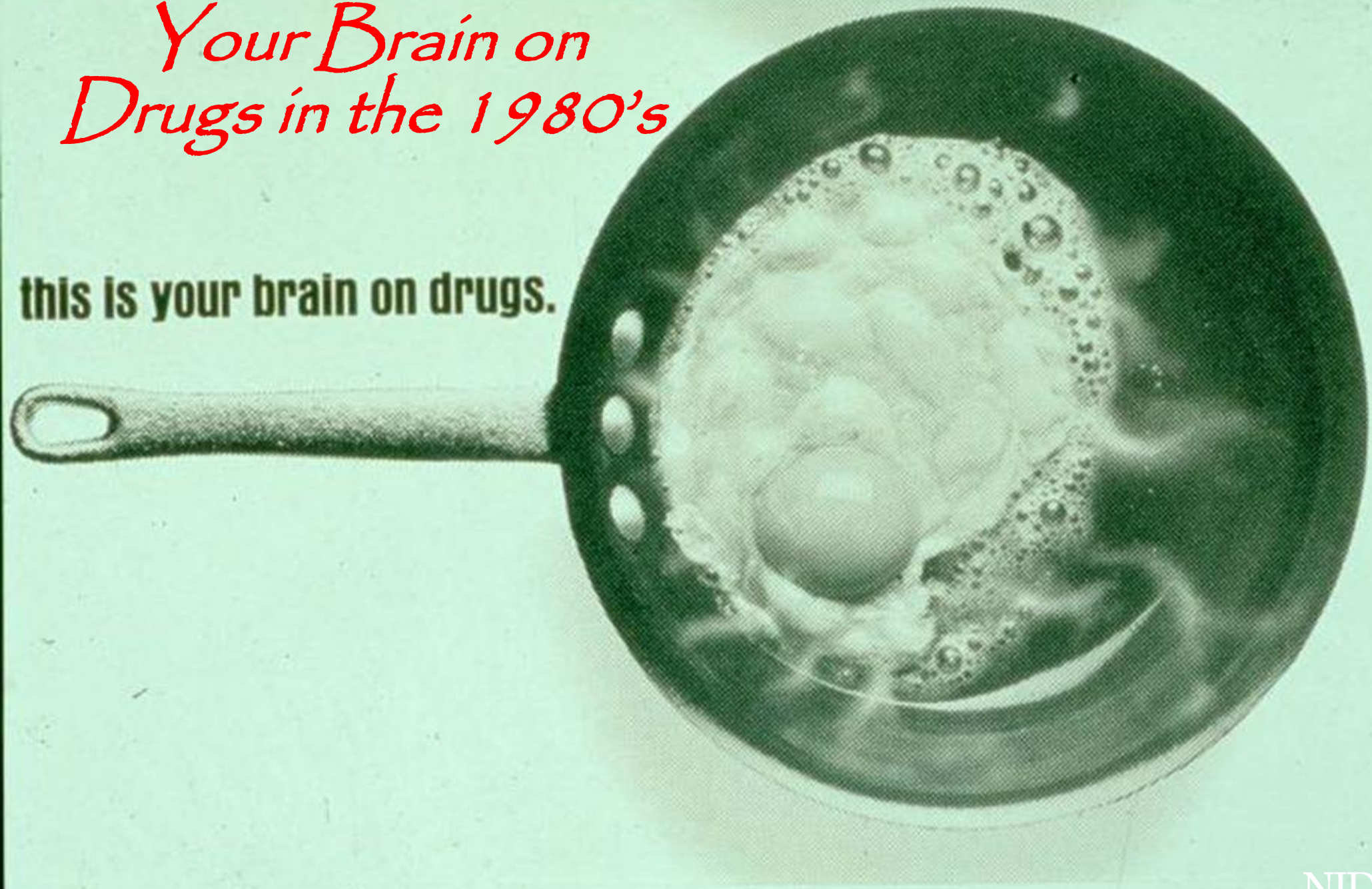
Advances in science have revolutionized our fundamental understanding of drug abuse and addiction.

Your Brain on Drugs in the 1980's



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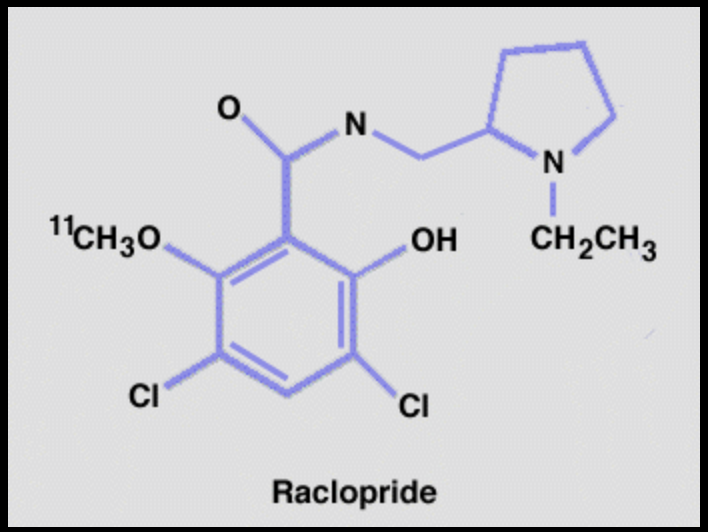
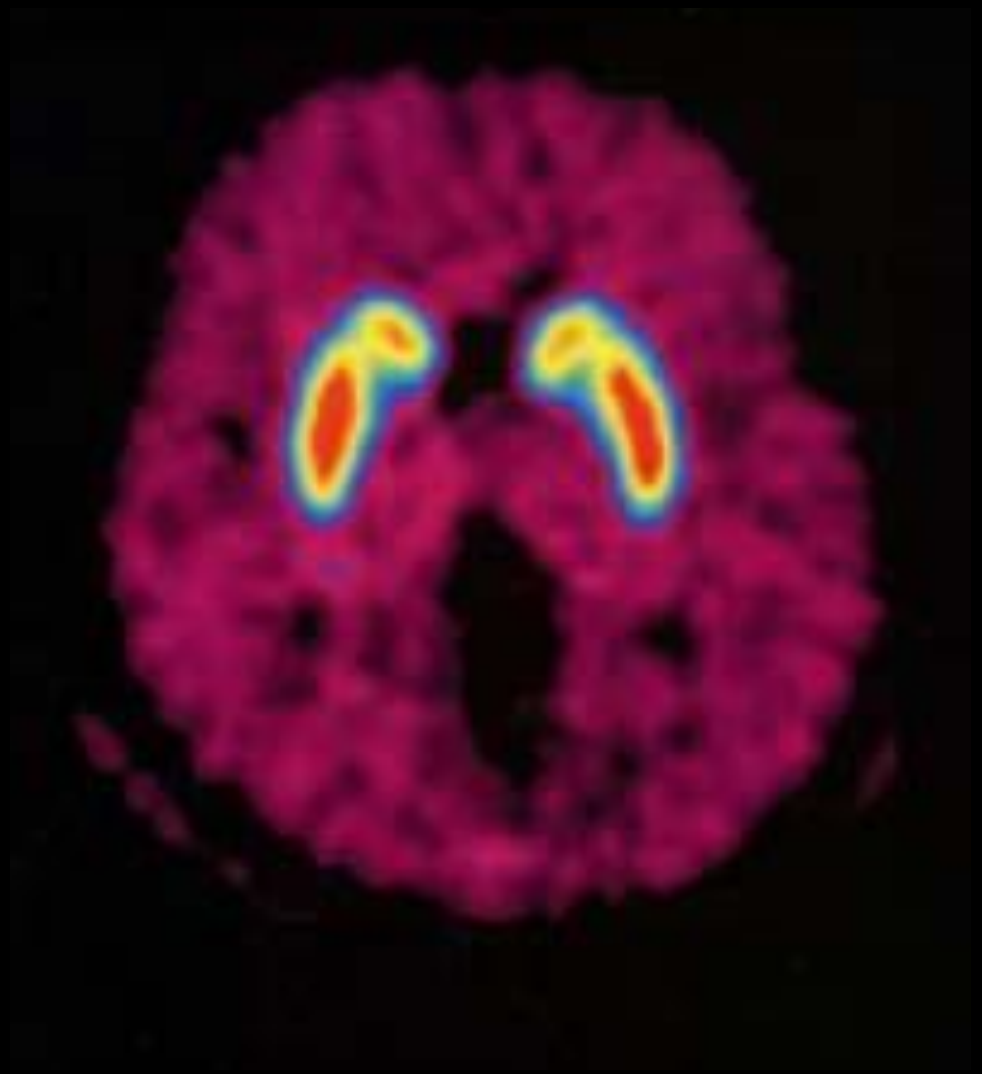
Your Brain on Drugs Today:
Functional Mapping with Specific Ligands

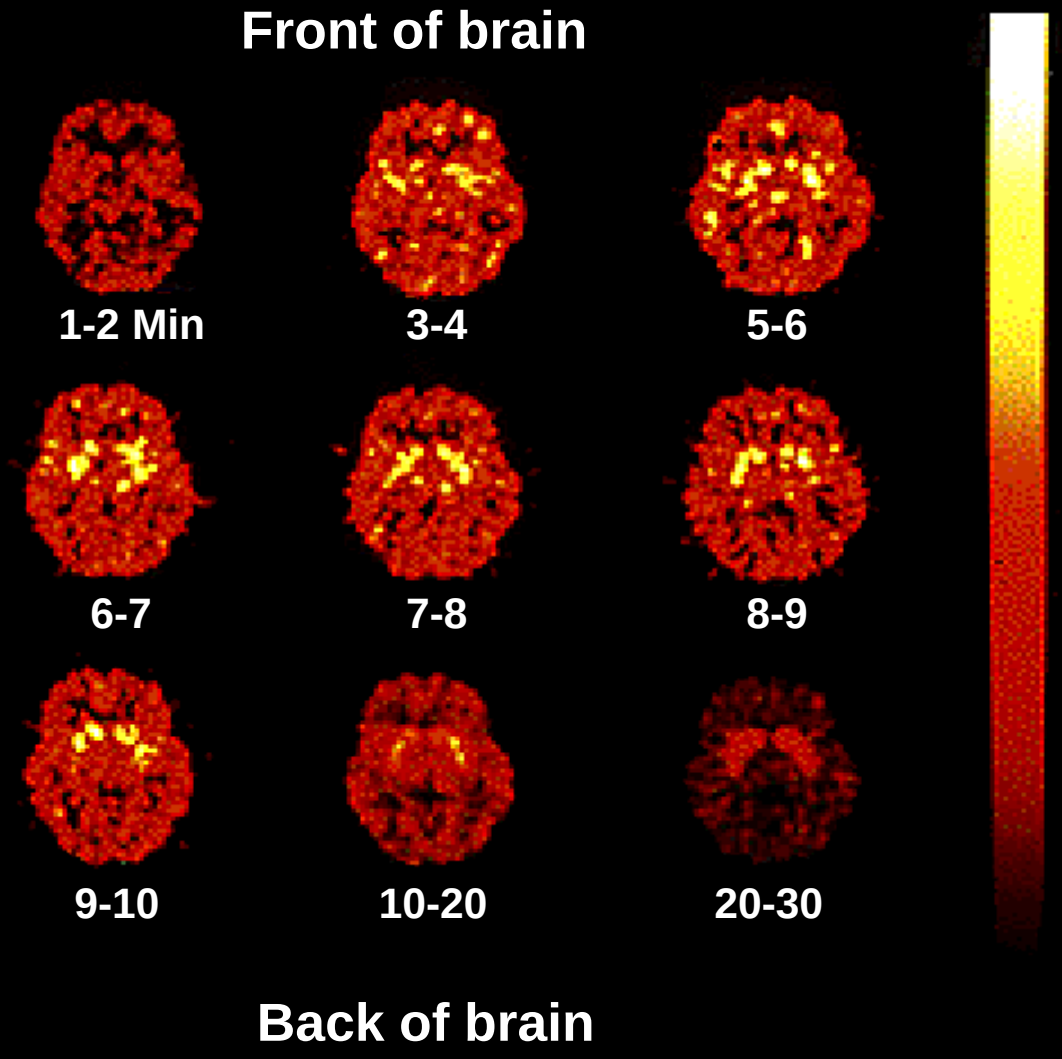


Dopamine receptor antagonist



Time Course of Cocaine Binding

YELLOW shows places in brain where cocaine binds (Striatum)

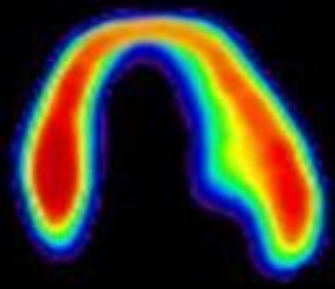


What have we learned?

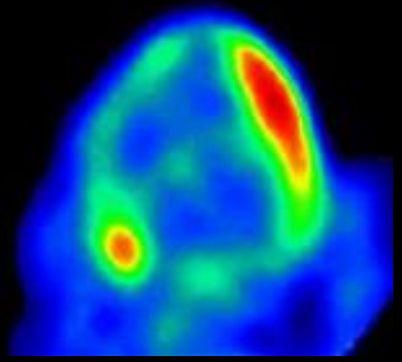
Addiction is Like Other Diseases…

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

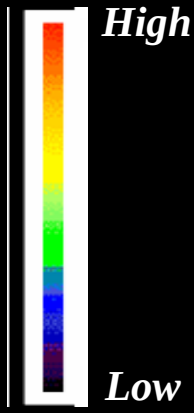
Decreased Heart Metabolism in Heart Disease Patient



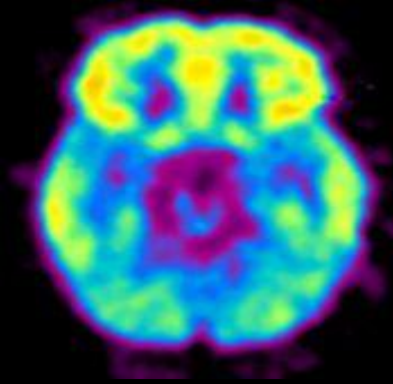
Healthy Heart



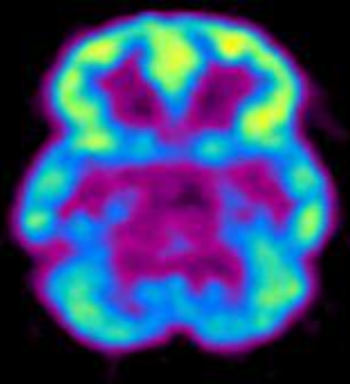
Diseased Heart



Decreased Brain Metabolism in Drug Abuser



Healthy Brain



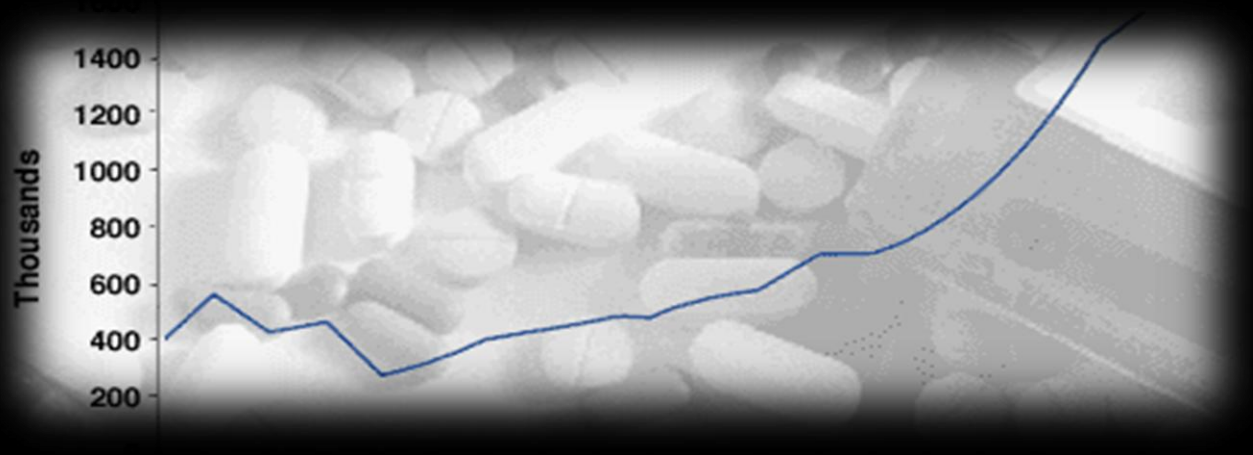
Diseased Brain/ Cocaine Abuser

NIDA

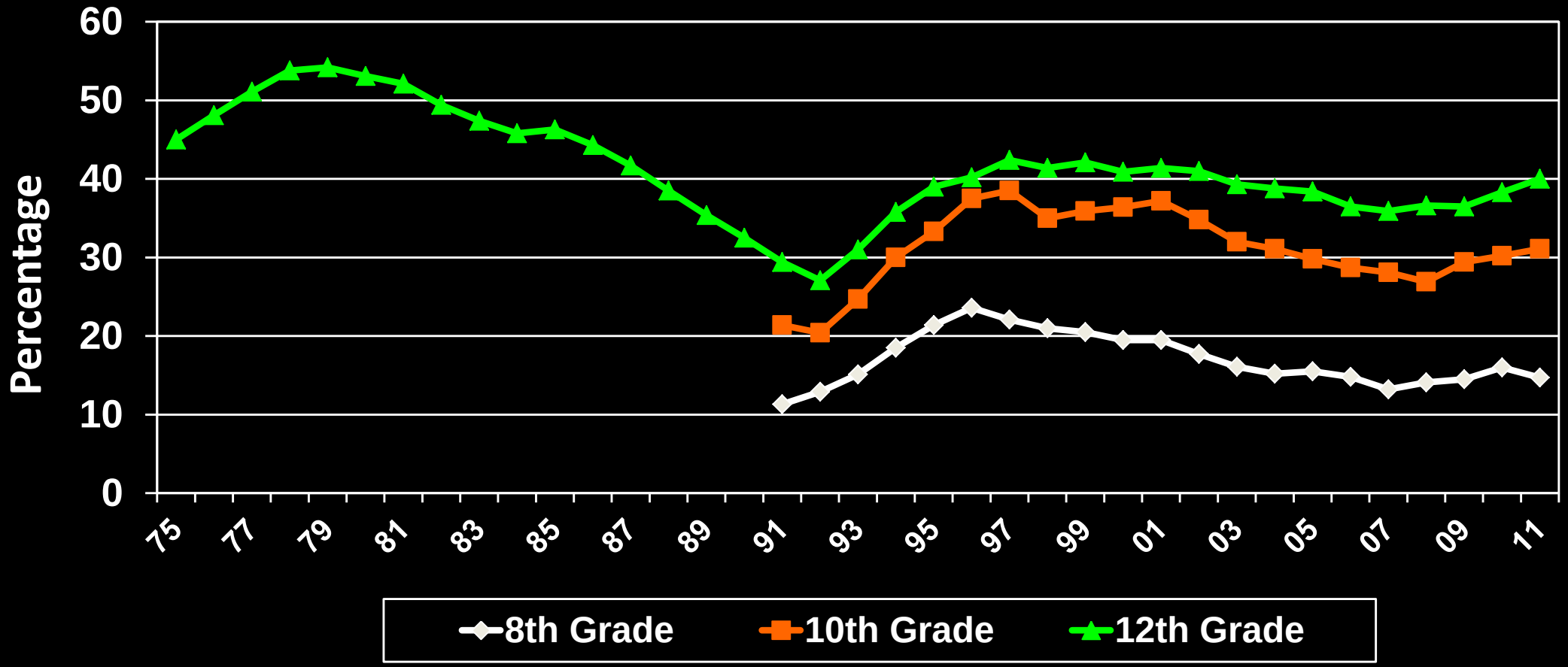
In 2010, an estimated 22.6 million Americans, or 8.9 percent of the population aged 12 or older, were current illicit drug users.

Source: National Survey on Drug Use and Health (NSDUH), SAMHSA, 2011

Disturbing trends in substance use

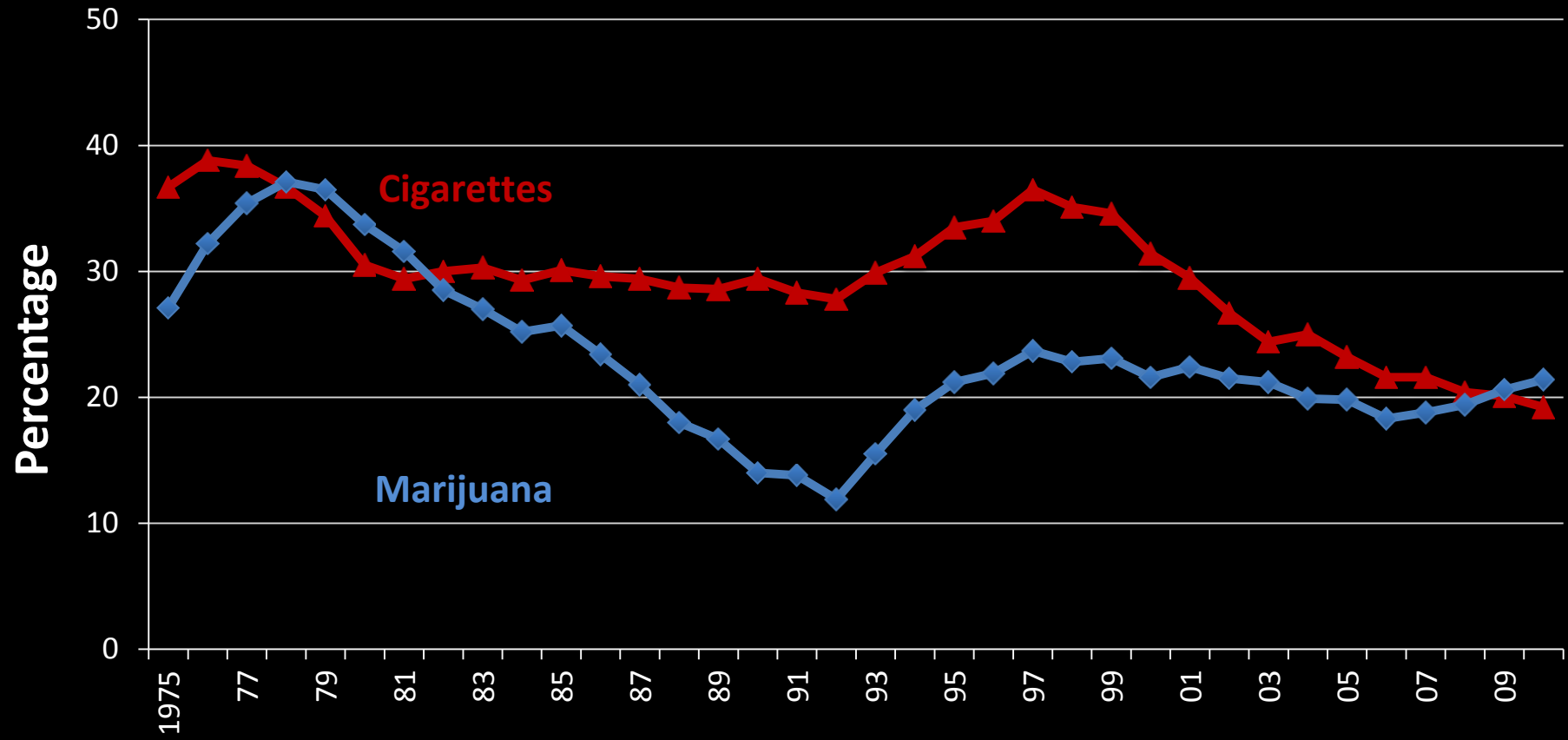


Percent of Students Reporting Any Illicit Drug Use in Past Year, by Grade



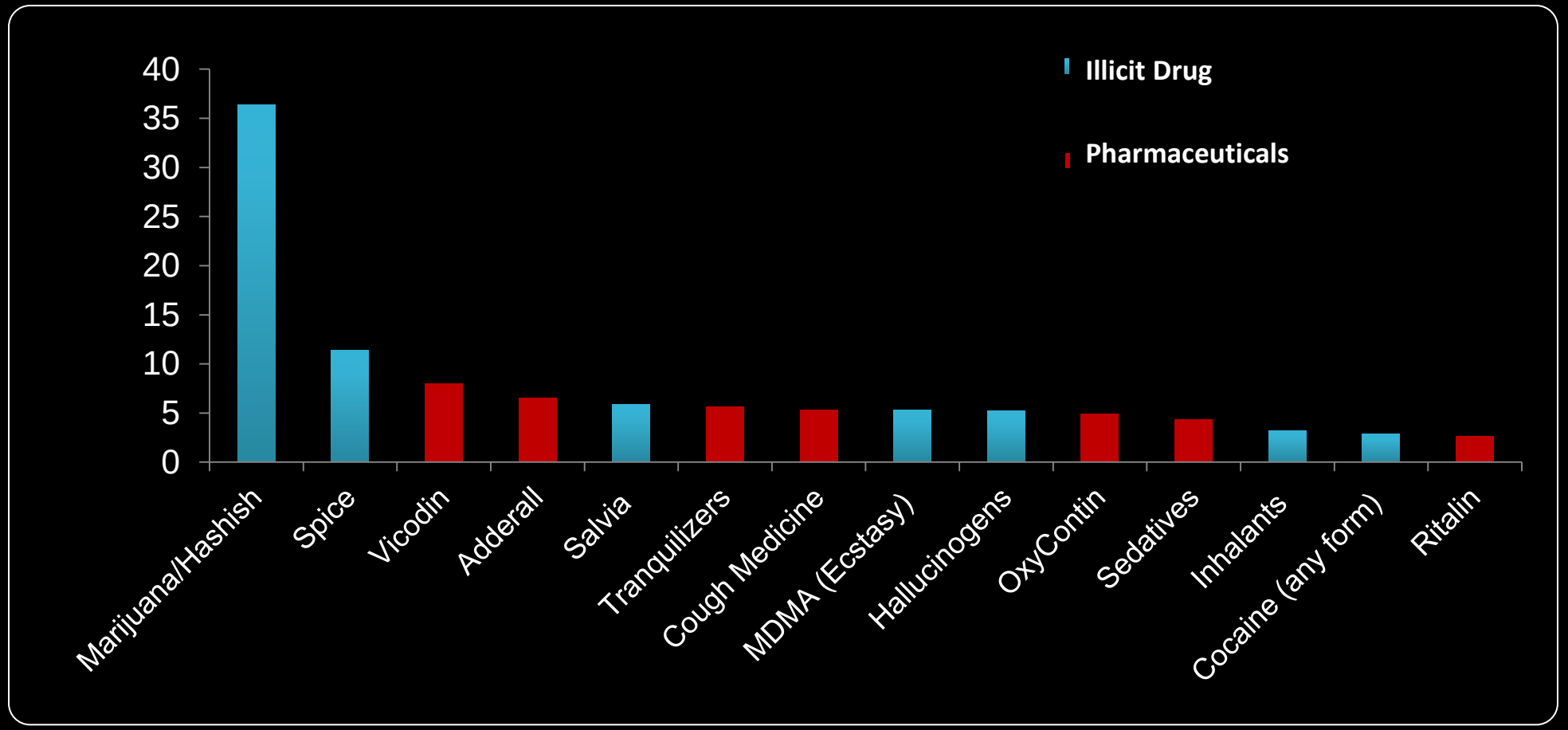
SOURCE: University of Michigan, 2011 Monitoring the Future Study

Percentage of 12th Grade Students Reporting Past Month Use of Cigarettes and Marijuana, 1975 to 2010



SOURCE: University of Michigan, 2010 Monitoring the Future Study

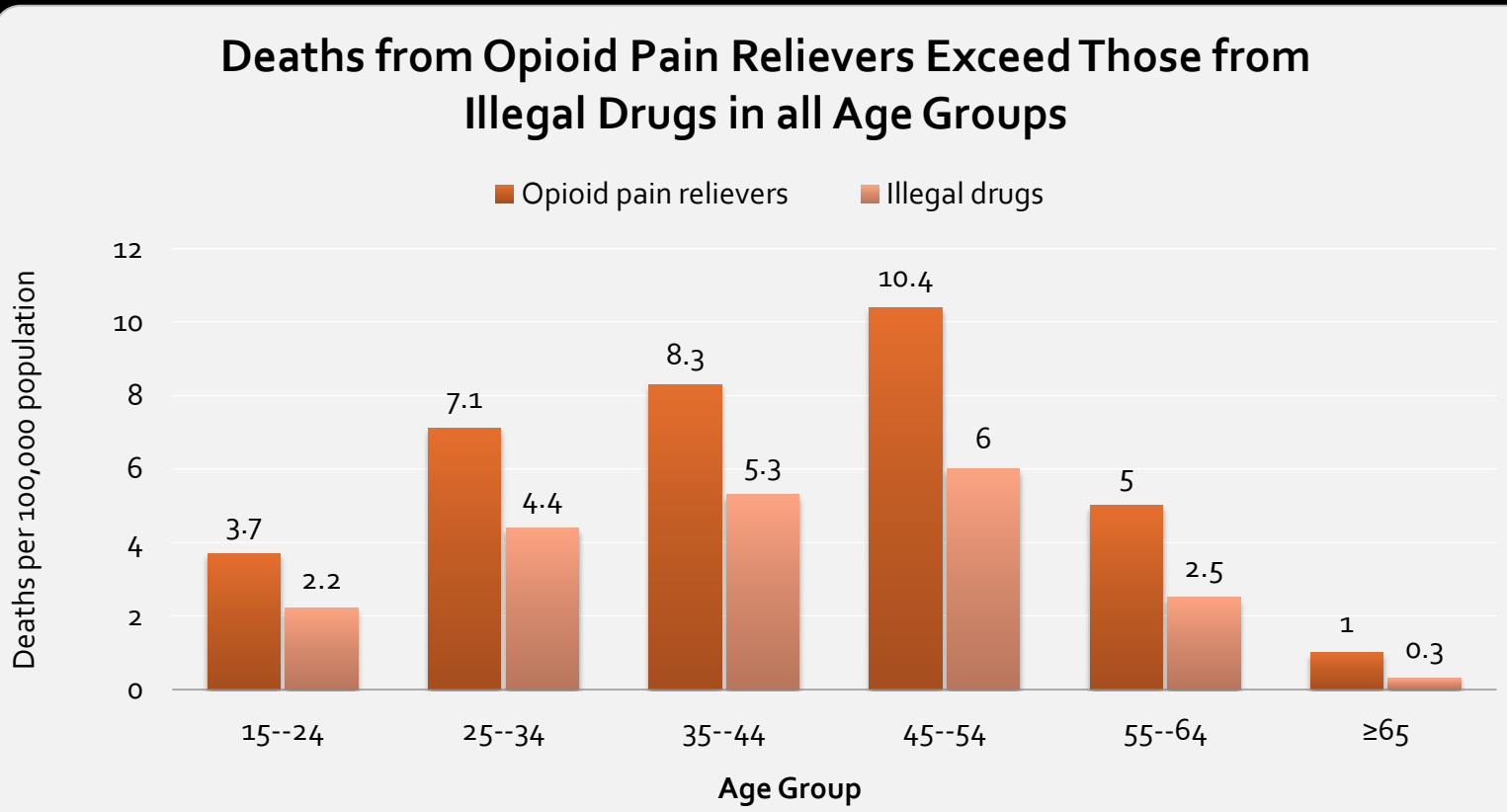
After Marijuana, Non-medical use of Pharmaceuticals Accounts for Most of the Commonly Abused Drugs by 12th-Graders (*in the past year*)



Categories are not mutually exclusive
SOURCE: University of Michigan, 2011 Monitoring the Future Study

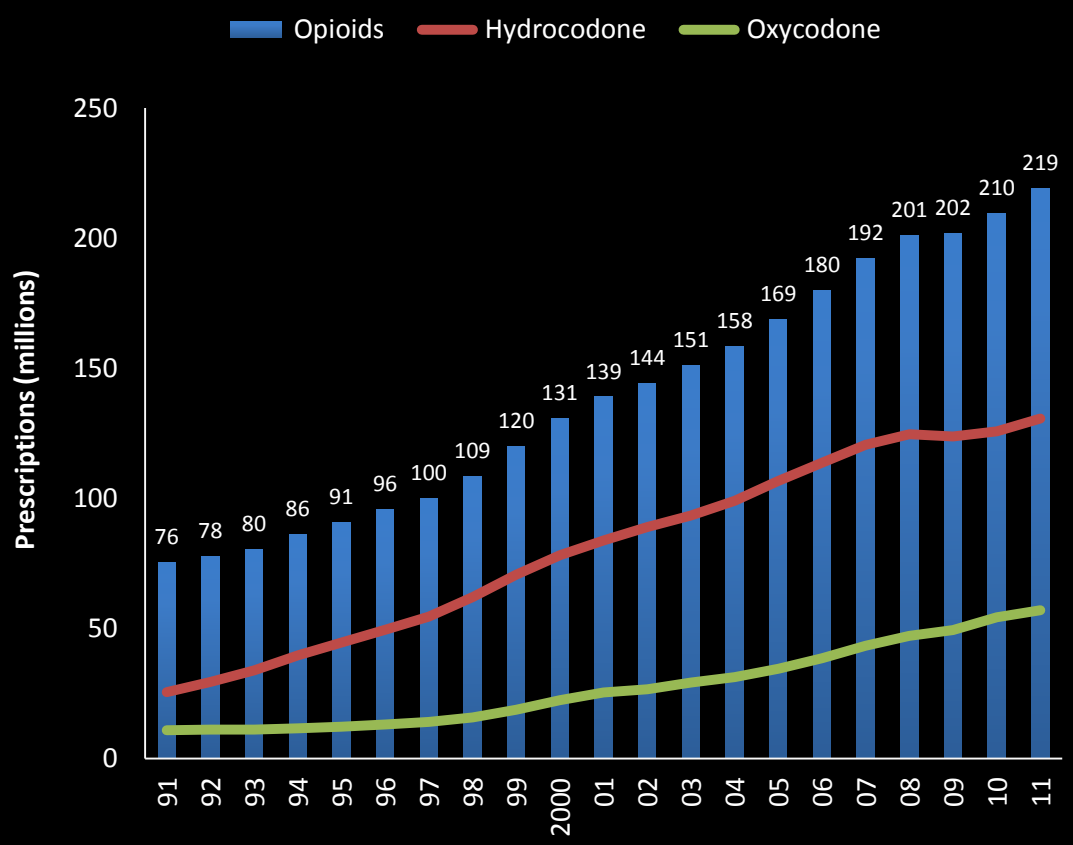
Consequences of Rx Drug Abuse are Increasing

Unintentional Overdose Deaths have quadrupled since 1998

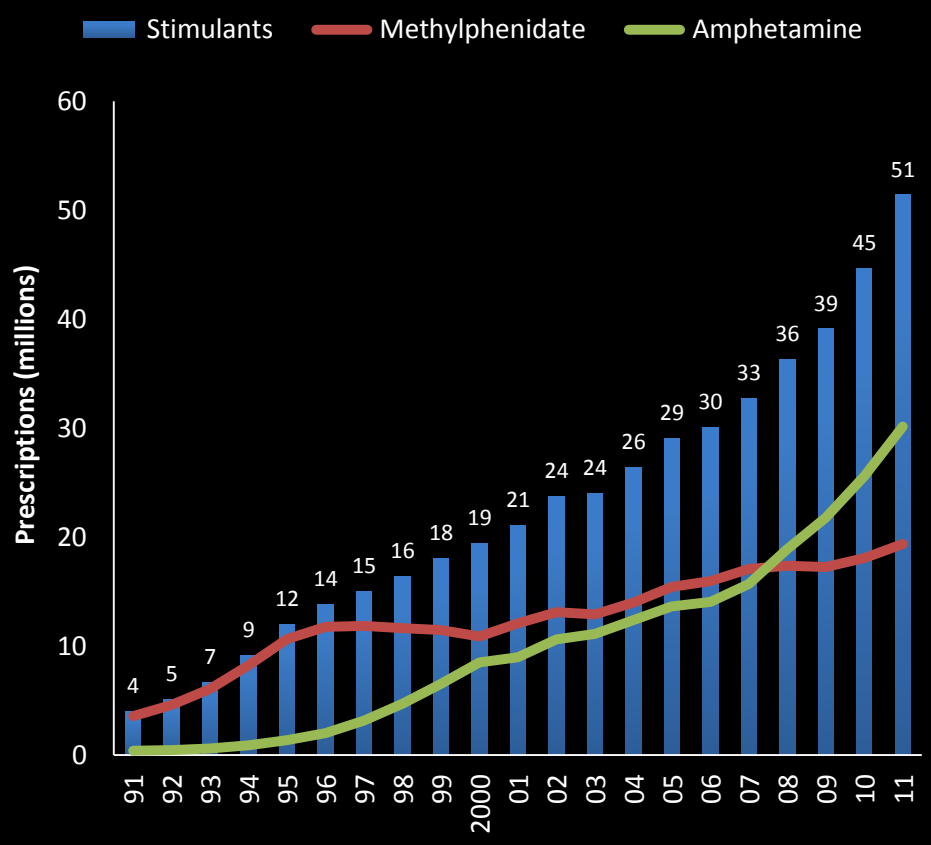


More Drug Overdose Deaths are Associated with Opioid Pain Relievers than with Illegal Drugs. Data are for 2008. Illegal drug deaths include deaths from overdose of heroin, cocaine, hallucinogens, or stimulants. Source: CDC, Morbidity and Mortality Weekly Report, 60(43): 1489, 2011.

Steady Increases in Opioid and Stimulant Prescriptions Dispensed by U.S. Retail Pharmacies, 1991-2011

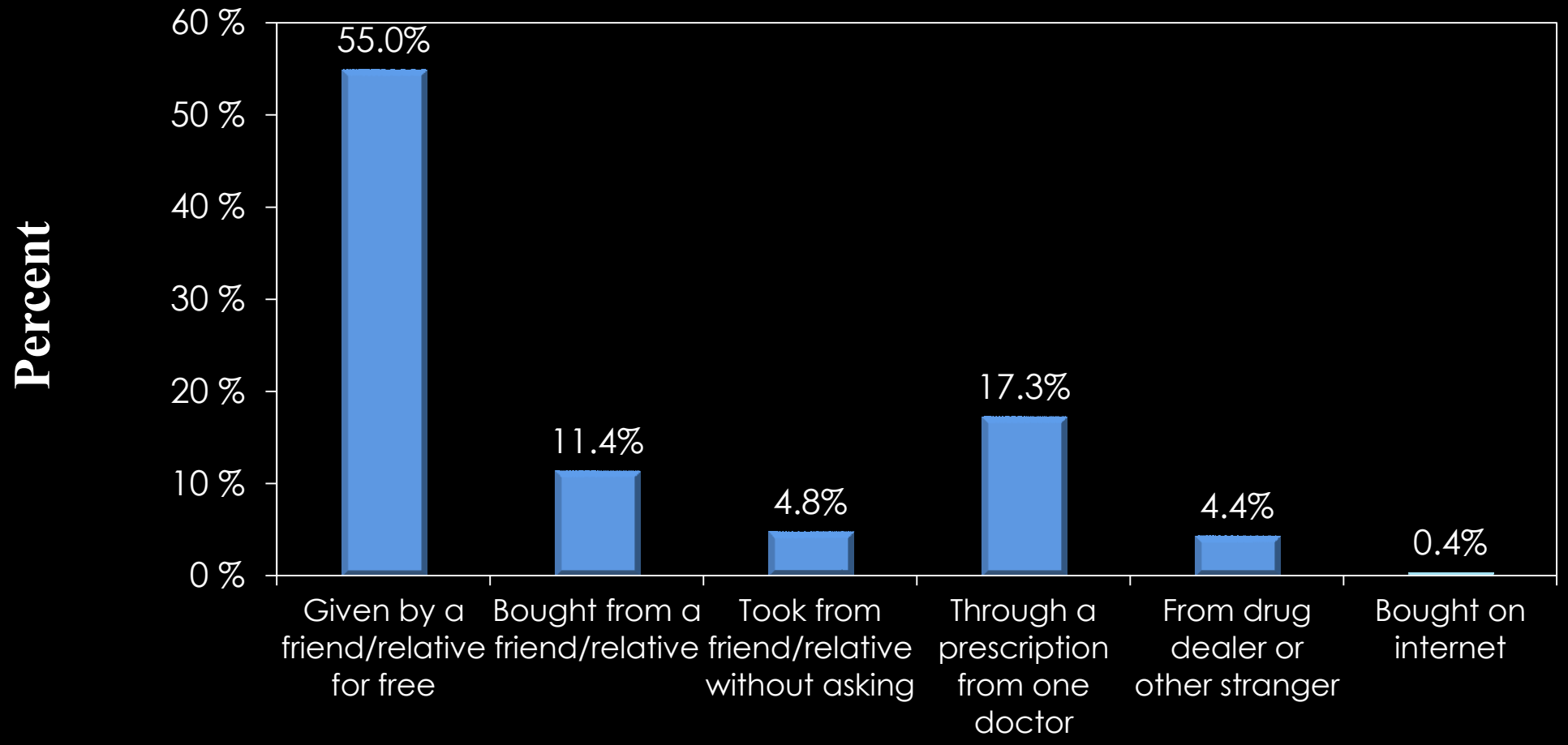


IMS's Source Prescription Audit (SPA) & Vector One®: National (VONA)



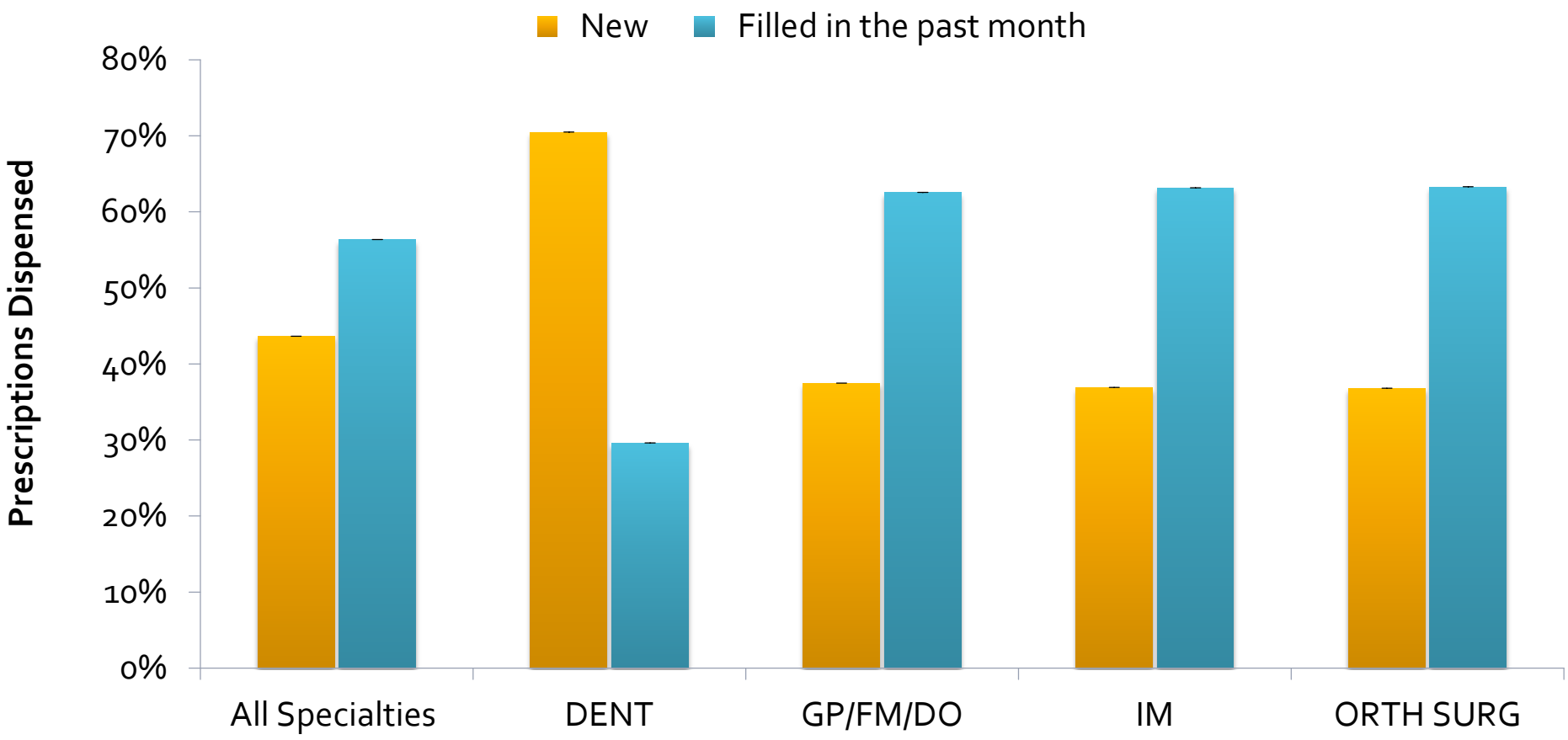
IMS's Source Prescription Audit (SPA) & Vector One®: National (VONA)

Source of or Rx drugs most recently used non-medically (averaged across 2009 and 2010)



National Survey on Drug Use and Health, SAMHSA 2011

More than half of patients receiving an opioid prescription had filled a Rx from the same drug class within the previous month (2009)



Volkow, N. D. et al. JAMA 2011;305:1299-1301

Solutions Needed: Training & Education

Enhance clinical training for physicians, nurses, dentists, and pharmacists in the areas of pain management, opioid pharmacology, abuse and addiction

CoEPEs
CENTERS OF EXCELLENCE IN PAIN EDUCATION

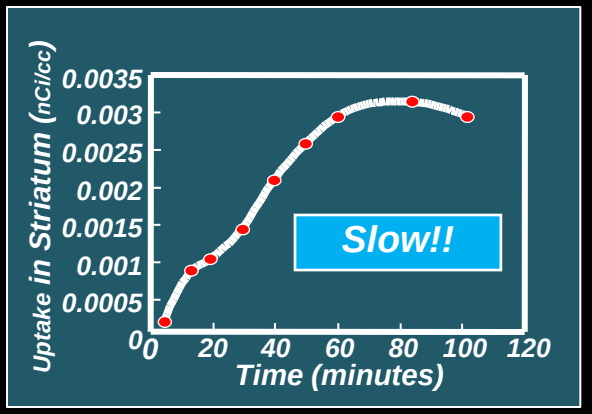
Increase patient, lay public, and policy makers' awareness of the potential risks for abuse inherent in all opioid analgesics

Medications Research and Development

Develop medications with lower abuse potential including drugs that don't cross BBB (i.e., CbR2 agonist)

Develop slow release formulations (low dose and long duration)

Develop novel formulations including drug combinations (e.g., naloxone and buprenorphine); meds with limited shelf life



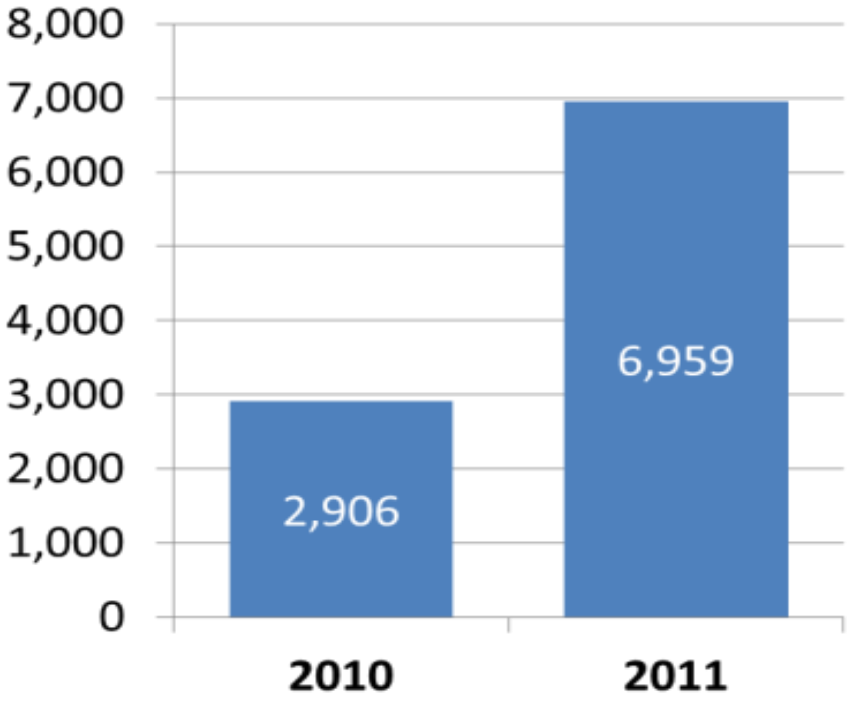
Emerging Drugs: Synthetics

Cannabinoids

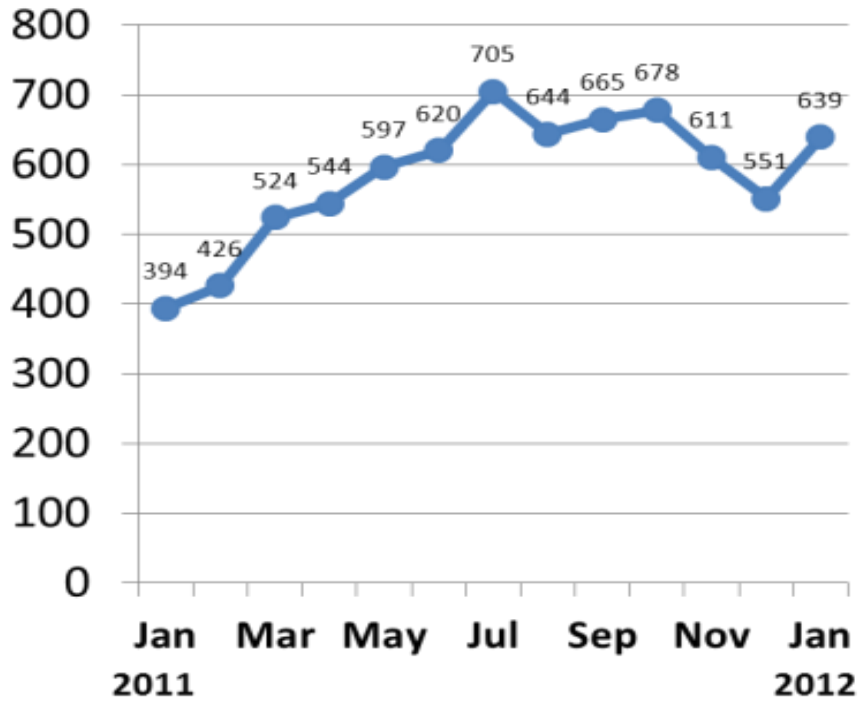
Cathinones

Calls Received by Poison Control Centers for Human Exposure to Synthetic Marijuana, 2010 to January 2012

The number of calls in 2011 are more than double that in 2010.



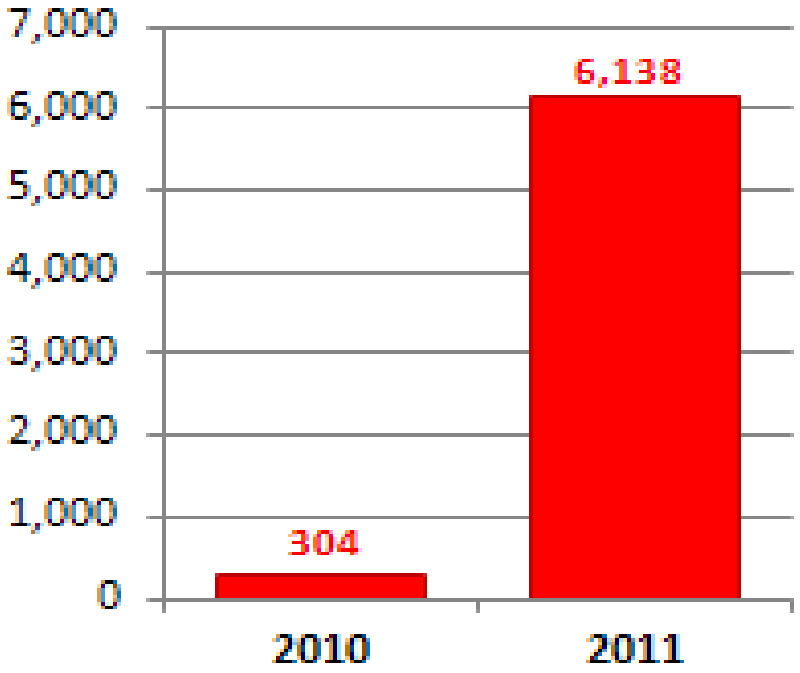
Calls remain high since a steady rise from January to July 2011.



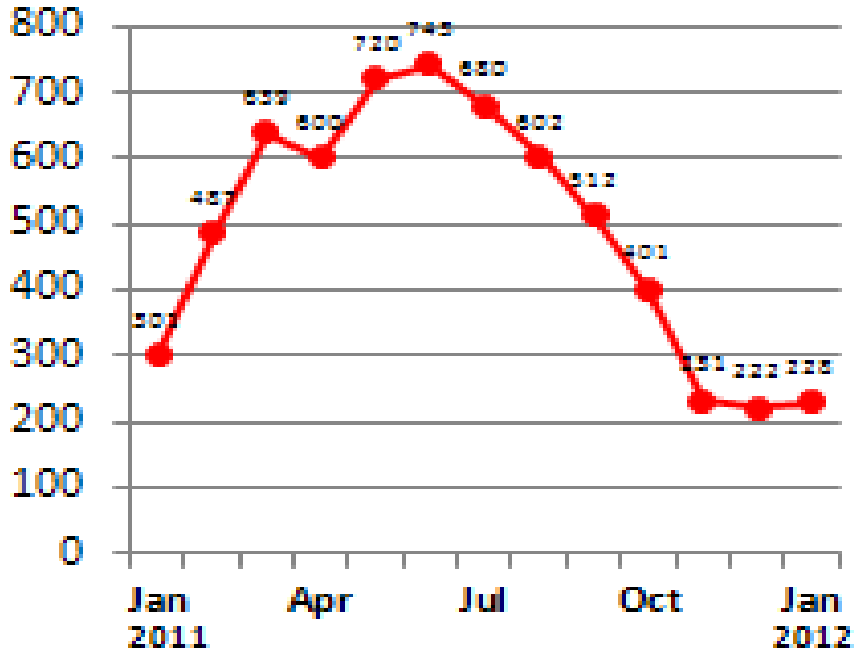
Source: American Association of Poison Control Centers, *Synthetic Marijuana Data,* Updated February 8, 2012 (Preliminary data).

Calls To Poison Control Centers for Human Exposure to Bath Salts, 2010 to January 2012

The number of calls in 2011 are over 20 times that in 2010.



In early 2011, calls in each month spiked through June, then gradually declined and is level in the past 3 months.*



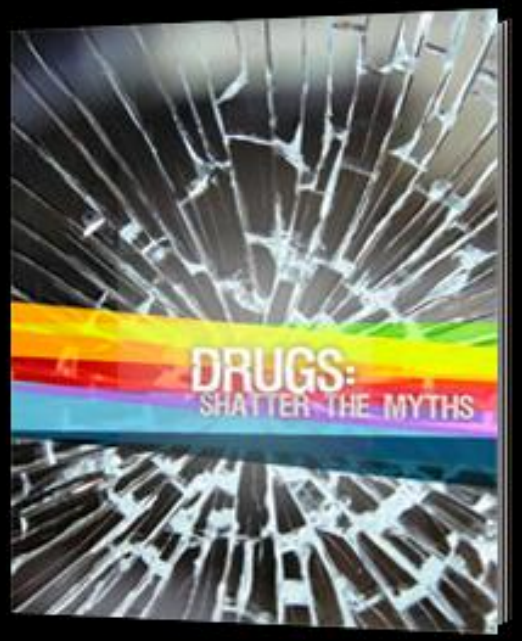
**Numbers may change as cases are closed and additional information is received.*

Source: American Association of Poison Control Centers, *Bath Salts Data*, Updated February 8, 2012 (Preliminary data).

2/2012

What can we do?

- *Regulate (DEA emergency scheduling)*
- *Develop drug detection tests*
- *Persuade shops that are selling these items to remove them from the shelves*
- *Counter the "New business model" (dual use research)*
- *Educate the public*



Why Do People Take Drugs in The First Place?

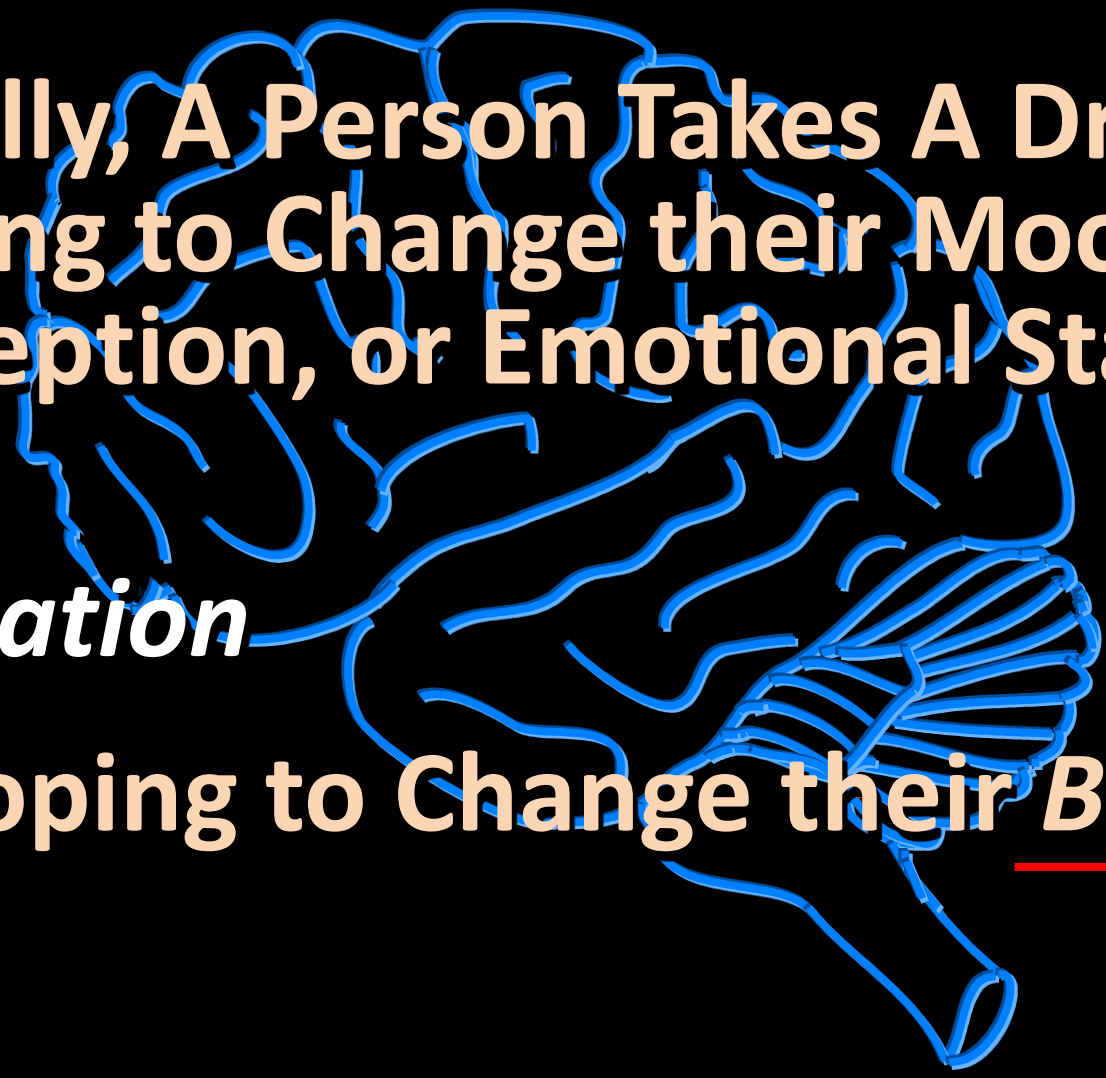
To Feel Good

To have novel:
feelings
sensations
experiences
AND
to share them

To Feel Better

To lessen:
anxiety
worries
fears
depression
hopelessness

NIDA



Initially, A Person Takes A Drug Hoping to Change their Mood, Perception, or Emotional State

Translation

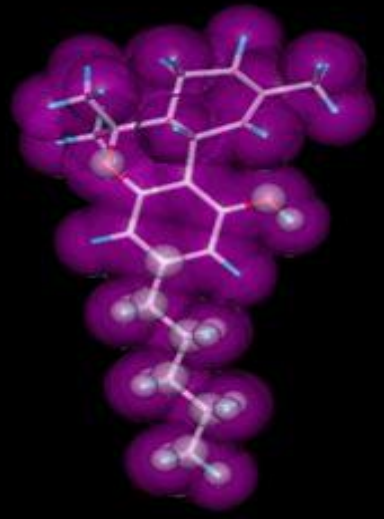
…Hoping to Change their *Brain*

Drugs can be "Imposters" of Brain Messages

Brain's Chemical

Anandamide

Drug

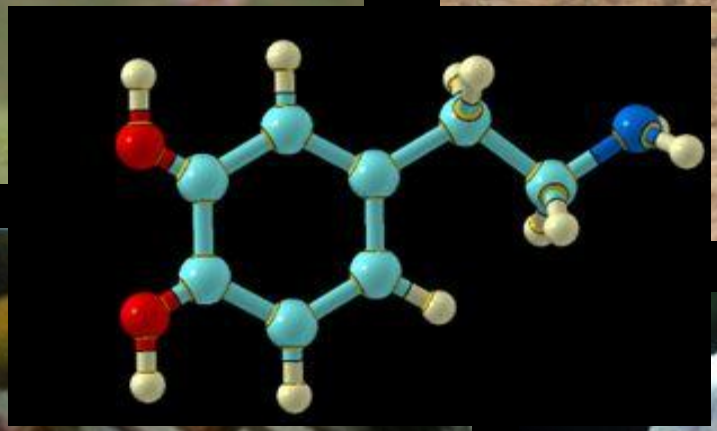


THC

NIDA

Movement

Motivation

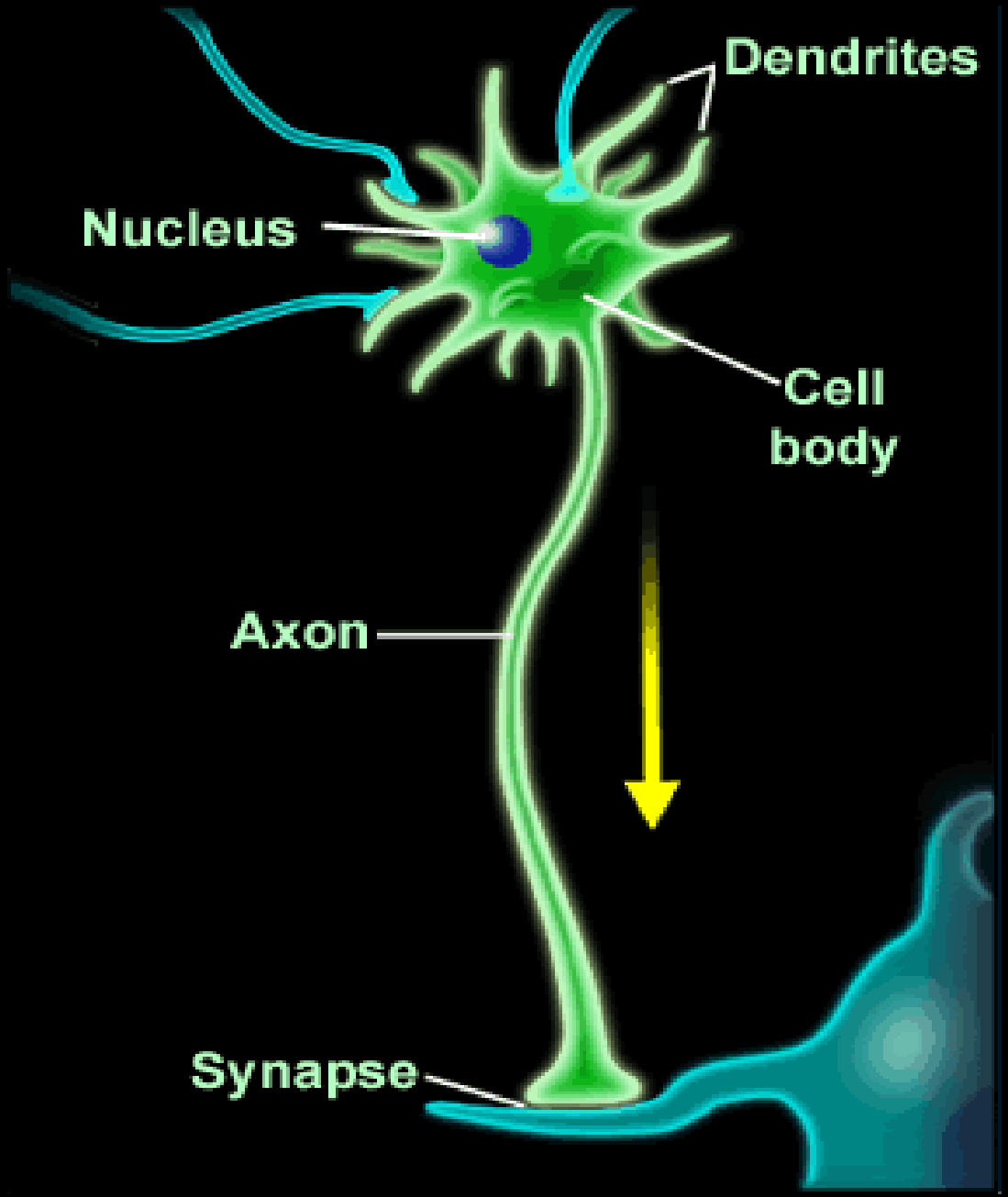


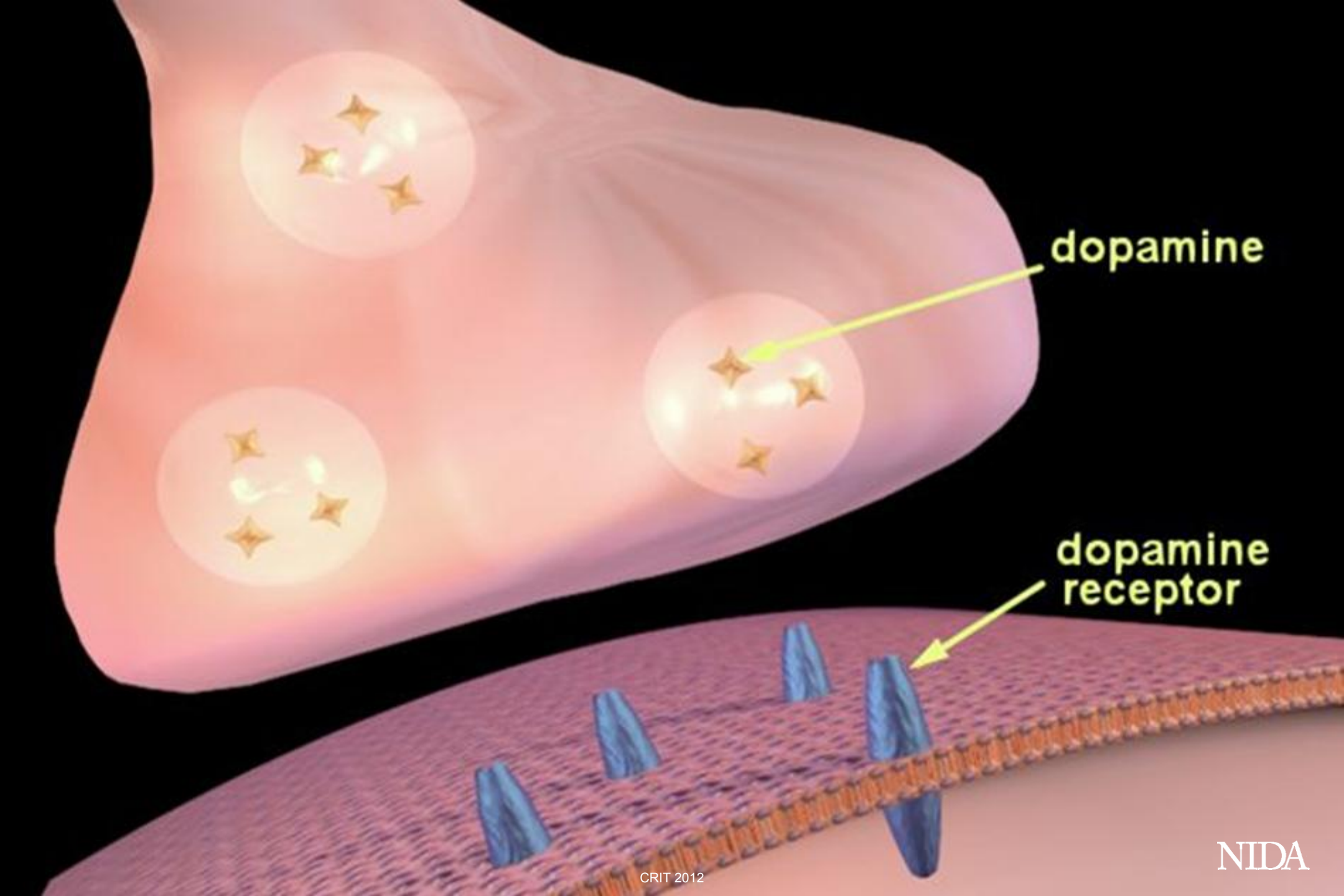
Dopamine

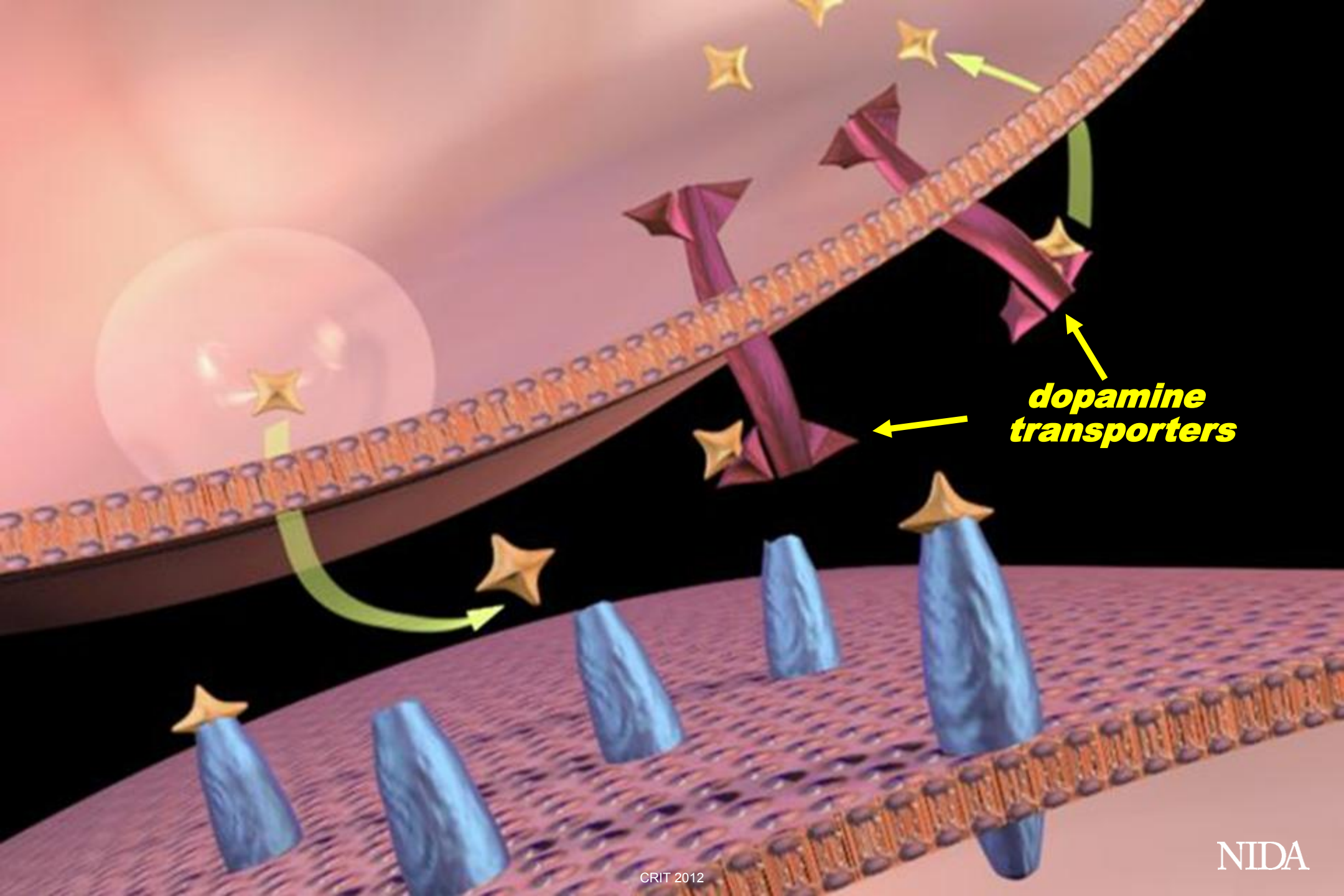
Addiction

Reward & well-being

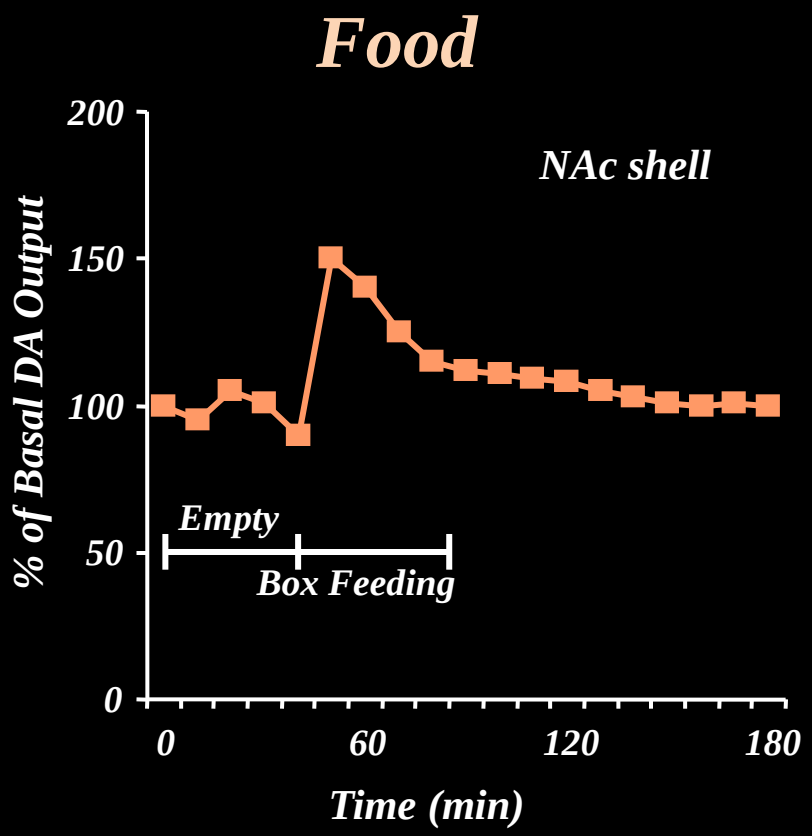
The Neuron: How the Brain's Messaging System Works

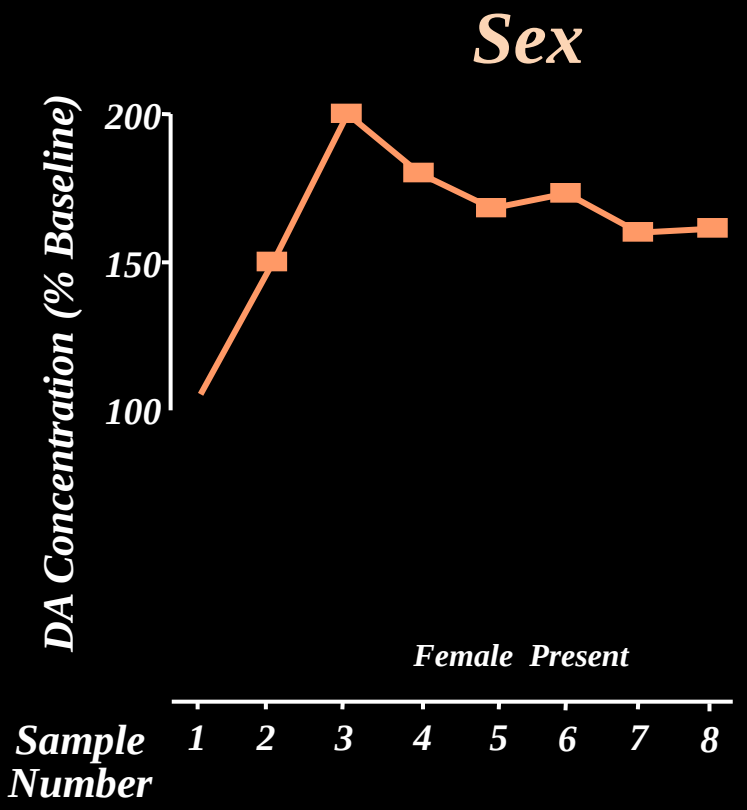



dopamine
dopamine receptor
NIDA


dopamine
transporters
NIDA

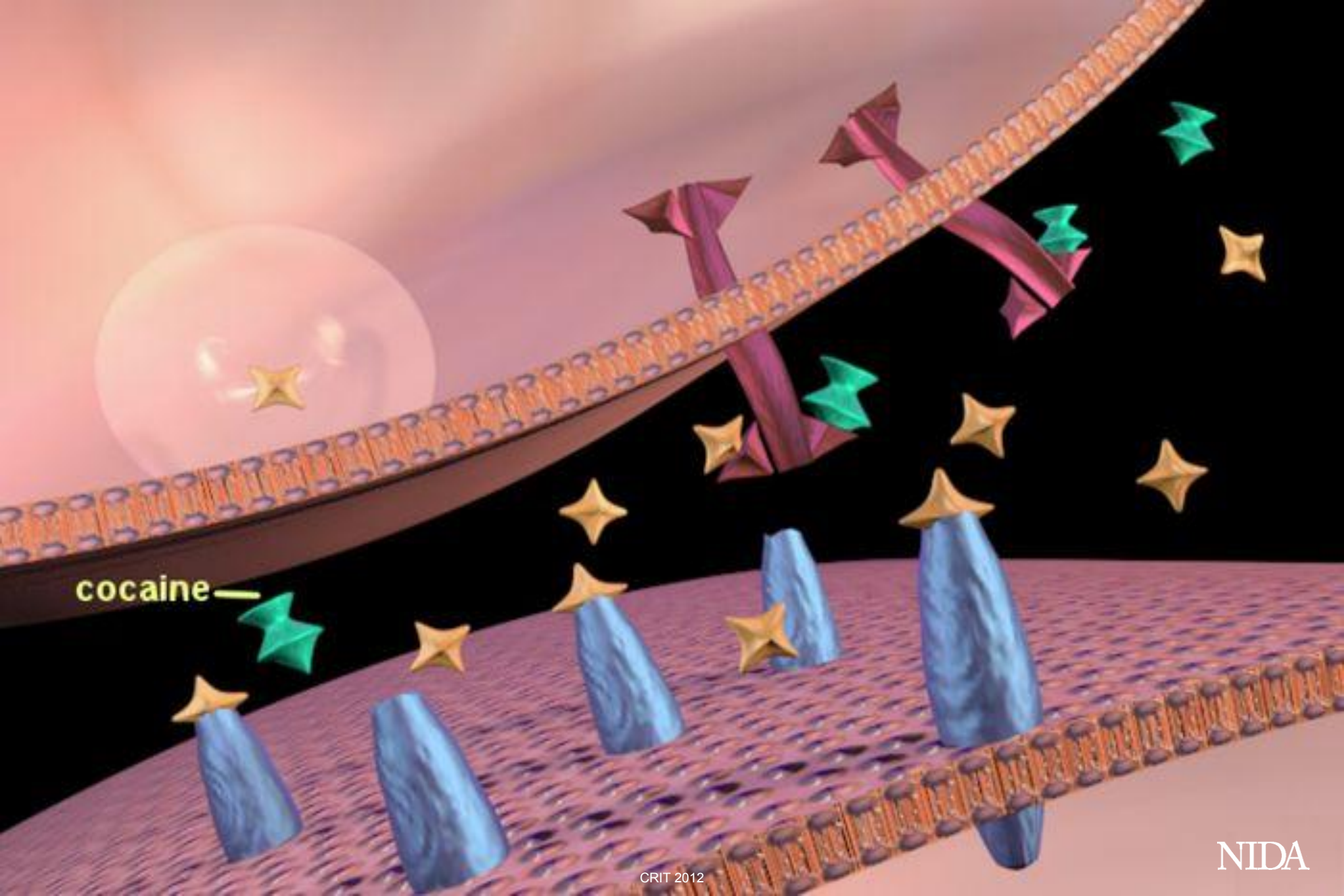
Natural Rewards Elevate Dopamine Levels



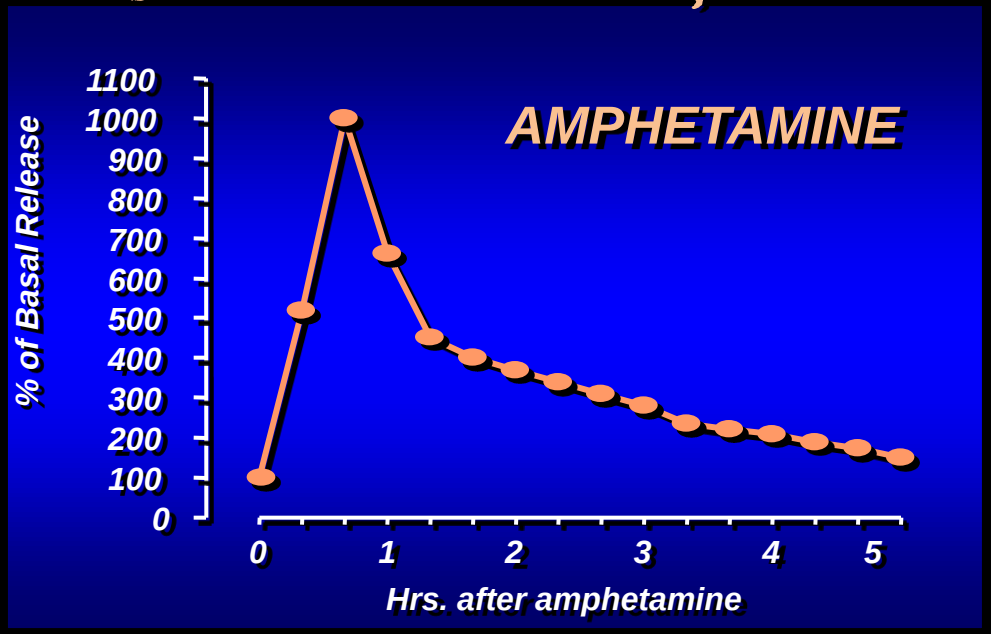


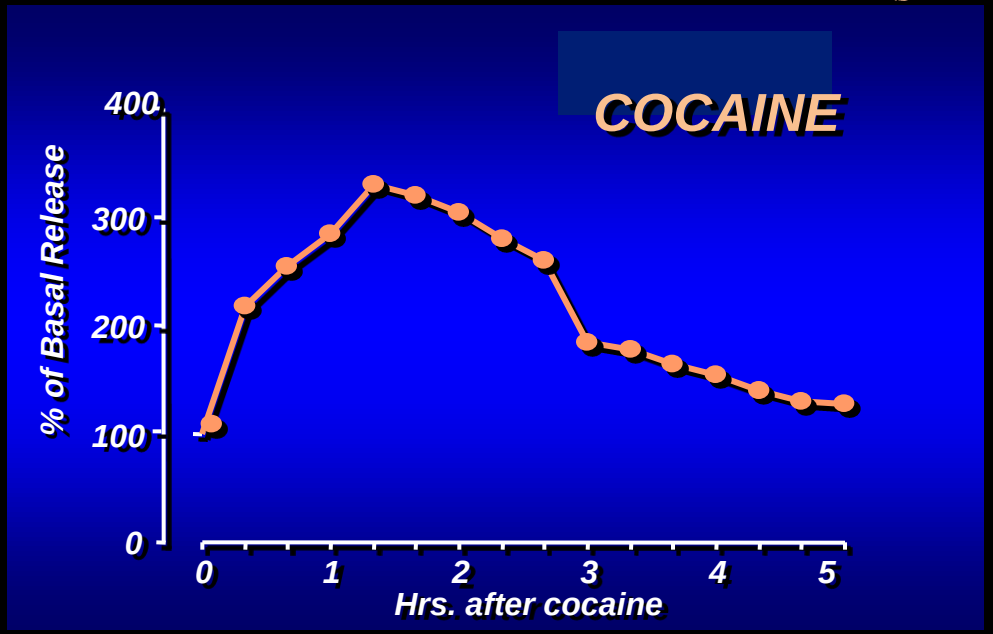
Di Chiara et al., Neuroscience, 1999.,Fiorino and Phillips, J. Neuroscience, 1997.

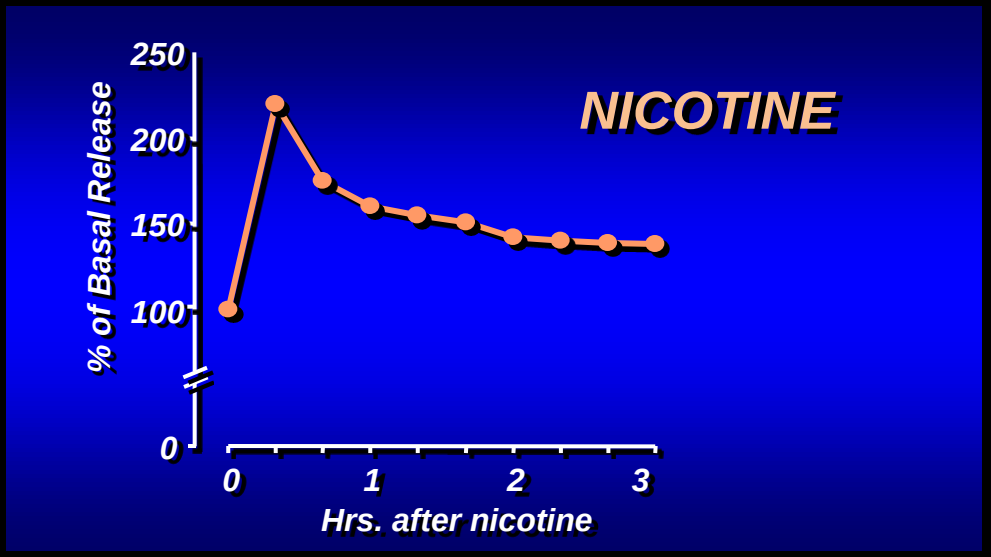
NIDA

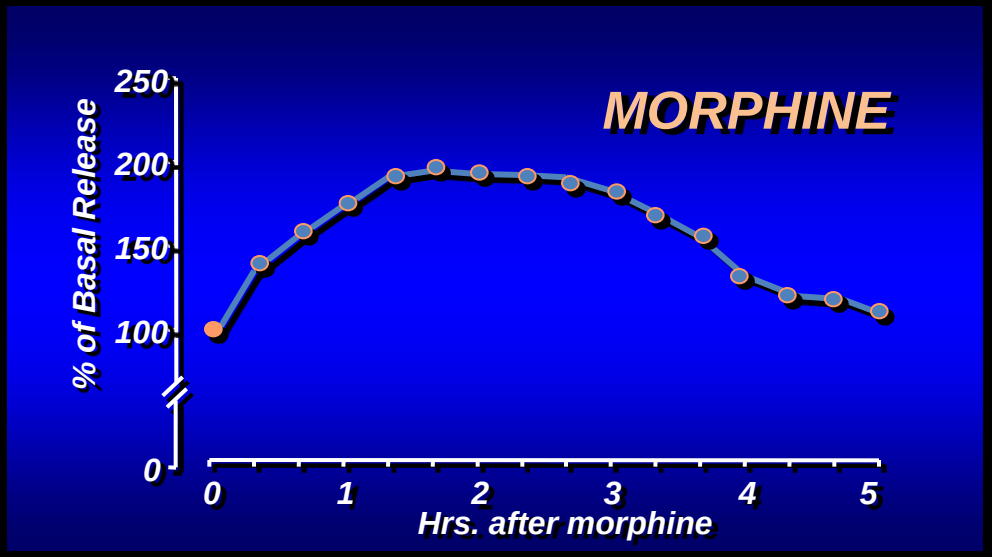

cocaine
NIDA

Drugs Elevate Dopamine Levels More or For Longer



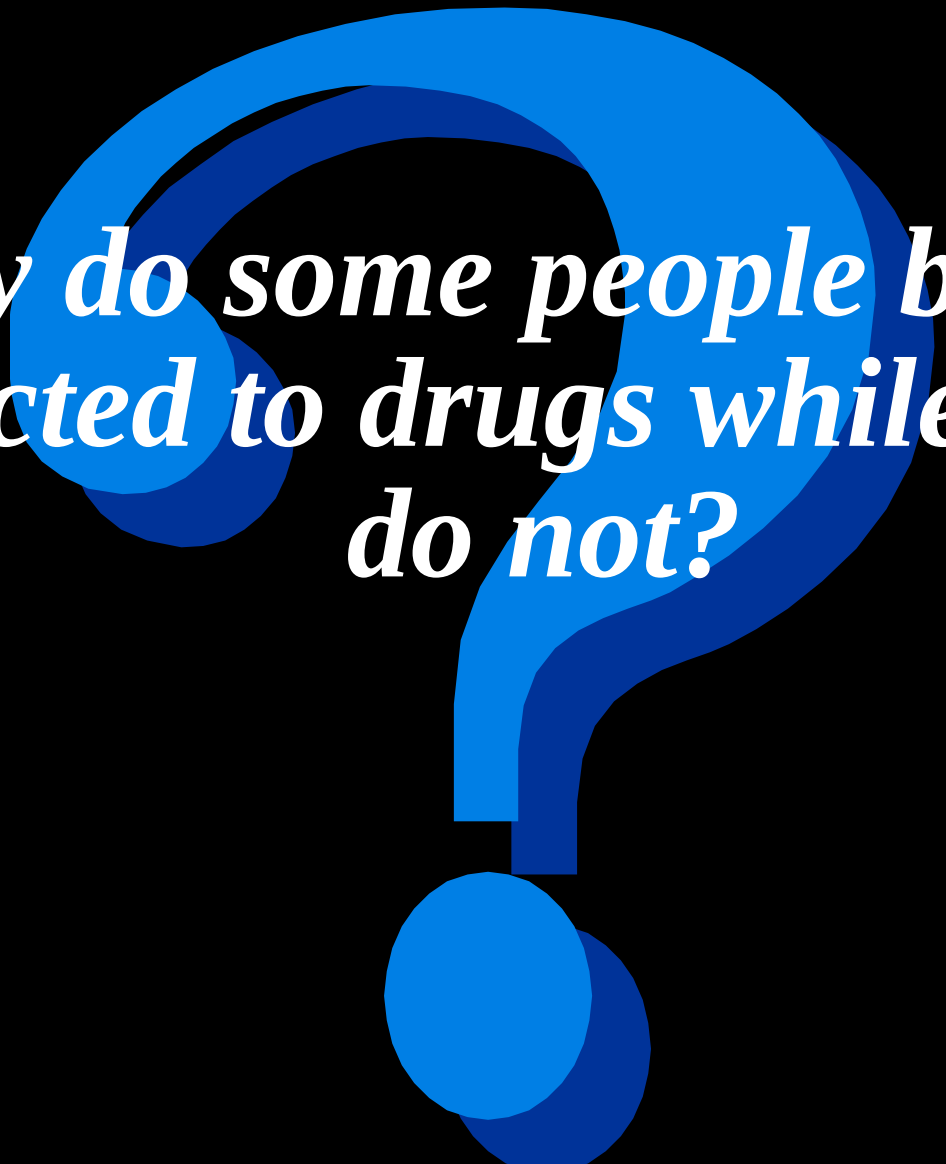






Source: Di Chiara and Imperato

Vulnerability



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

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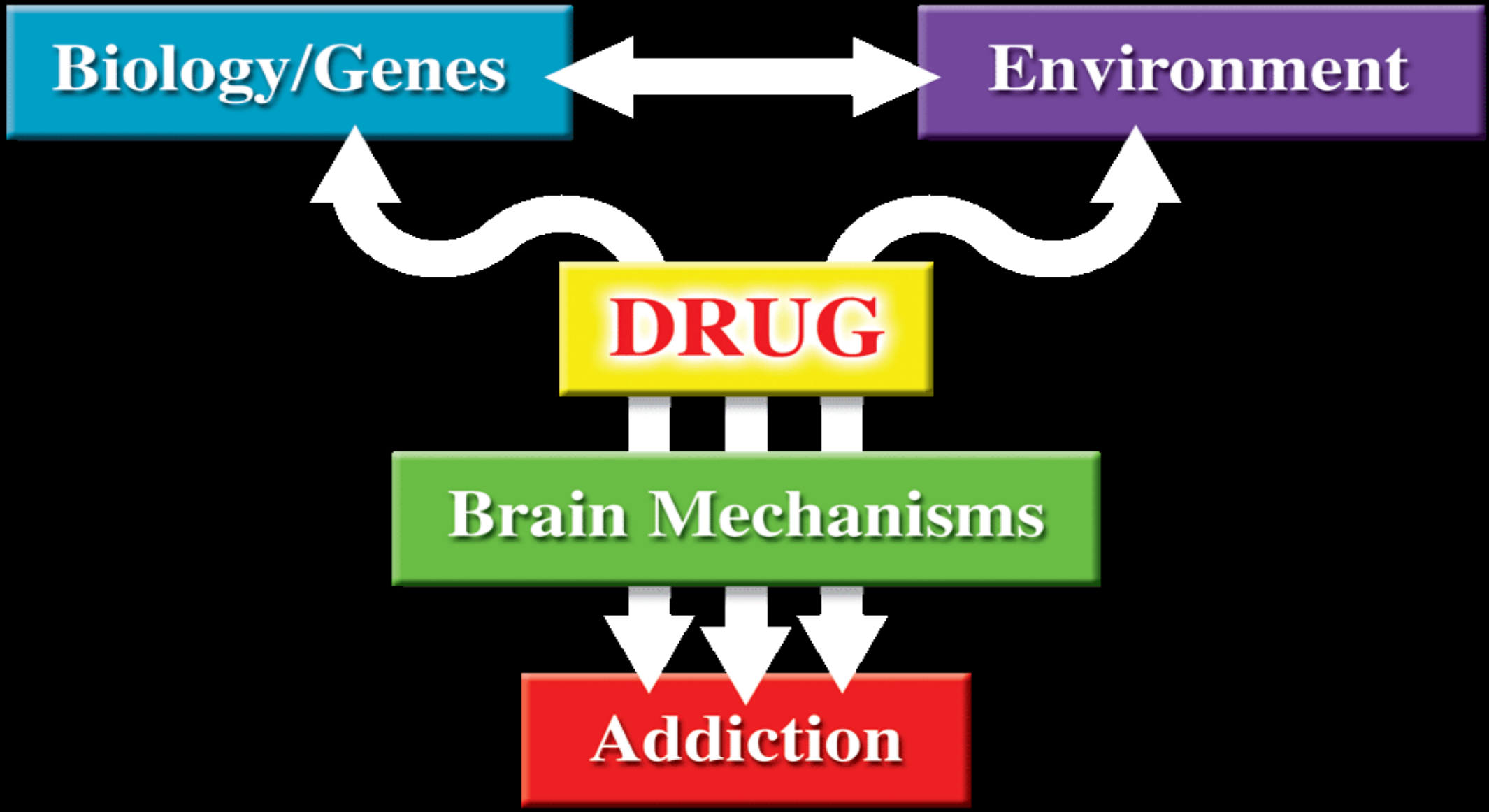
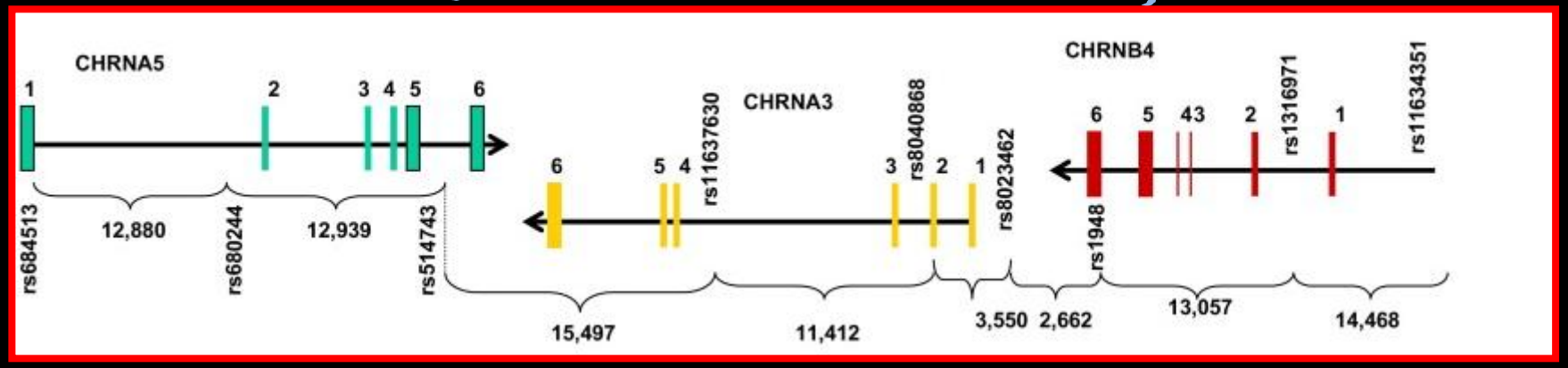
Addiction Involves Multiple Factors



Genetics is a Big Contributor to the Risk of Addiction...

…and the nature of this contribution is very complex

Gene Cluster is Associated with Vulnerability to Nicotine Dependence



Human Molecular Genetics, 2007, Vol. 16, No. 1 24–
doi:10.1093/hmg/ddl441
Advance Access published on December 7, 2006

Novel genes identified in a high-density genome wide association study for nicotine dependence

Laura Jean Bierut[1,*], Pamela A.F. Madden[1], Naomi Breslau[2], Eric O. Johnson[3],
Dorothy Ha
Louis Fox[1]
Nicholas G
Jen C. War

Molecular Psychiatry (2008), 1–6

www.nature.com/mp

IMMEDIATE COMMUNICATION

α-5/α-3 nicotinic receptor subunit alleles increase risk for heavy smoking

W Berrettini[1,2,3], X Yuan[2,3], F Tozzi[2,3], K Song[2,3], C Francks[2,3], H Chilcoat[4], D Waterworth[2,3], P Muglia[2,3,5] and V Mooser[2,3]

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The CHRNA5/A3/B4 Gene Cluster Variability as an Important Determinant of Early Alcohol and Tobacco Initiation in Young Adults

Isabel R. Schlaepfer, Nicole R. Hoft, Allan C. Collins, Robin P. Corley, John K. Hewitt, Christian J. Hopfer, Jeffrey M. Lessem, Matthew B. McQueen, Soo Hyun Rhee, and Marissa A. Ehringer

Vol 452|3 April 2008|doi:10.1038/nature06846

A variant associated with nicotine dependence, lung cancer and peripheral arterial disease

Thorgeir E. Thorgeirsson[1]*, Frank Geller[1]*, Patrick Sulem[1]*, Thorunn Rafnar[1]*, Anna Wiste[1,2], Kristinn P. Magnusson[1], Andrei Manolescu[1], Gudmar Thorleifsson[1], Hreinn Stefansson[1], Andres Ingason[1],

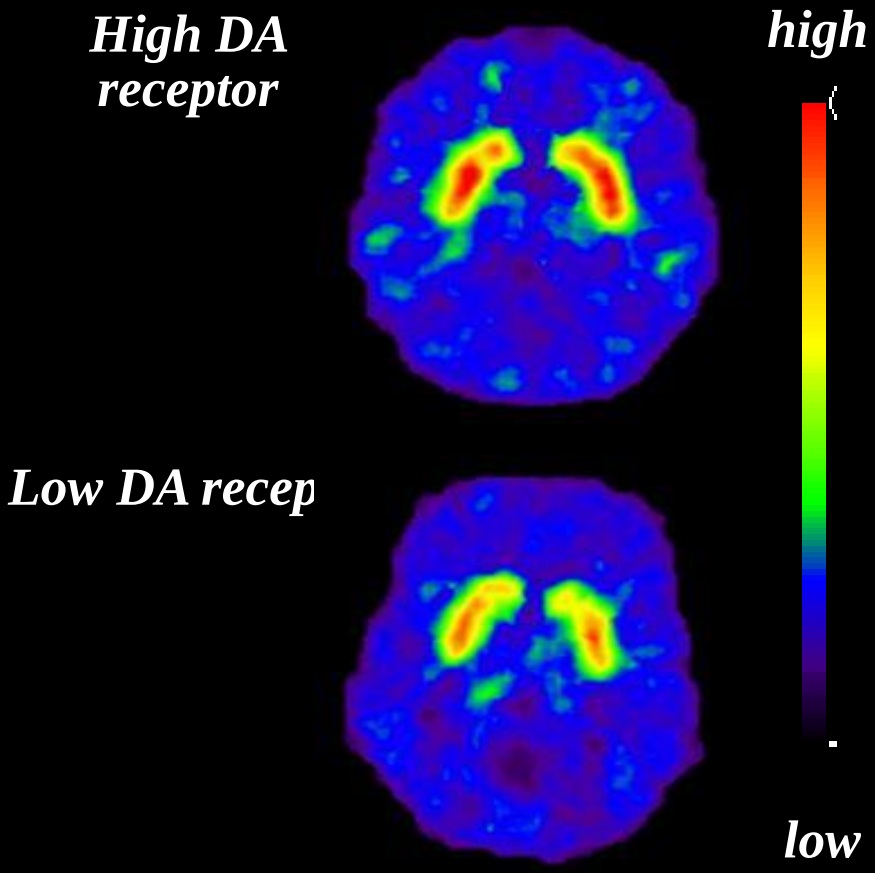
Some Gene Variants Implicated in Addiction

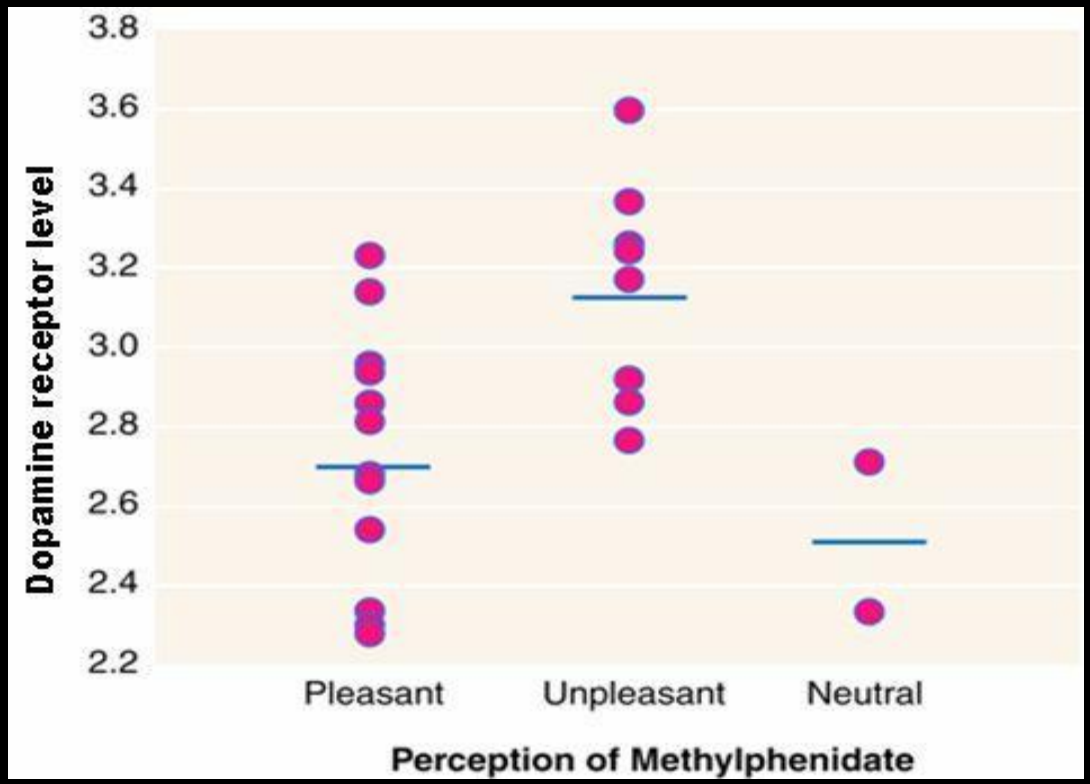
- **FAAH -** associated with drug dependence
- **OPRM1** - associated with opiates and alcoholism
- **CYP2A6, CYP2B6** - associated with smoking and smoking cessation
- **ALDH2** - associated with protection against alcoholism
- **DBH** (Dopamine beta-hydroxylase) – cocaine-induced paranoia
- **DRD2, 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

Variations in Dopamine Receptor Levels Predict Pleasure afforded by Methylphenidate administration



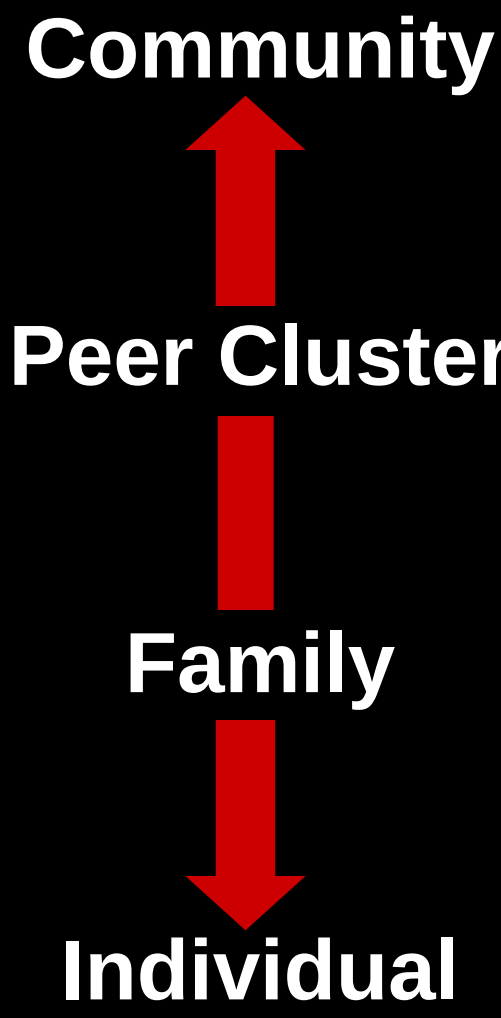


As a group, subjects with low receptor levels found MP pleasant while those with high levels found MP unpleasant

NIDA

But it isn't all genetics

Drug Abuse Risk Factors



What Environmental Factors Contribute to Addiction?

Drug availability

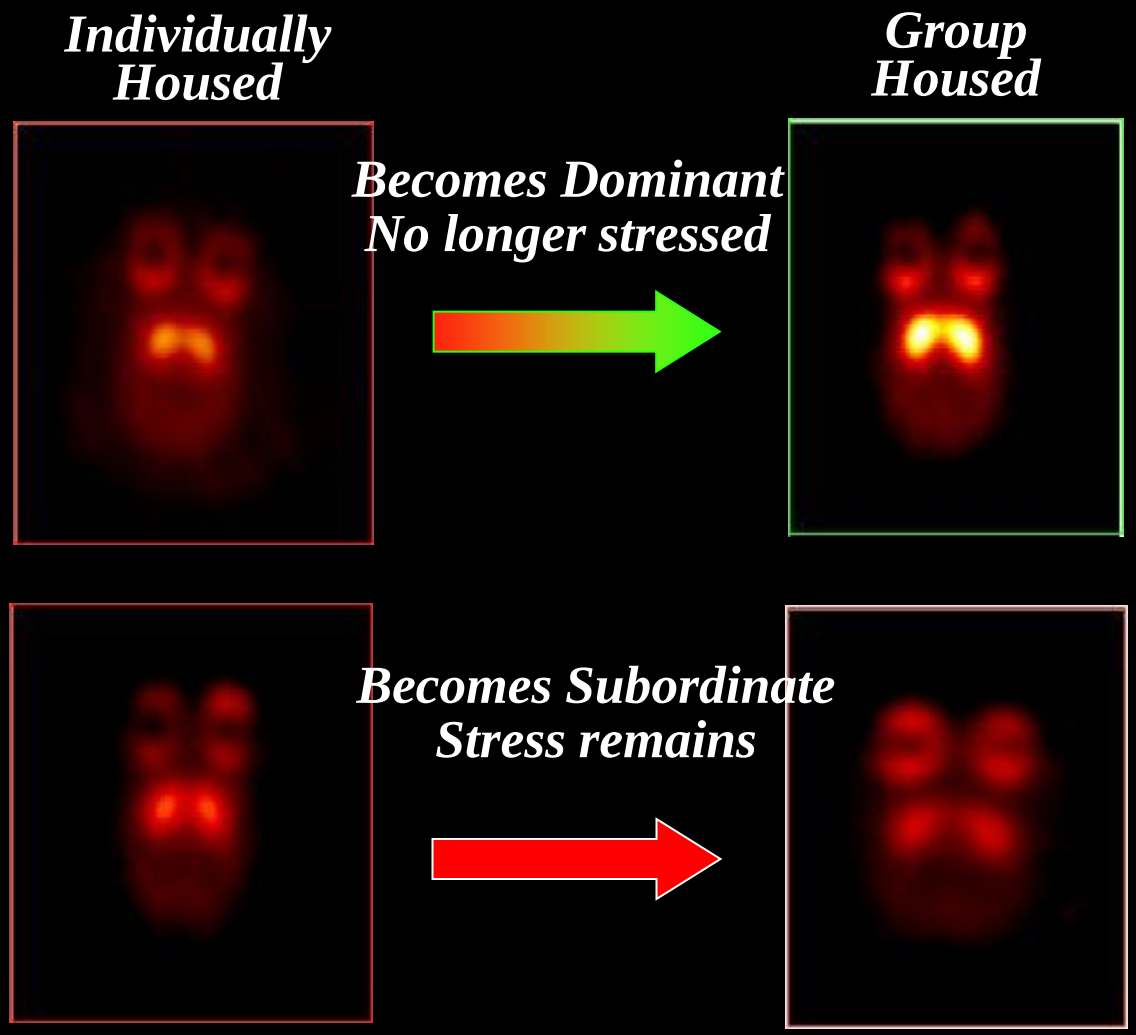
Peers who use drugs

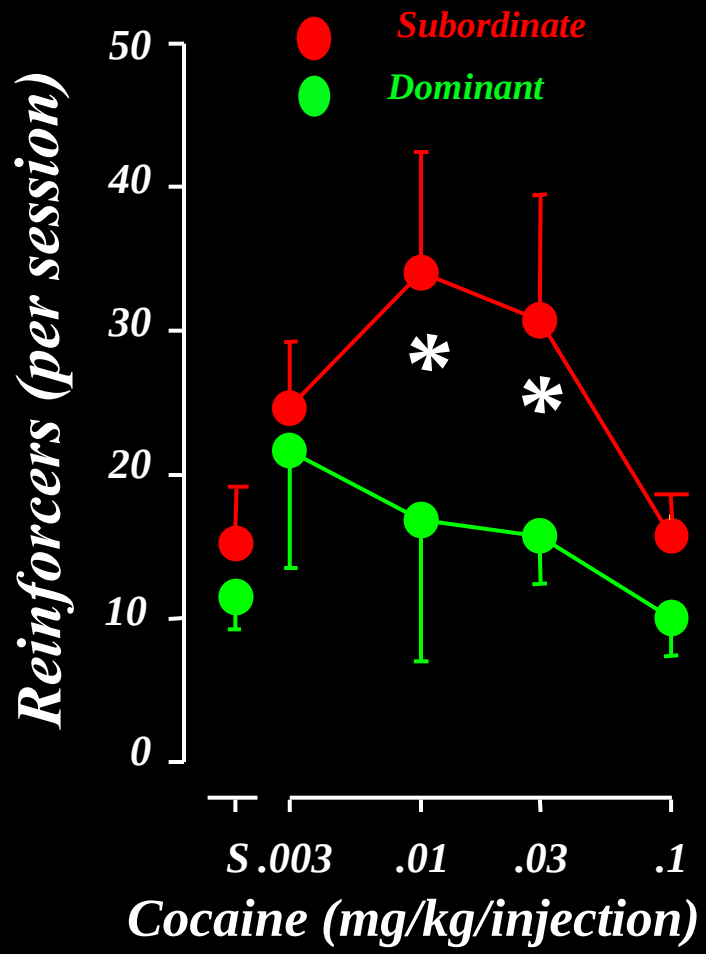
Family Problems

Early physical or sexual abuse

Stress in general

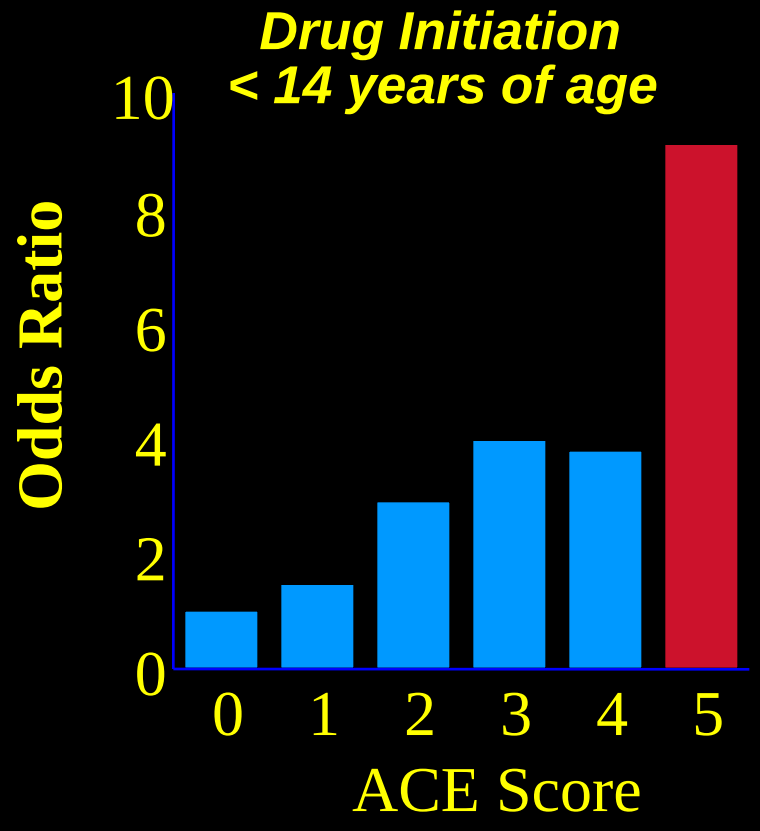
Social Factors Affect Brain DA D2 Receptors and Drug Self-Administration

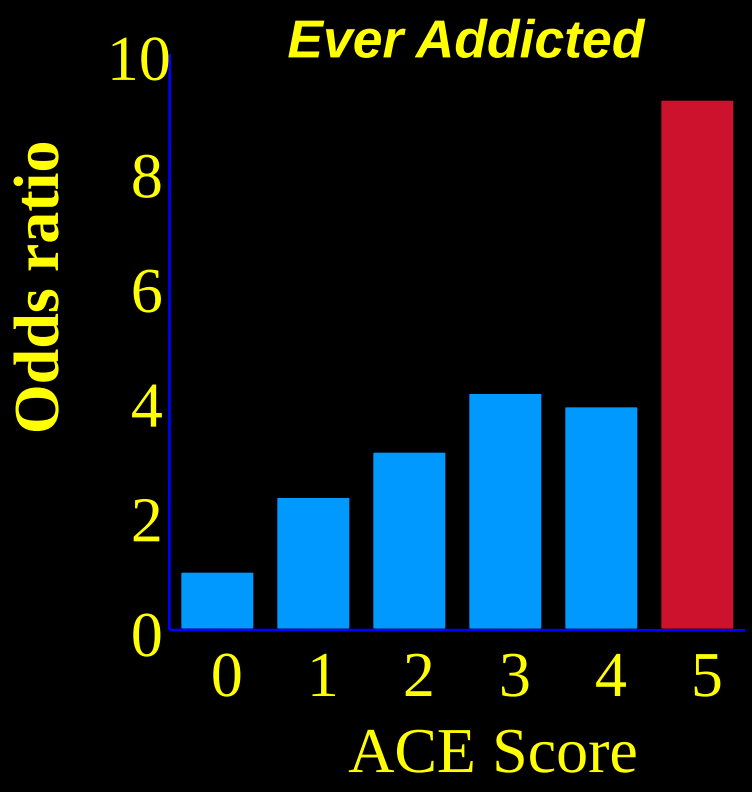




NIDA

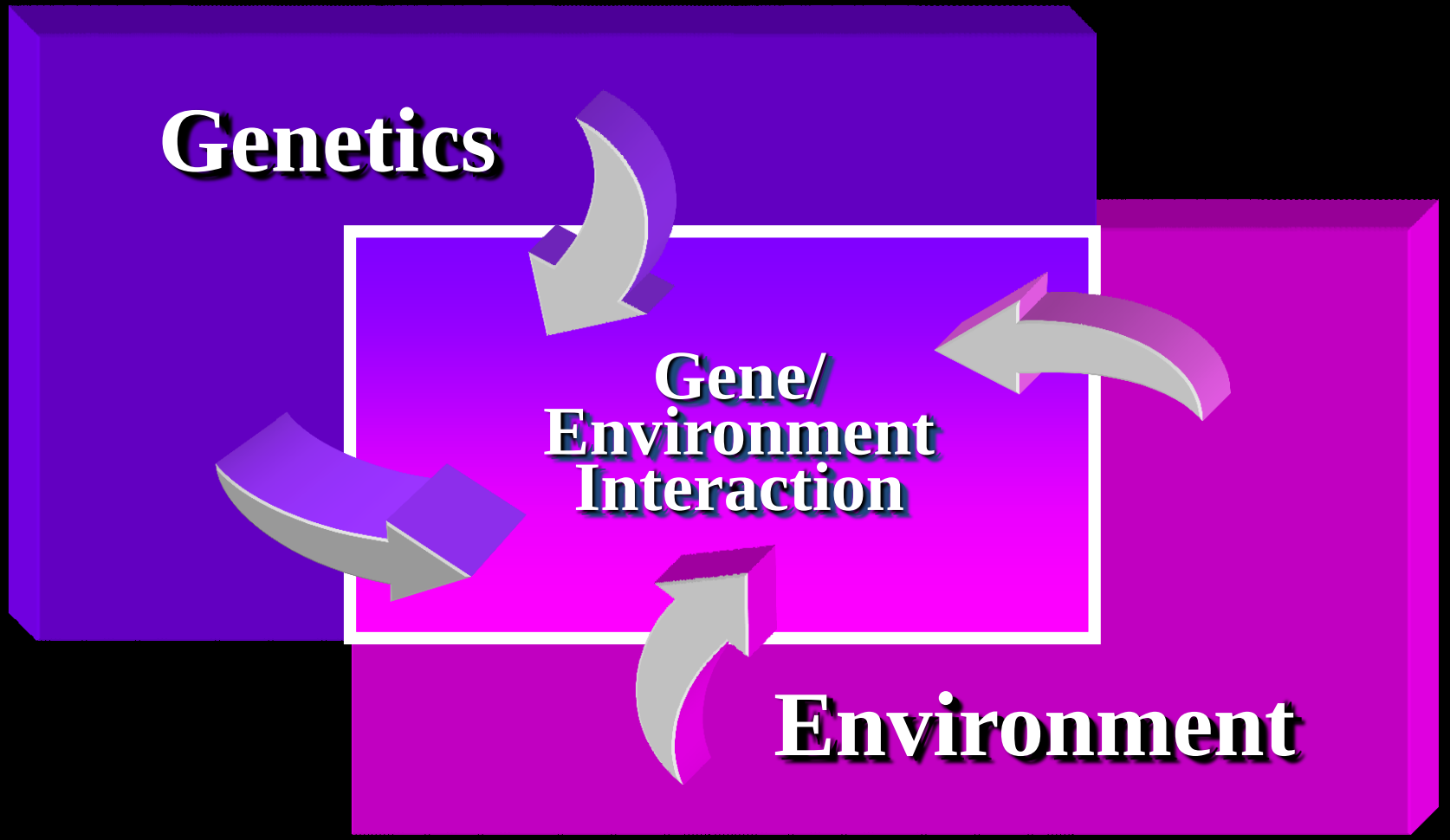
Adverse Childhood Experiences (ACE) and Illicit Drug Use (n = 8603)



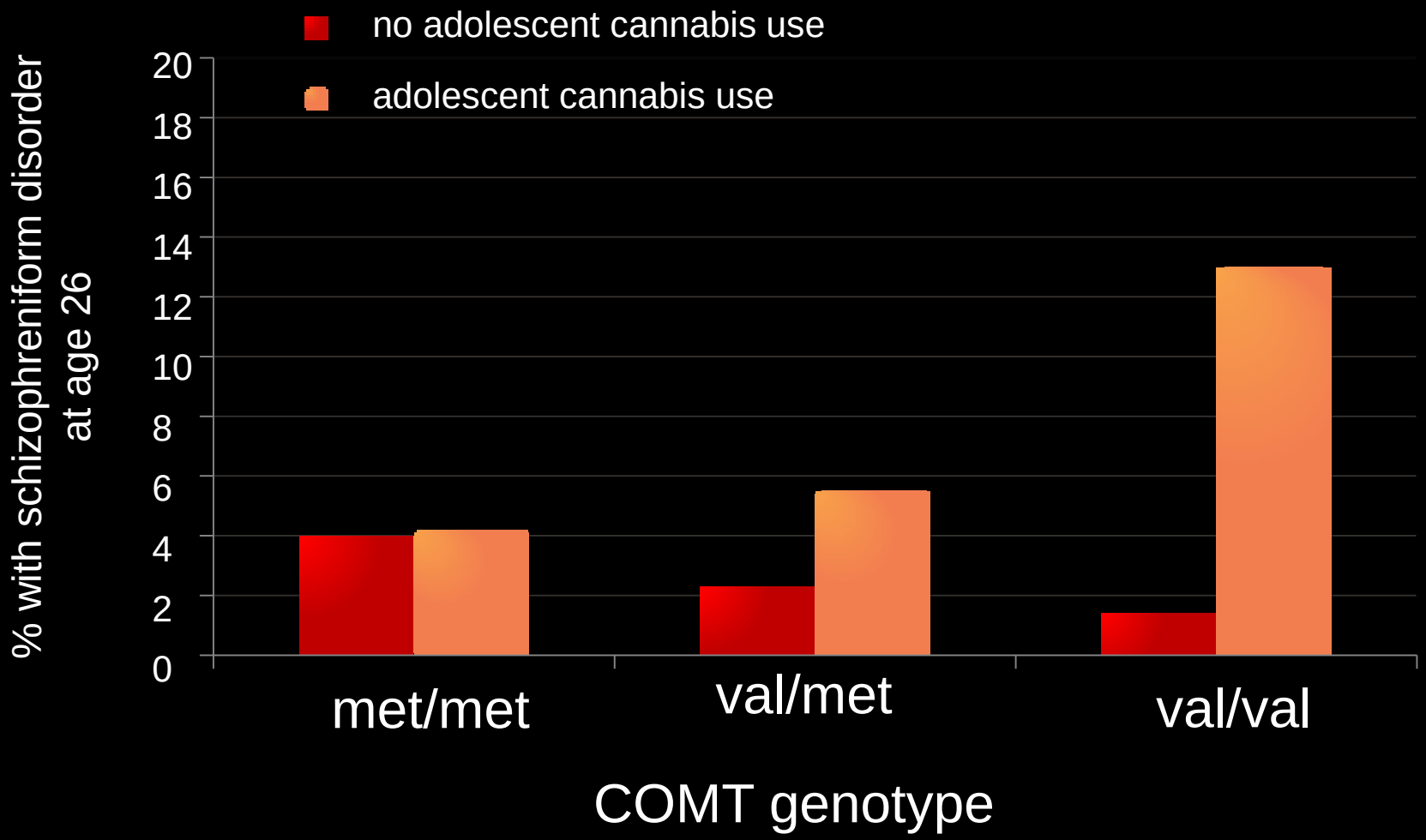


ACE account for one half to two third of serious problems with drug use.

PEDIATRICS 111: 564-572, 2003


Genetics
Gene/
Environment
Interaction
Environment

Gene X Environment X Development Interaction: Adolescent Cannabis Use Increases the Risk for Adult Psychosis in Genetically Vulnerable Individuals



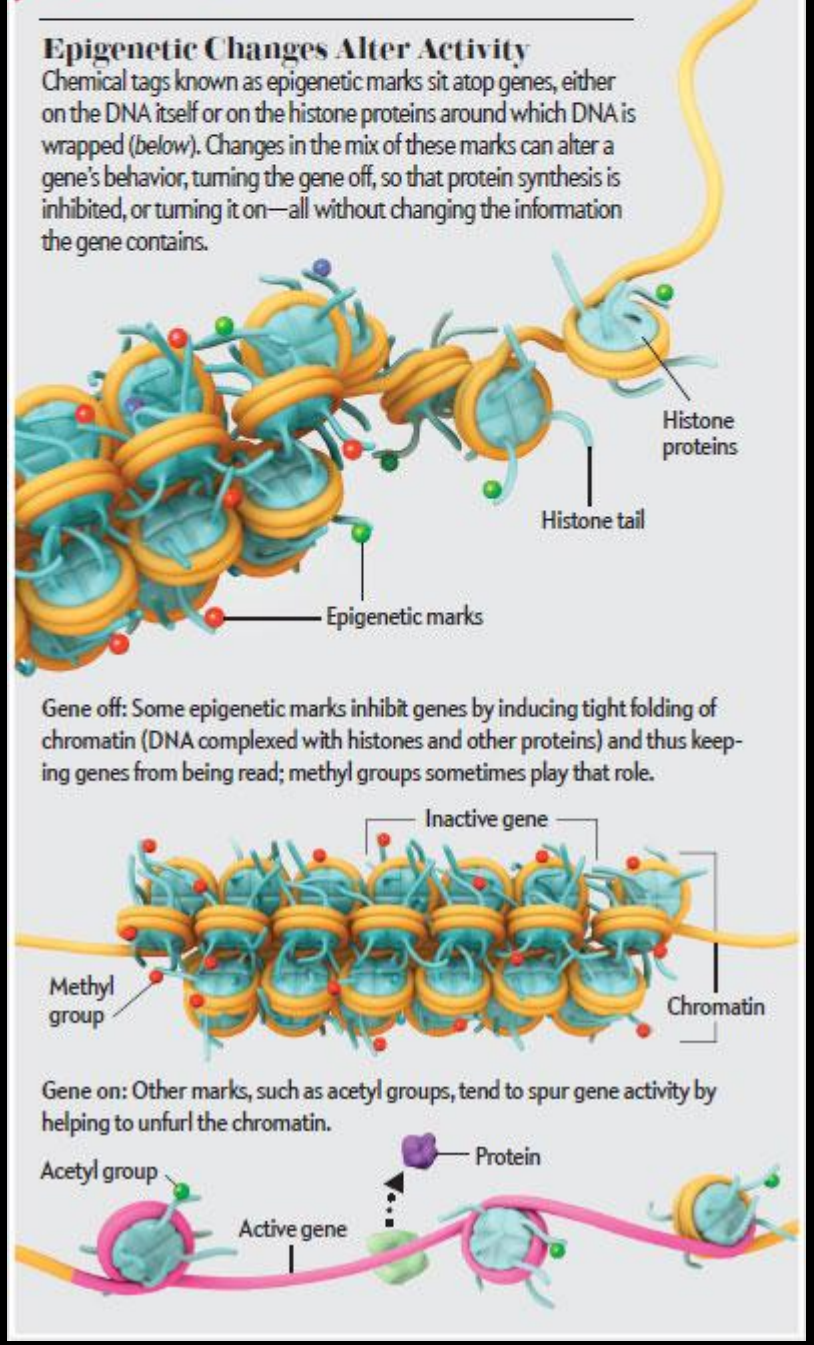
Source: Caspi, A. et al., Biol. Psychiatry, 57: 1117-1127; 2005.

What are the mechanisms by which environmental events can affect addiction vulnerability?

Epigenetics

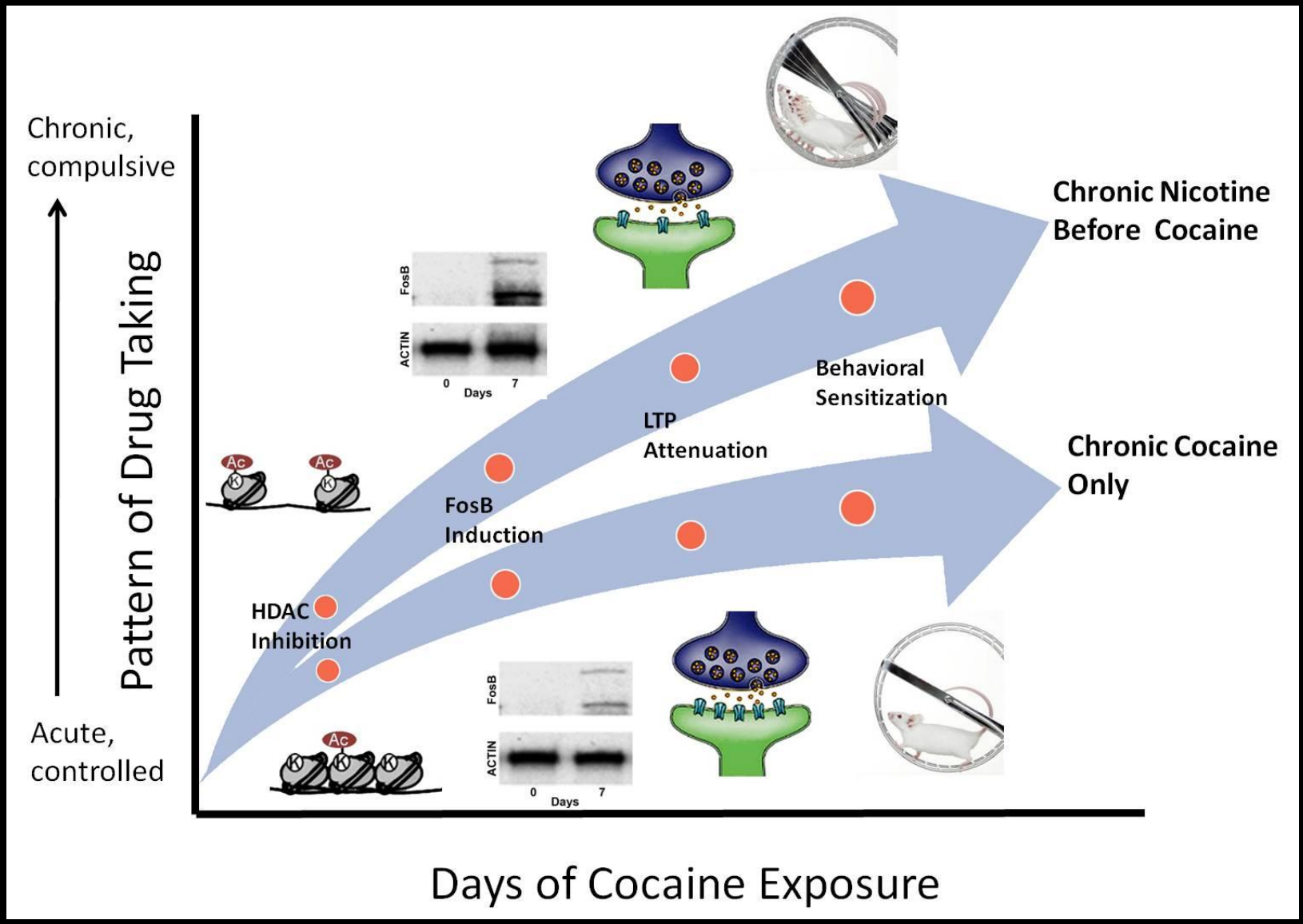
1999

2009



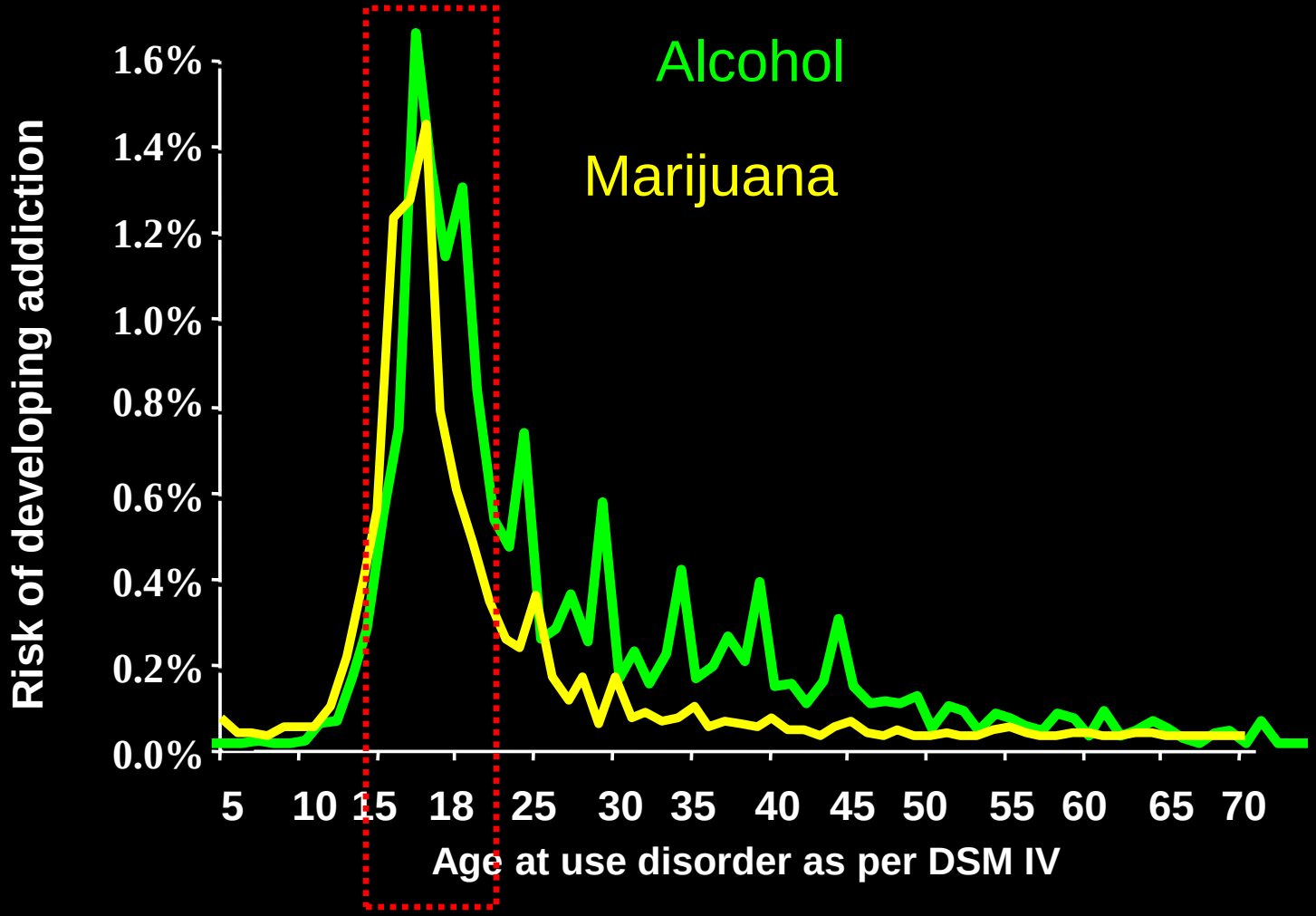
Epigenetic changes can silence or activate genes for long periods of time and can be inherited

Nicotine as a Gateway Drug



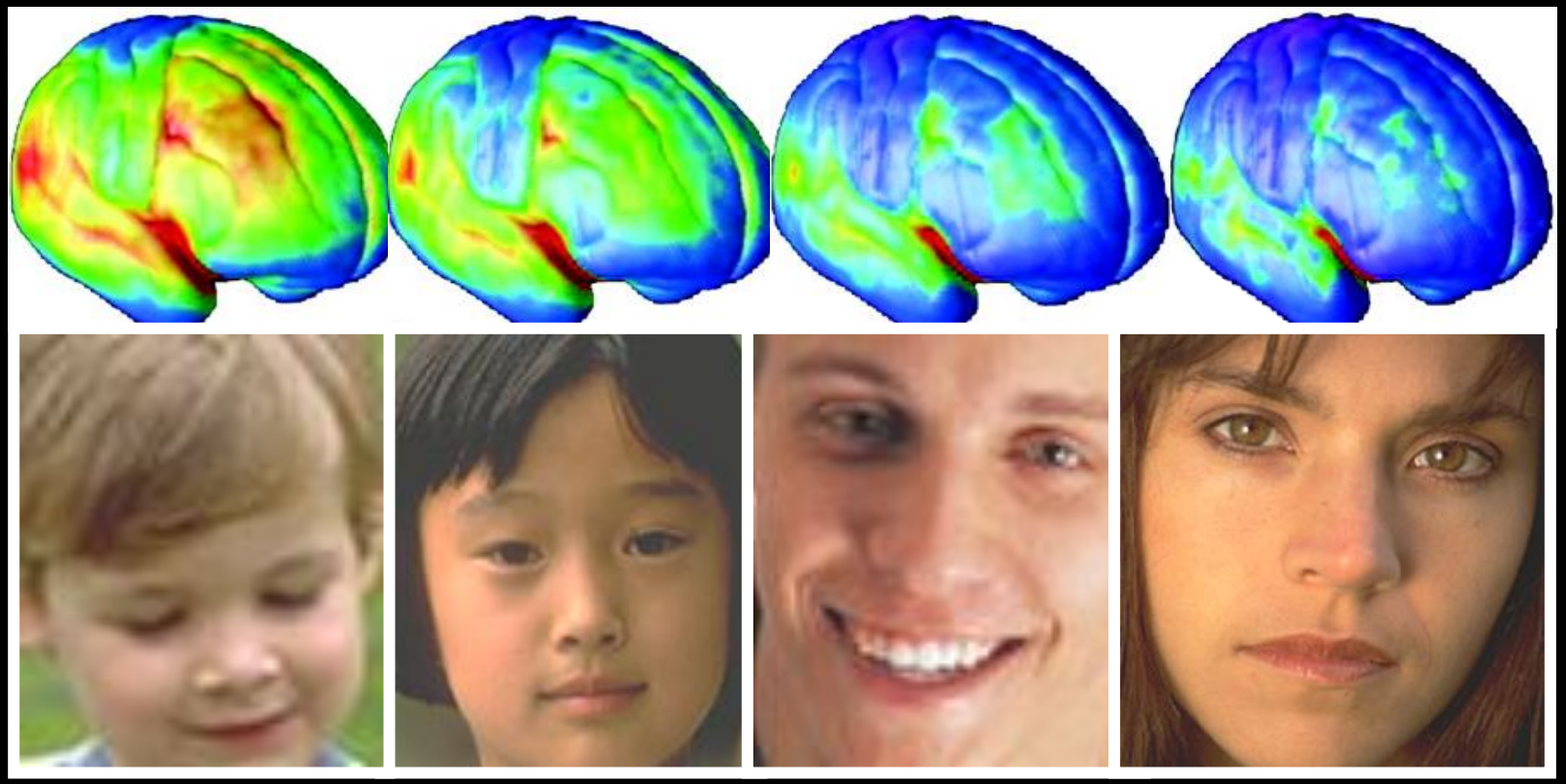
What else affects addiction vulnerability?

Addiction is a Developmental Disease: It starts in adolescence and even childhood



NIAAA National Epidemiologic Survey on Alcohol and Related Conditions, 2003

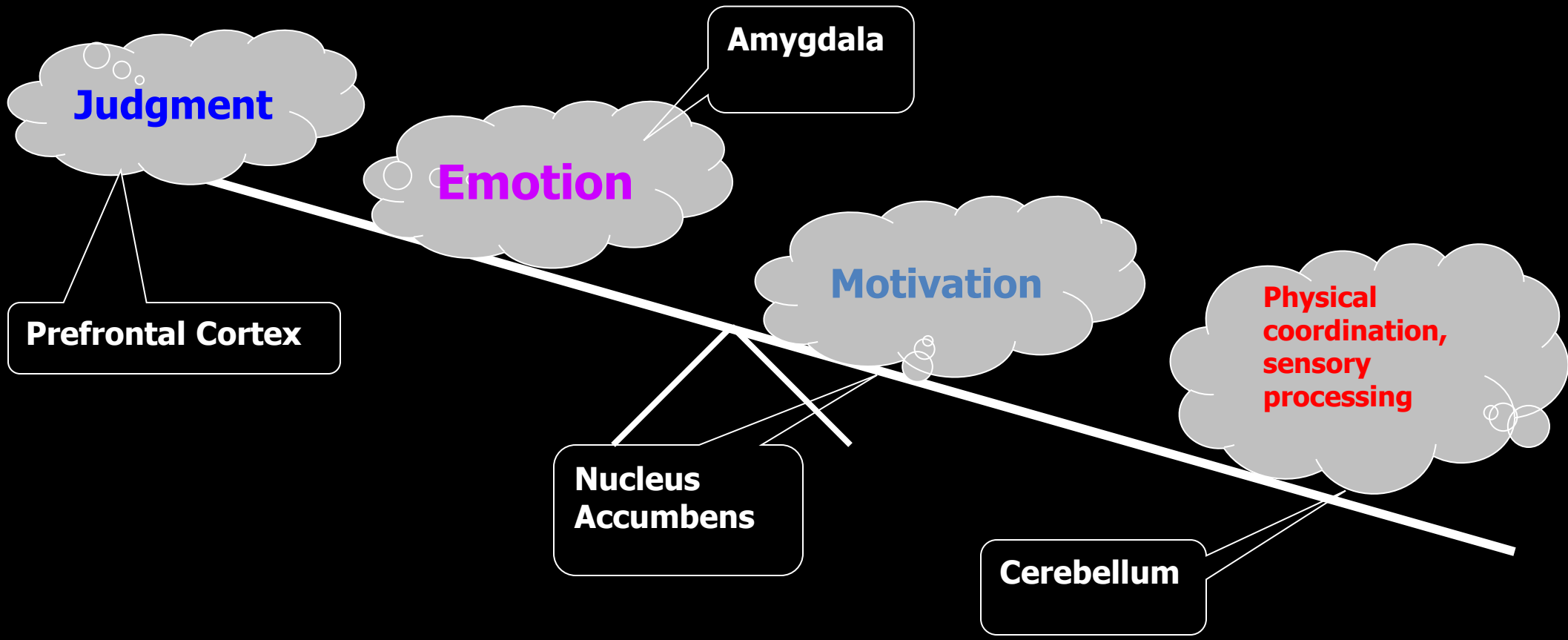
Adolescents' Brains Are Still Developing...



Implications for Prevention and Treatment?

Source: Gogtay, Nitin et al. (2004) Proc. Natl. Acad. Sci. USA 101, 8174-8179

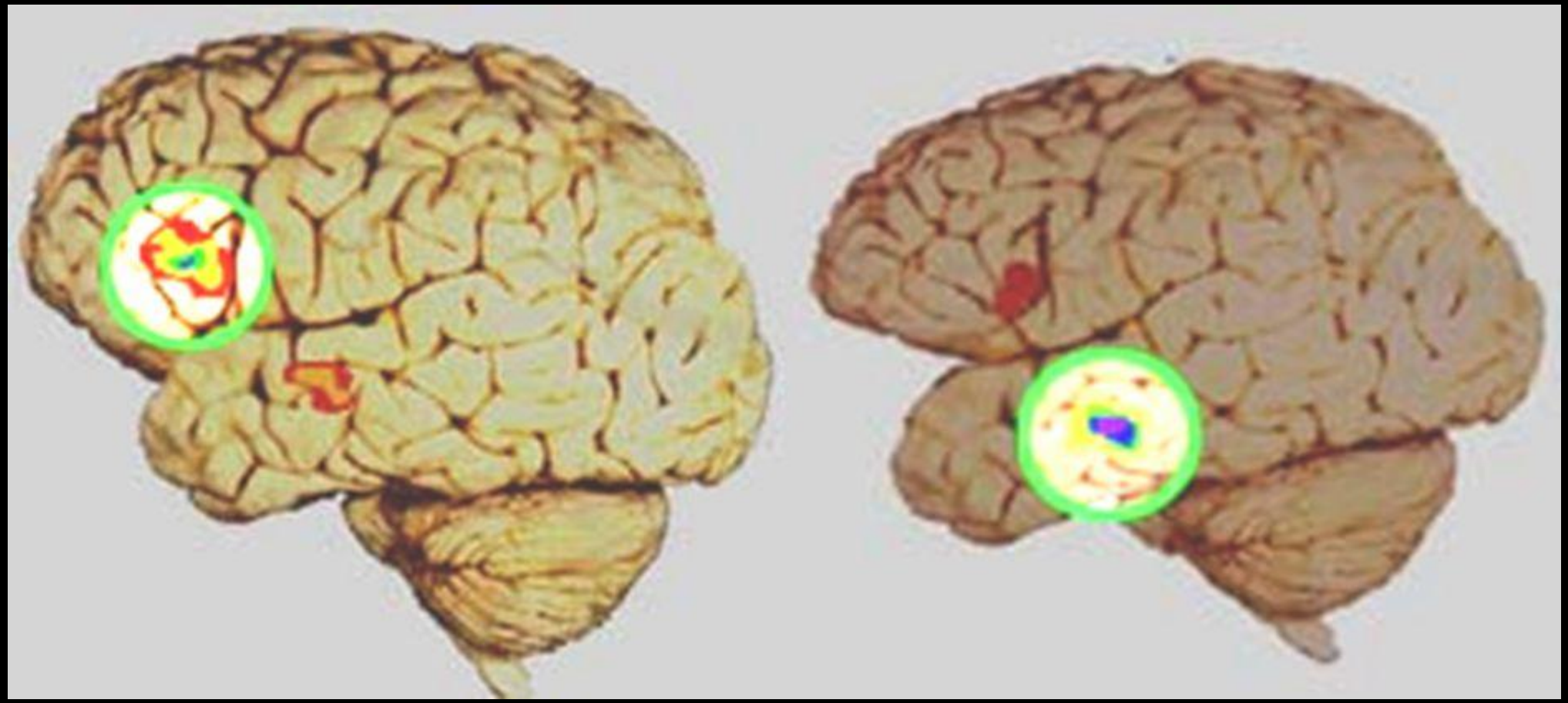
Maturation starts at the back of the brain ... and moves to the front



Notice: Judgment is last to develop!

Source: K. Winters

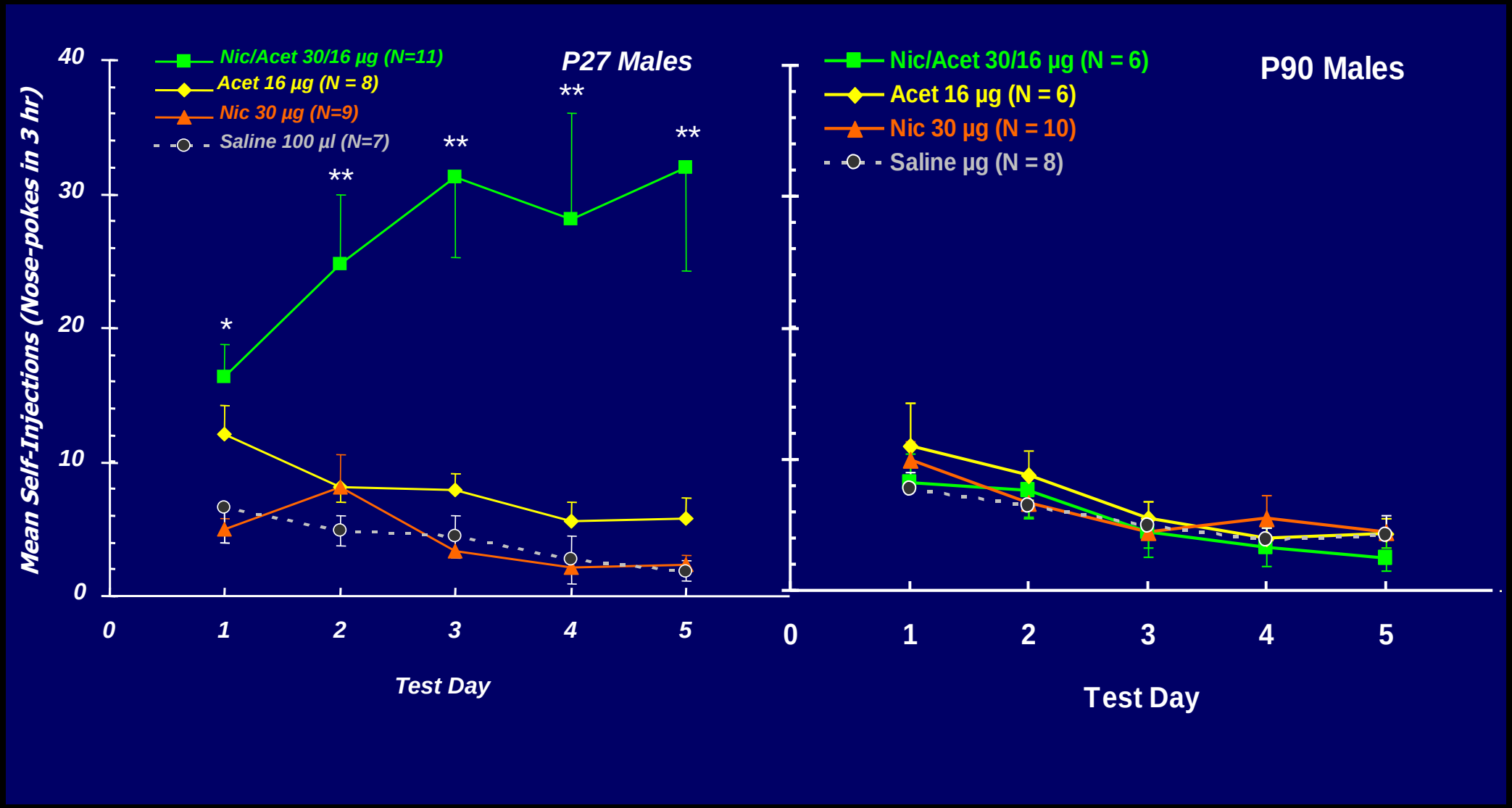
When Reading Emotion Adults Rely More on the Prefrontal Cortex while Teens Rely More on the Amygdala



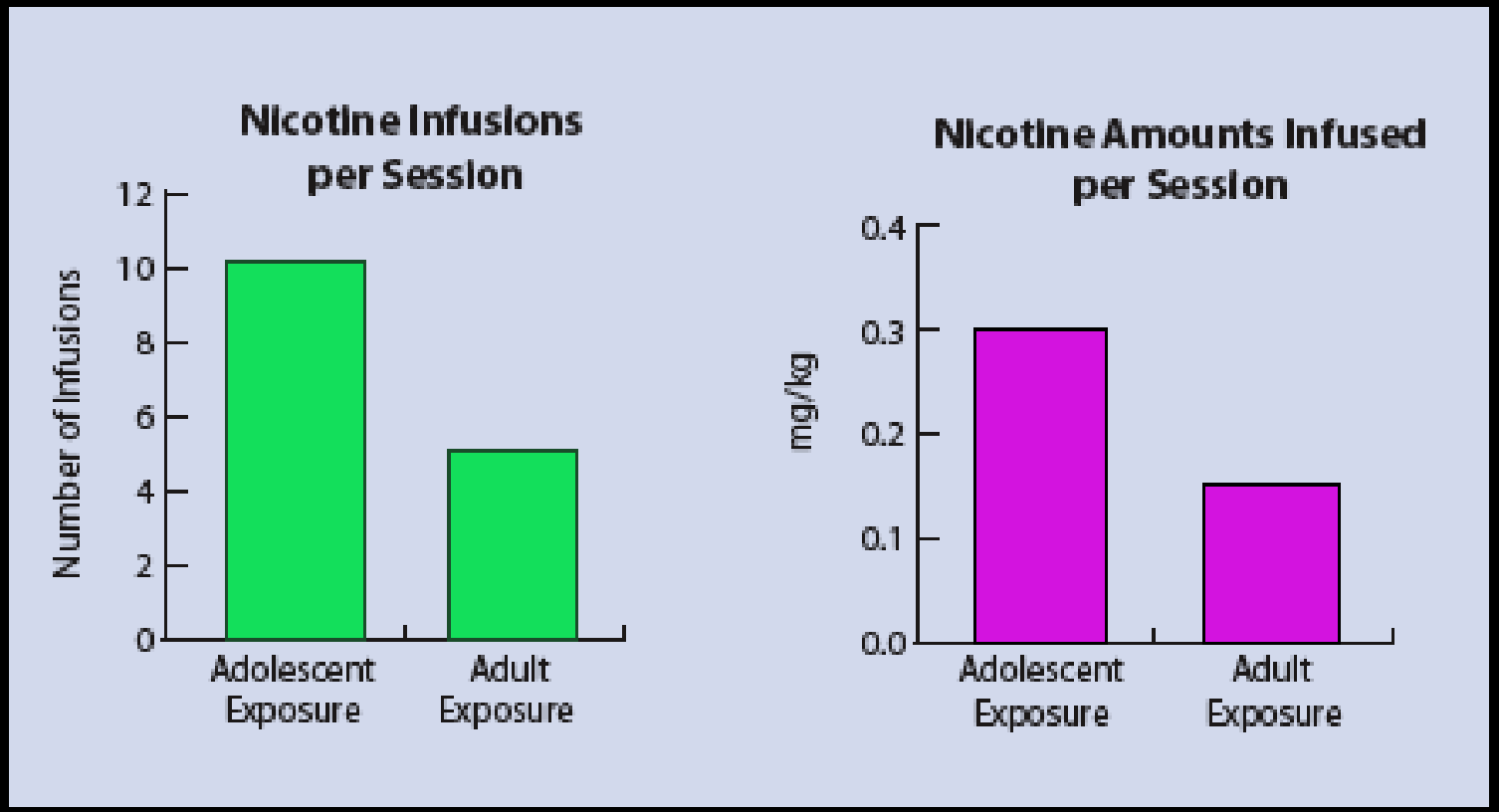
Do Adolescents React Differently than Adults to Substances of Abuse?

NIDA

Highly Rewarding Effect of Nicotine/Acetaldehyde During Adolescence

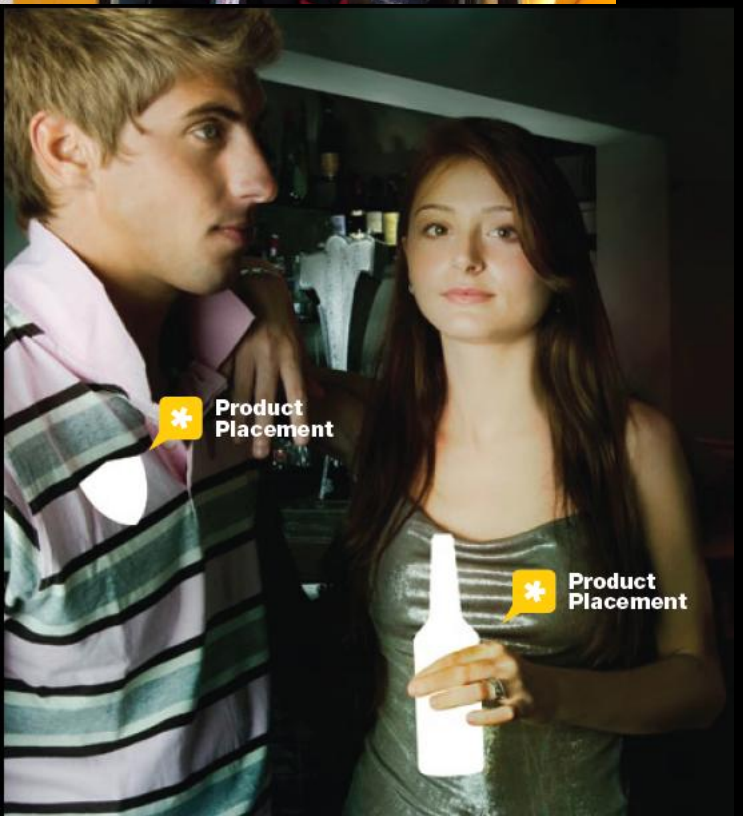


Rats Exposed to Nicotine in Adolescence Self-Administer More Nicotine Than Rats First Exposed as Adults



NIDA

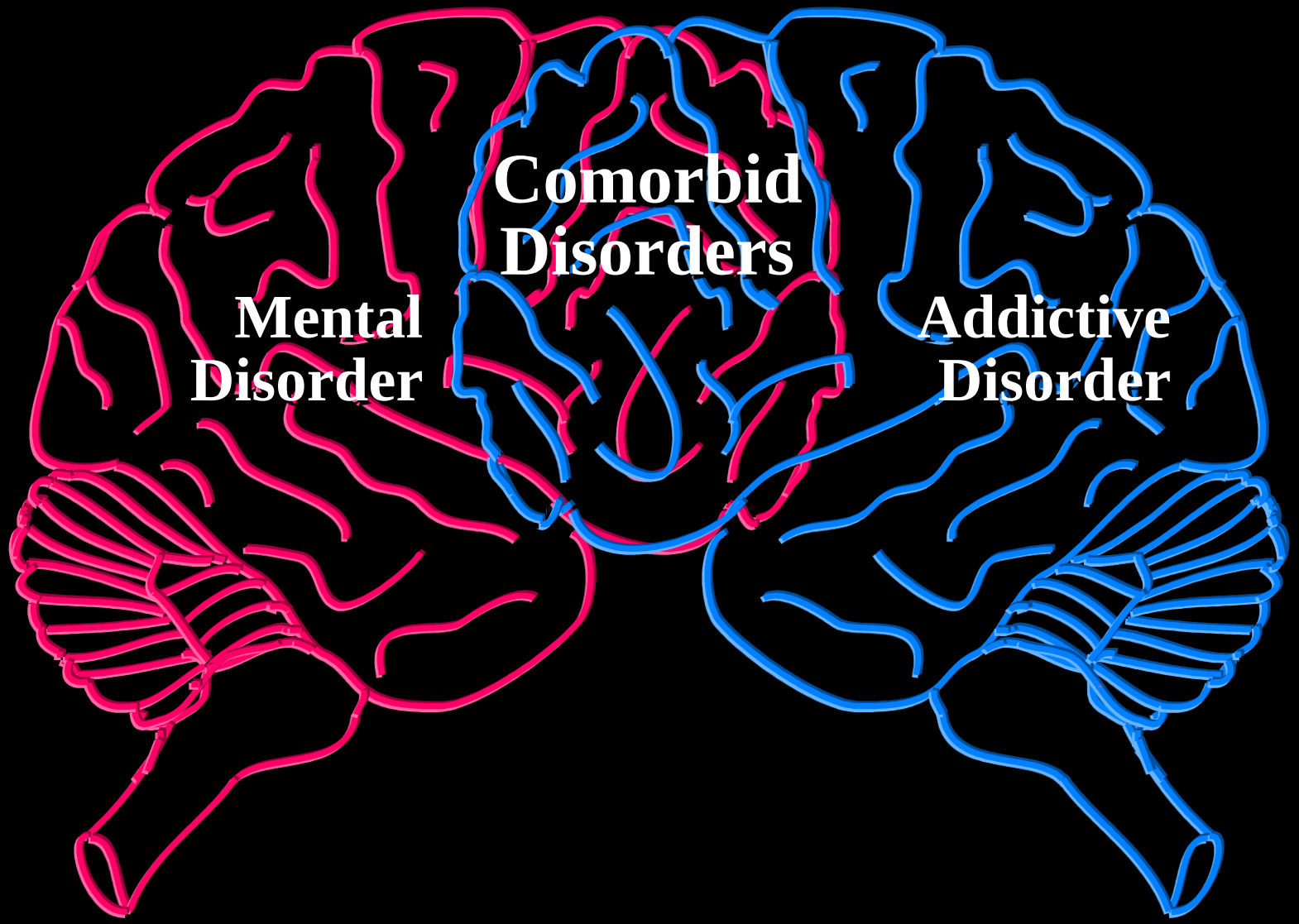
Do We Need Fundamentally Different Strategies For Adolescents?



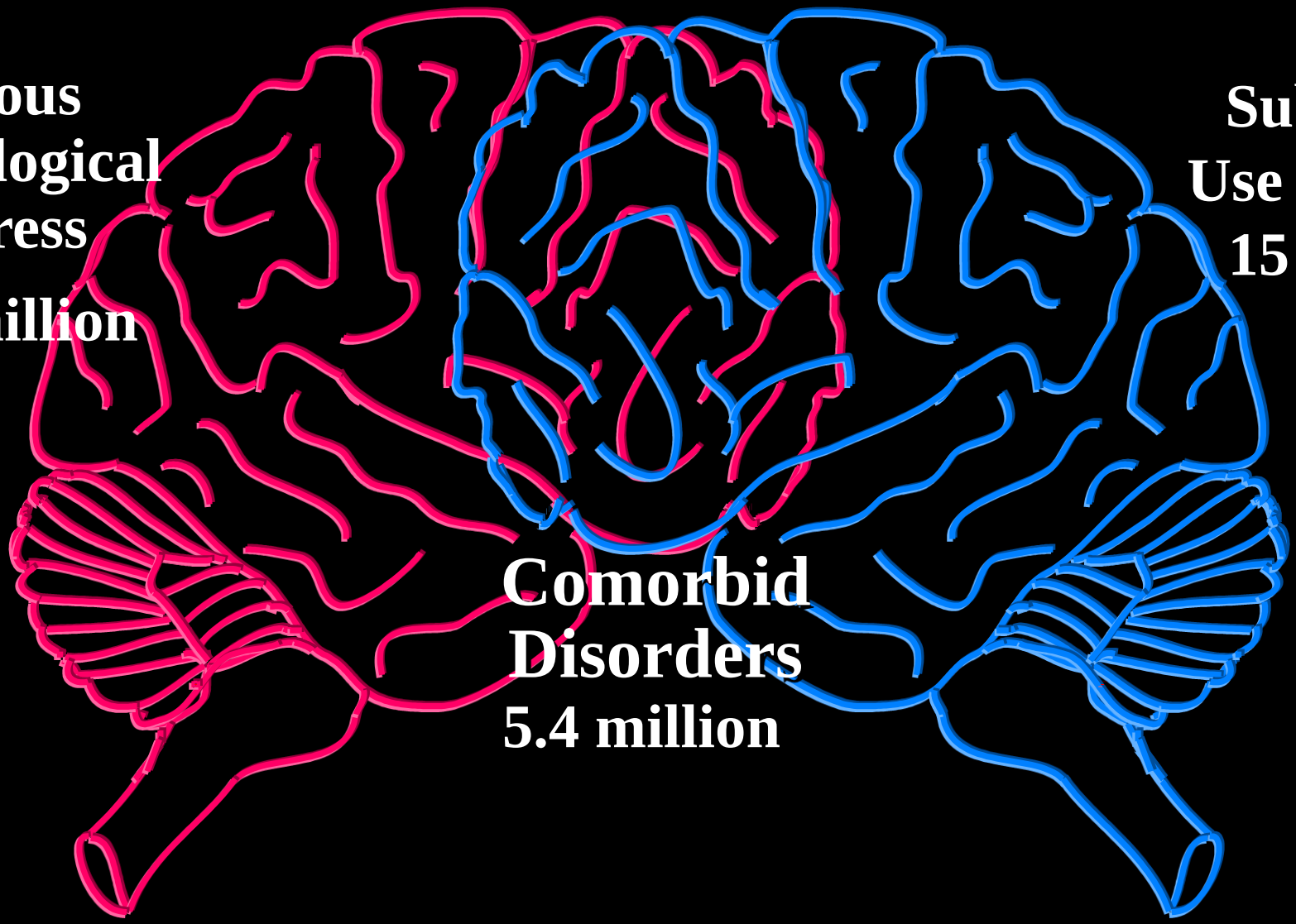
NIDA

What Else Affects Vulnerability to Addiction?

Addictive Disorders Often *Co-Exist* With Other Mental Disorders



Addictive Disorders Often *Co-Exist* With Other Mental Disorders



Serious Psychological Distress

24.3 million

Substance Use Disorder

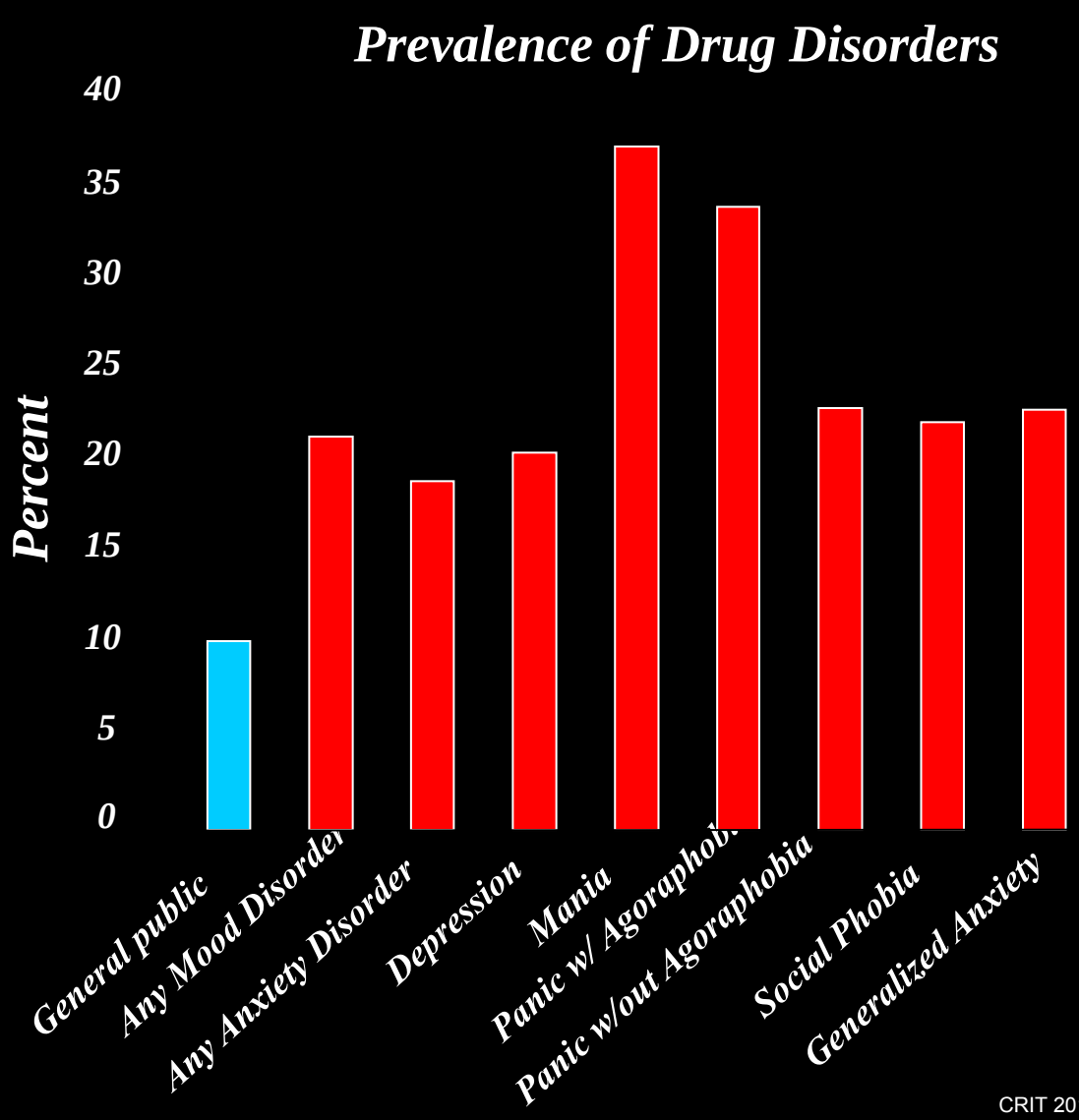
15 million

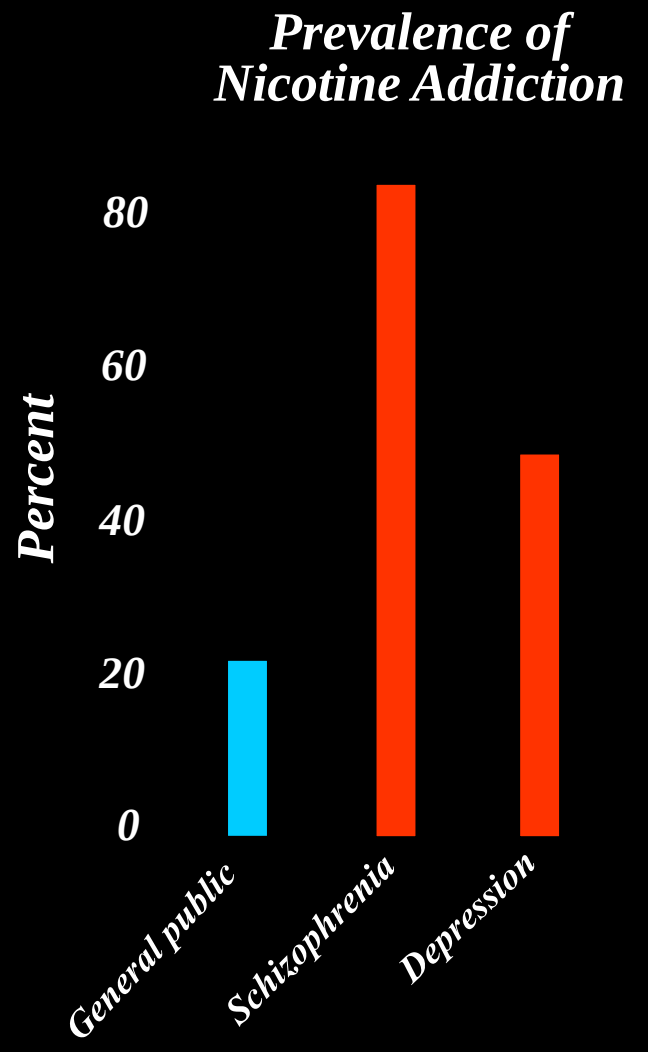
Comorbid Disorders

5.4 million

SAMHSA, Office of Applied Studies, National Survey on Drug Use and Health, 2007

Higher Rates of Drug Disorders Among Patients with Mental Illness

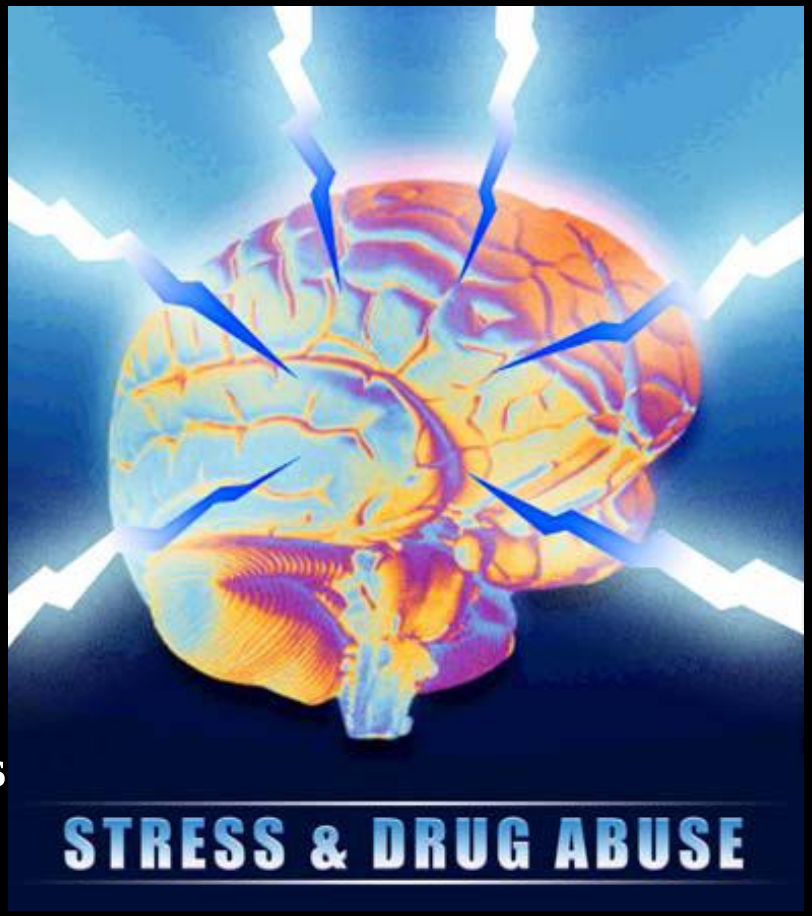




Many Common Factors Are Involved in Addiction and Mental Illness

Addiction:

- **Early Physical or Sexual Abuse**
- **Stress**
- **Family History**
- **Mental Illness**
- **Peers who use Drugs**



Mental Illness:

- **Early Physical or Sexual Abuse**
- **Stress**
- **Family History**
- **Drug and Alcohol Abuse**

Why do Mental Illnesses and Substance Abuse Co-occur?

- **Self-medication**
  - substance abuse begins as a means 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

NIDA

These may contribute to vulnerability to initial drug use

But what happens over time?

Science has Generated Much Evidence Showing that....

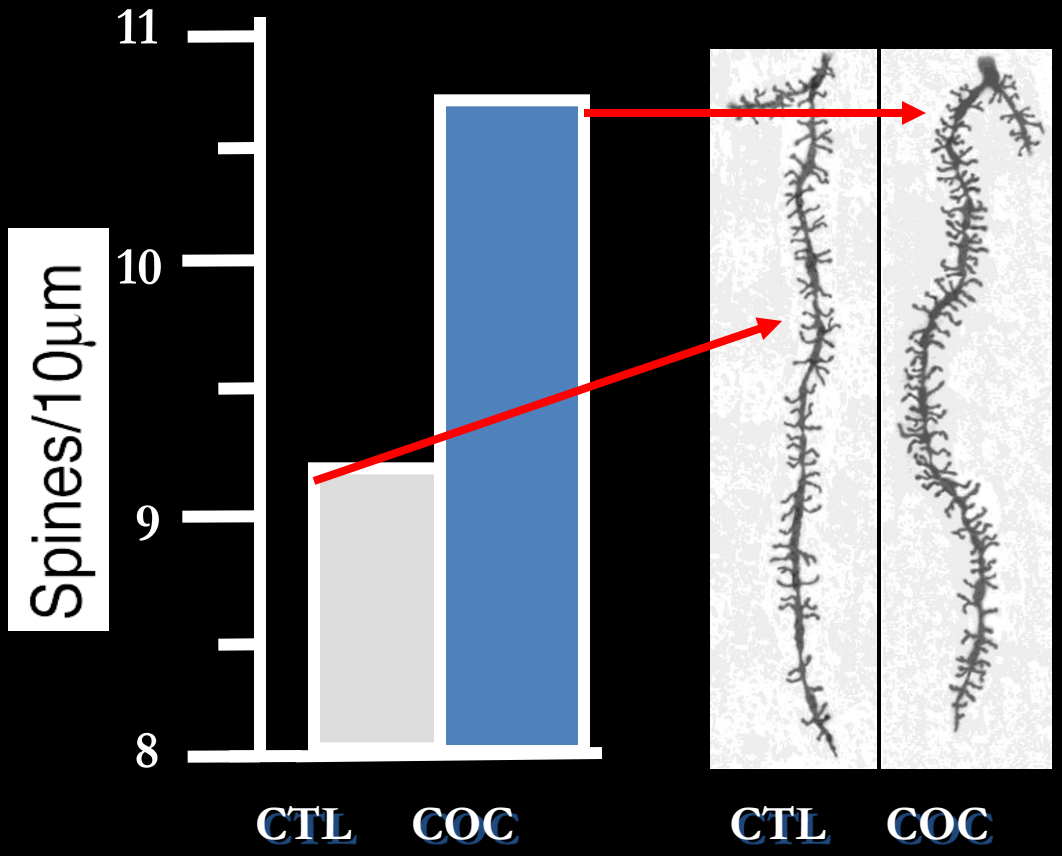
Prolonged Drug Use Changes the Brain In Fundamental and Long-Lasting Ways

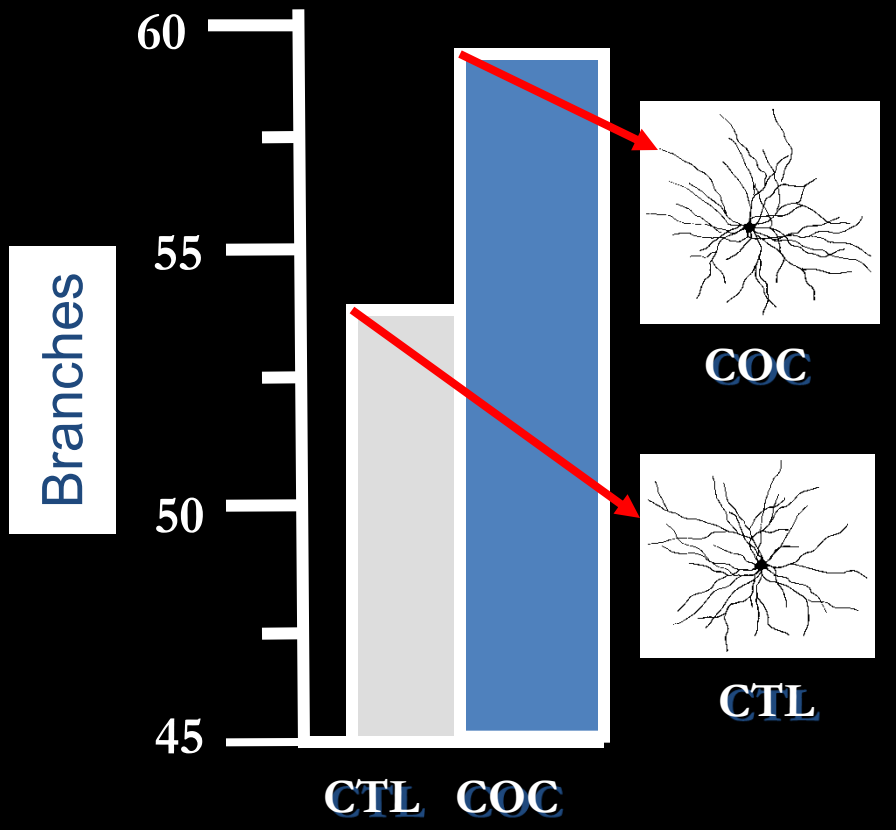
AND...

We Have Evidence That These Changes Can Be Both Structural and Functional

Structurally...

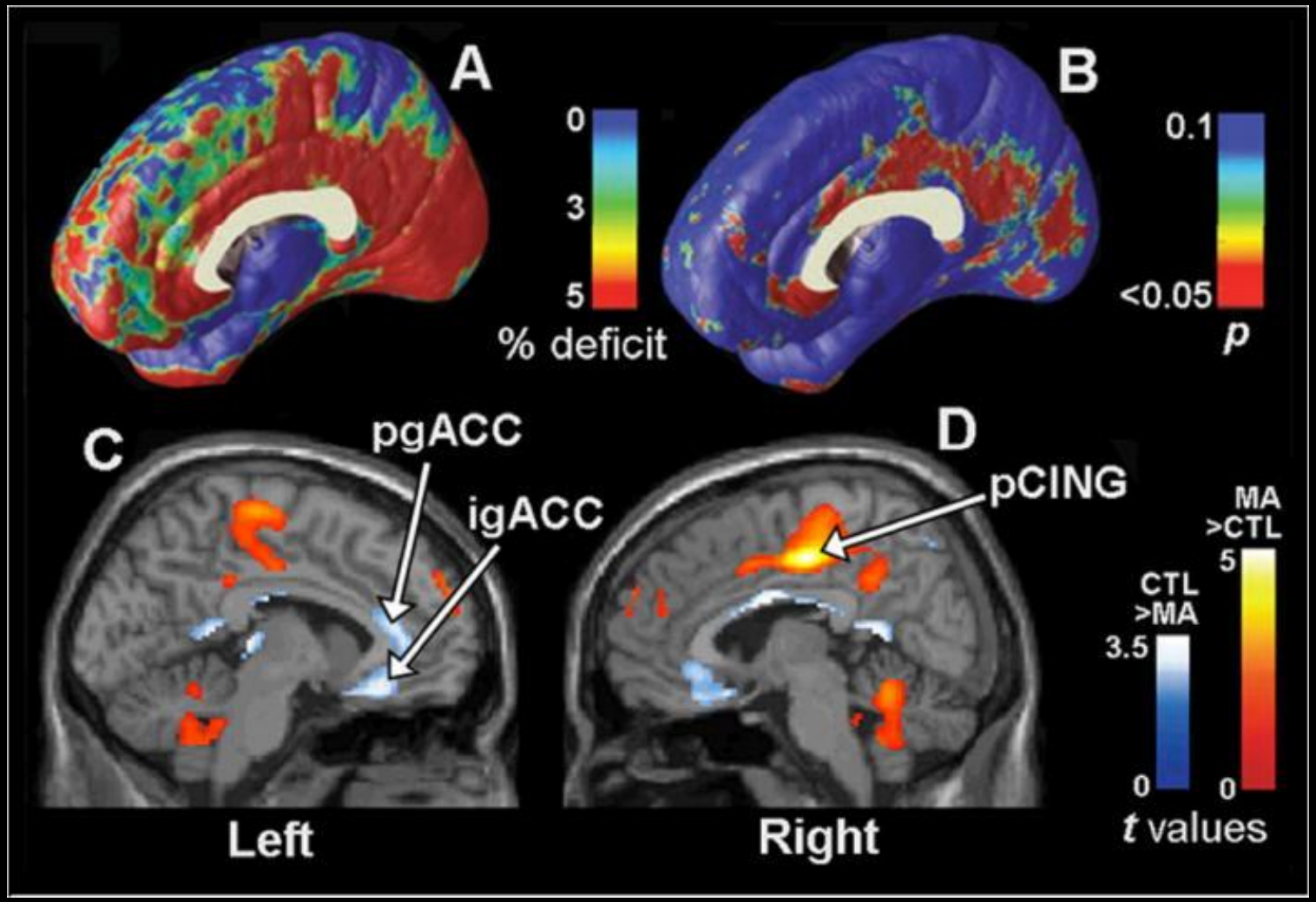
Chronic cocaine increases density of dendritic spines and neuronal branching in the nucleus accumbens





Robinson, T.E. & Kolb, B. Eur. J. of Neuro. 1999.
Ferrario, C.R. et al. Biol. Psychiatry, 2005.

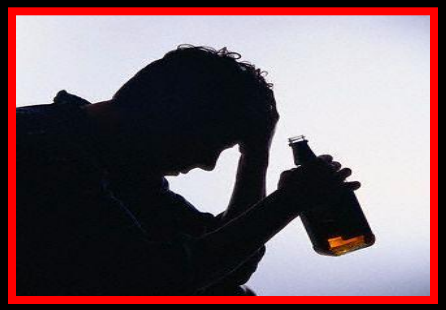
Amphetamine Abuse Produces *Structural* Abnormalities in the Brain



Source: Berman et al, Ann NY Acad Sci, 2008

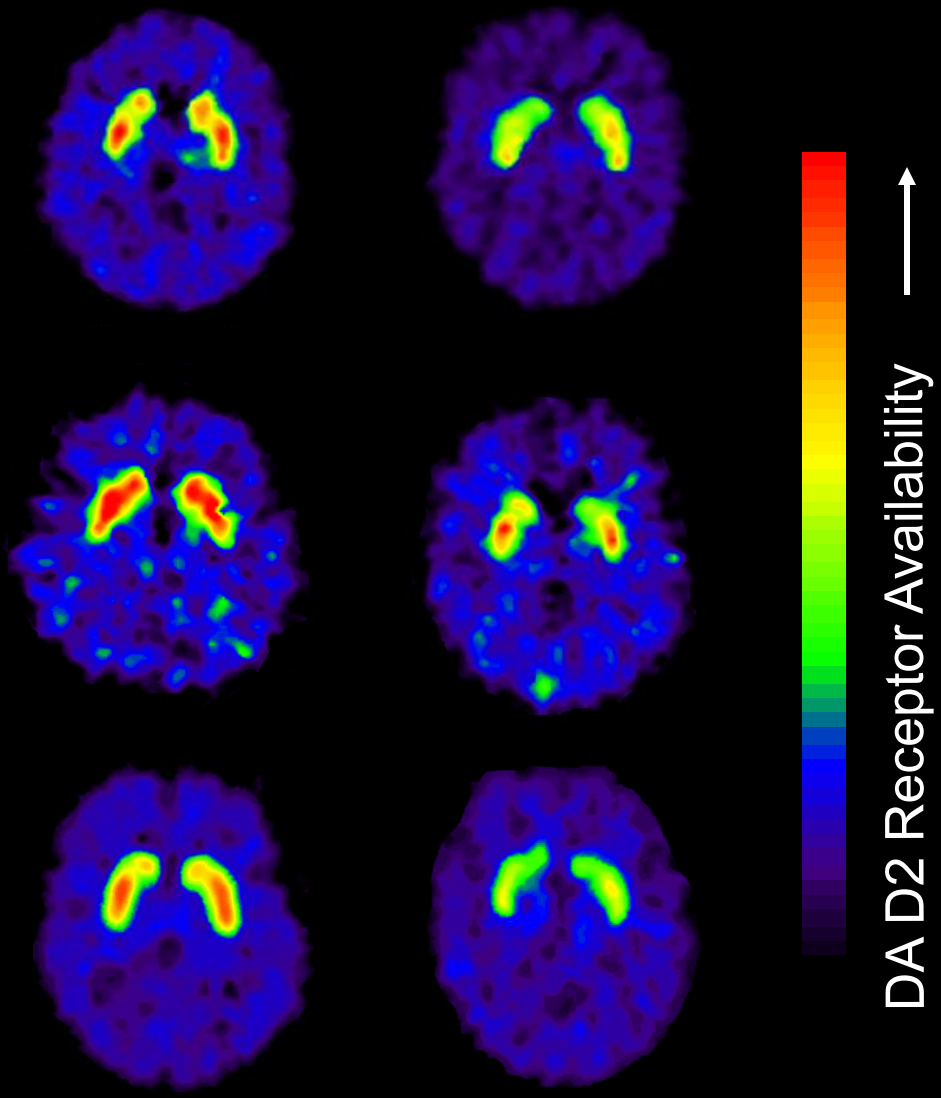
Functionally: Dopamine Receptors Lower in Addiction

Cocaine



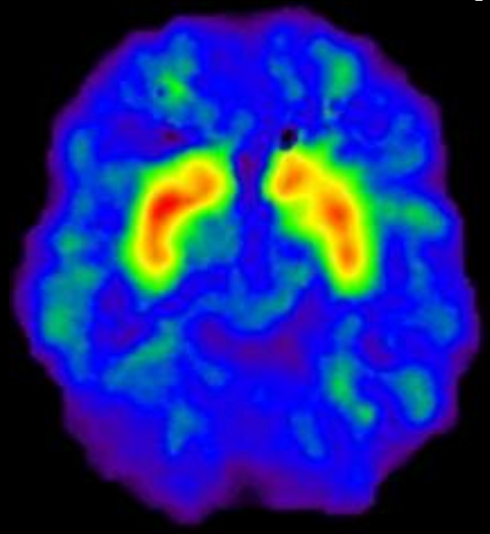
Alcohol

Heroin

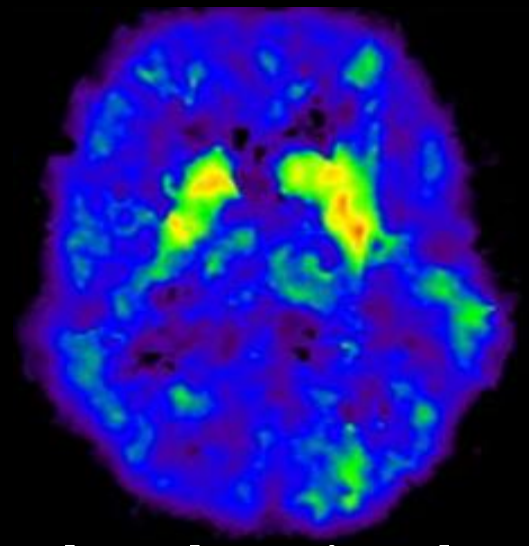


control **addicted**

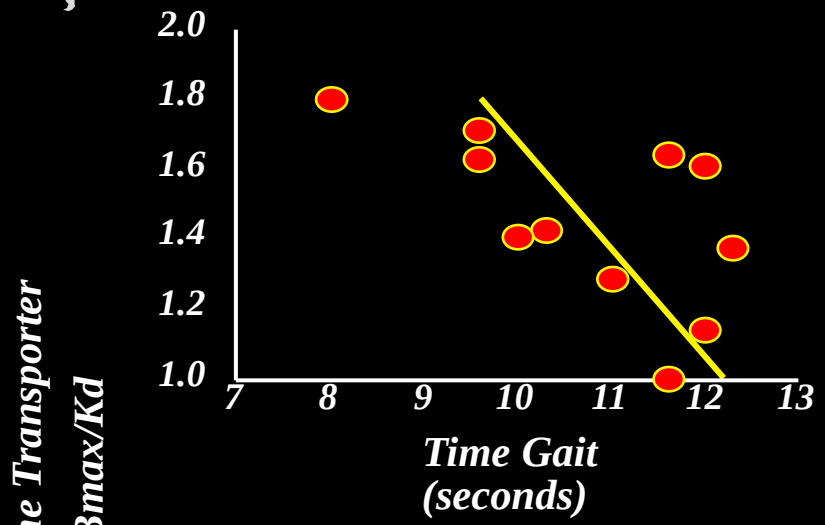
Functionally: Dopamine Transporters Lower in Methamphetamine Abusers



Normal Control

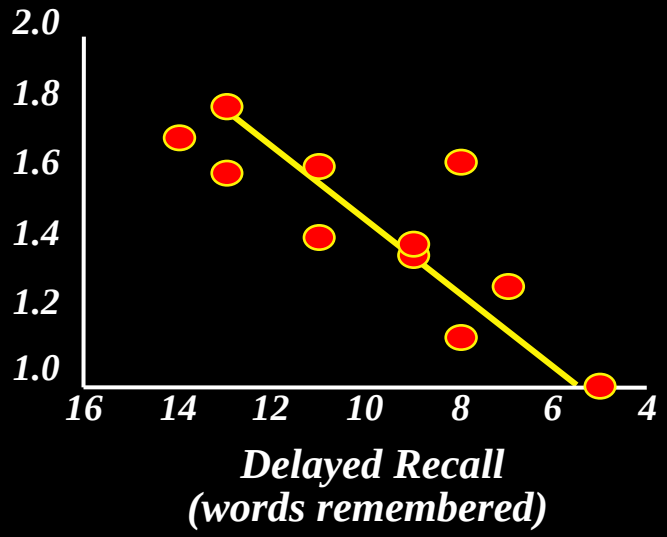


Methamphetamine Abuser



Motor Task

Loss of dopamine transporters in methamphetamine abusers may result in slowing of motor reactions.



Memory Task

Loss of dopamine transporters in methamphetamine abusers may result in memory impairment.

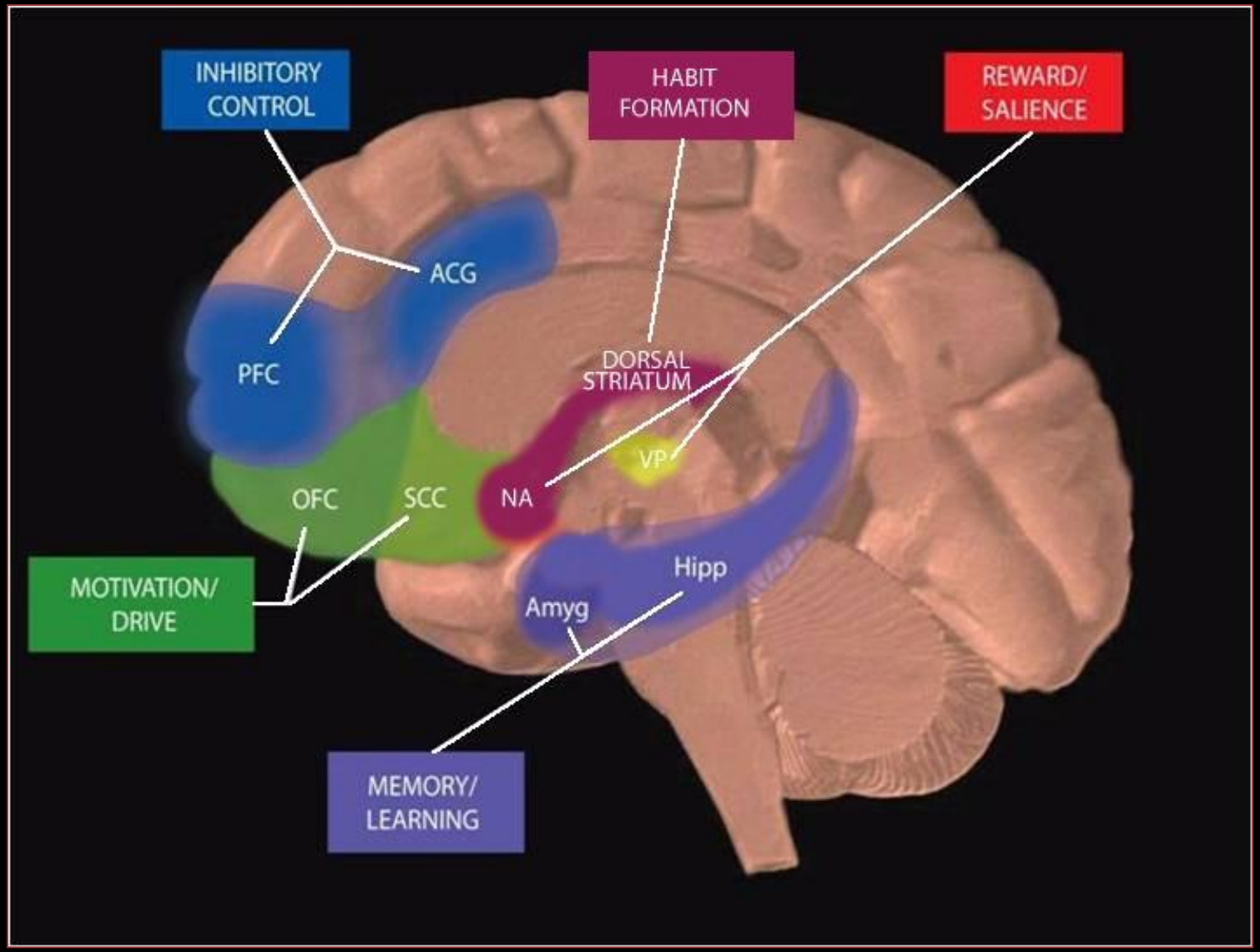
Volkow et al., Am. J. Psychiatry, 2001.

NIDA

But Dopamine/Reward are only Part of the Story

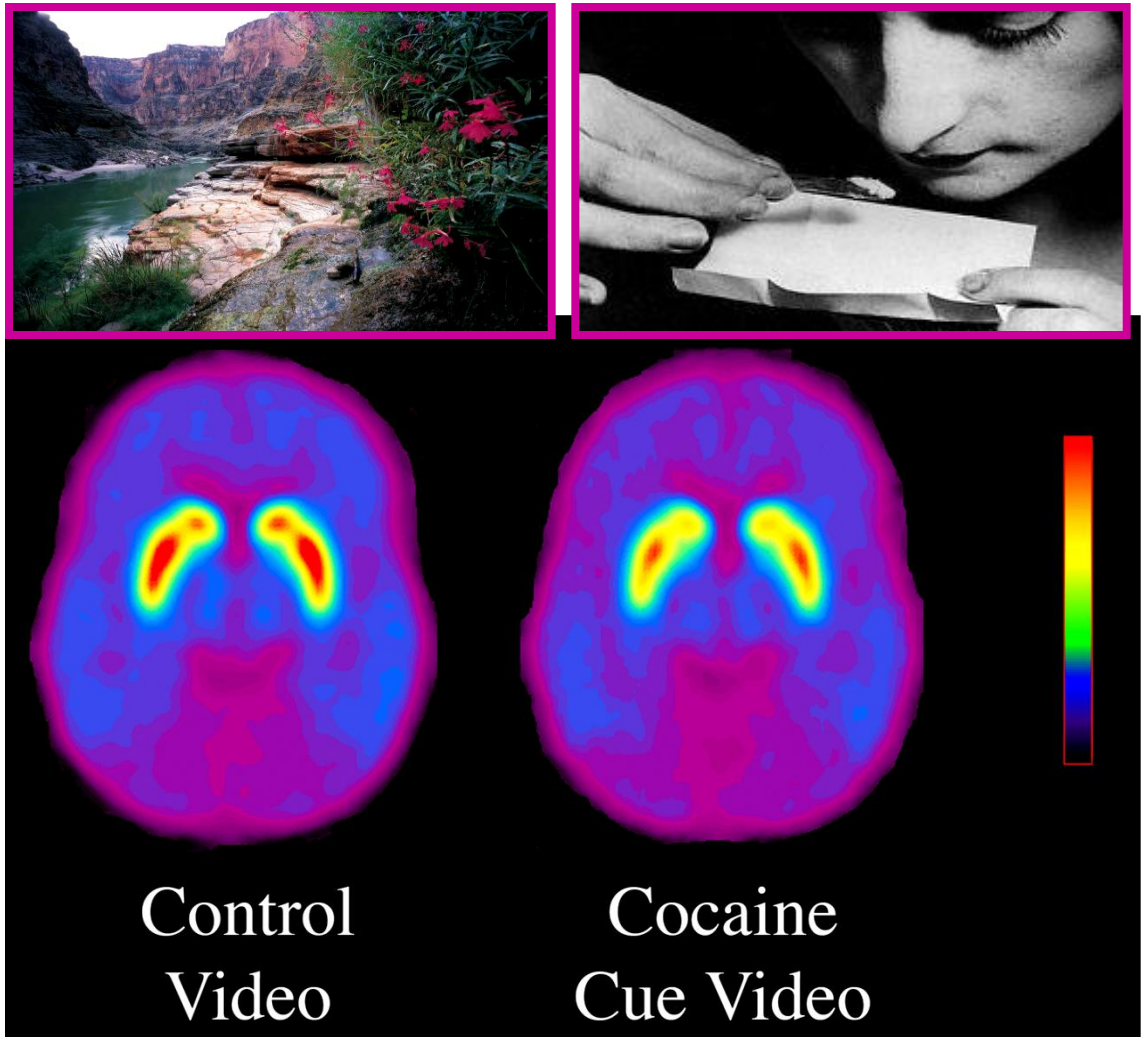
- Scientific research has shown that other neurotransmitters are also affected:
  - Serotonin
    - Regulates mood, sleep, etc.
  - Glutamate
    - Regulates learning and memory, etc.

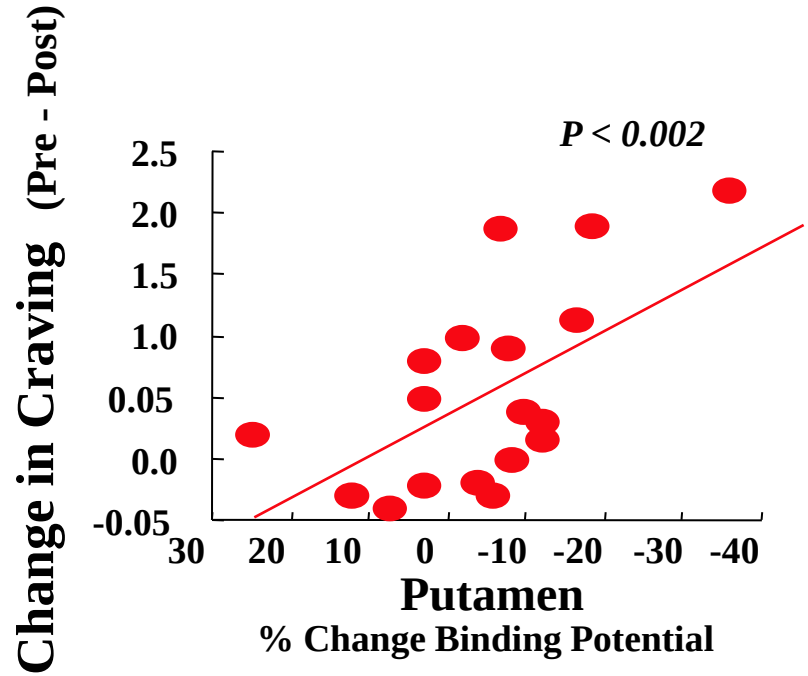
And Multiple Circuits Are Involved In Drug Abuse and Addiction



Memories/Conditioning are Critical Parts of Addiction

Reactivity of Dopamine System To Drug Cues (conditioned stimuli) in Addicted Subjects

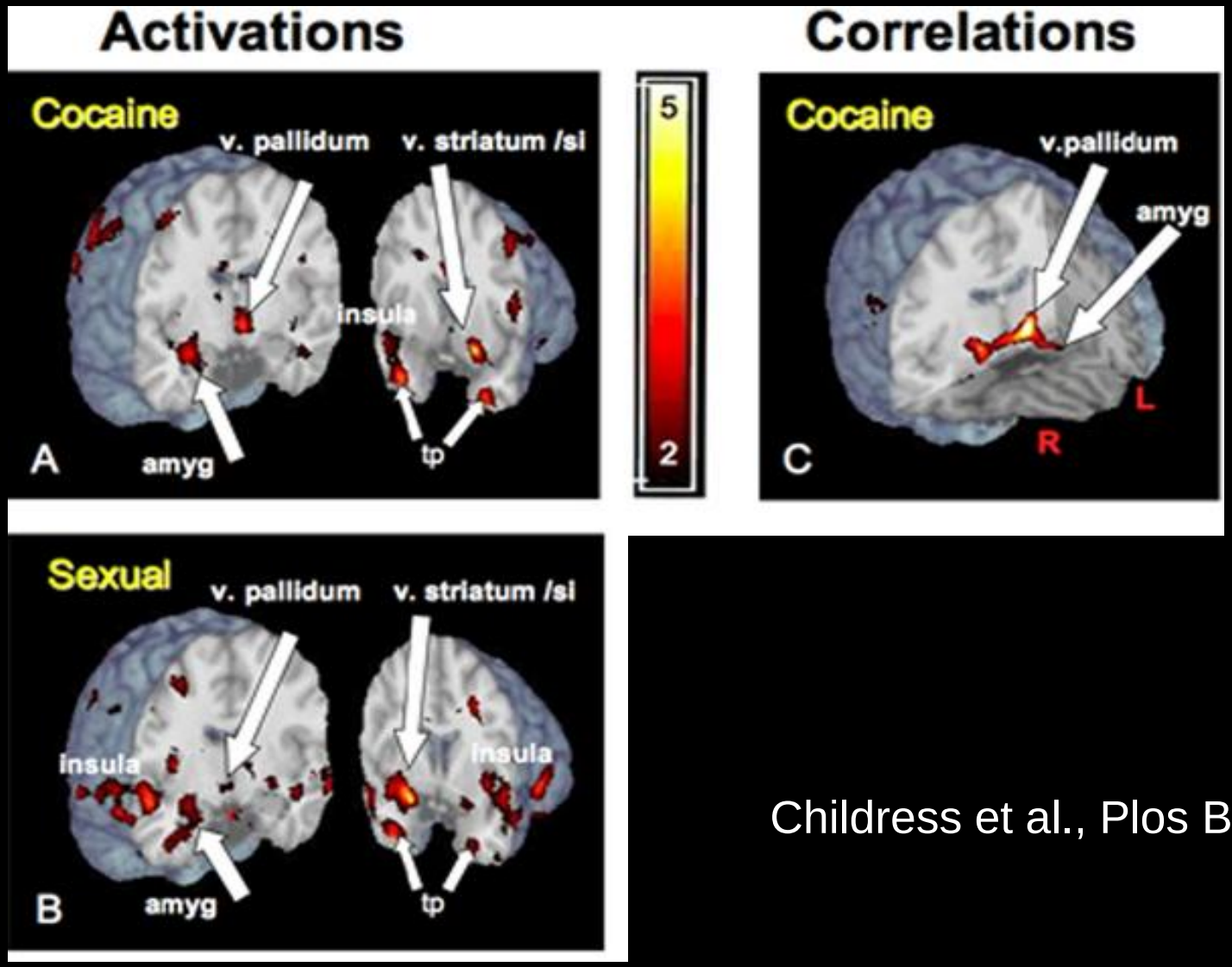




Cocaine abusers increased DA release when exposed to cues, which were associated with drug craving.

Volkow et al., J Neuroscience 2006.

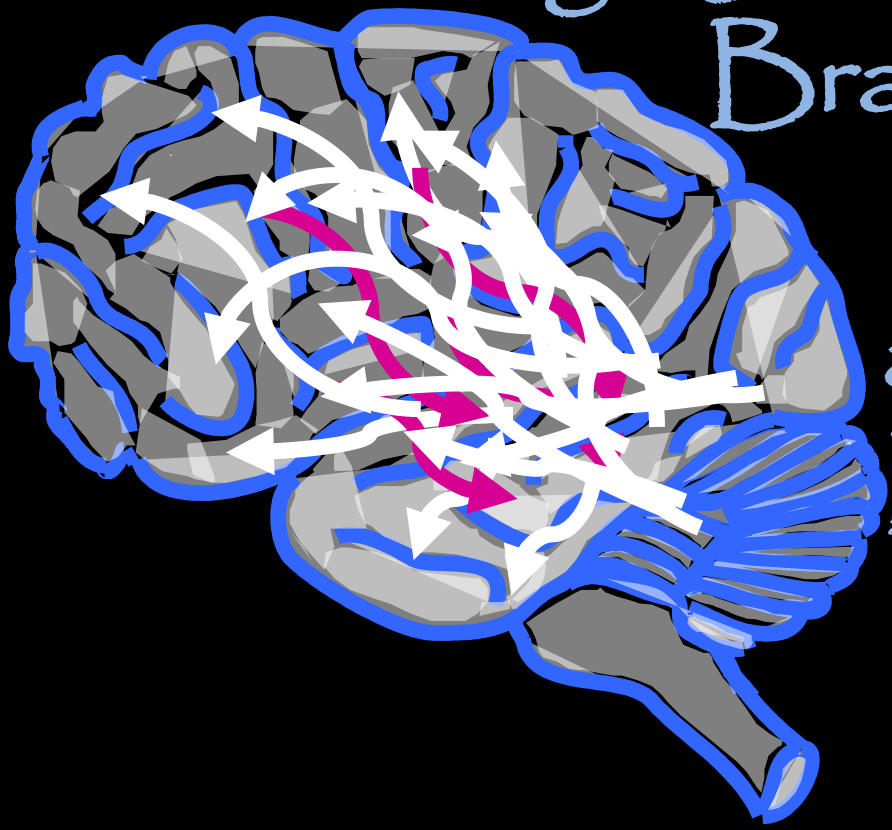
The brain reward circuitry responds to drug and sexual cues that are presented *outside* of our awareness (33 msec.)



Childress et al., Plos Biology Jan. 2008

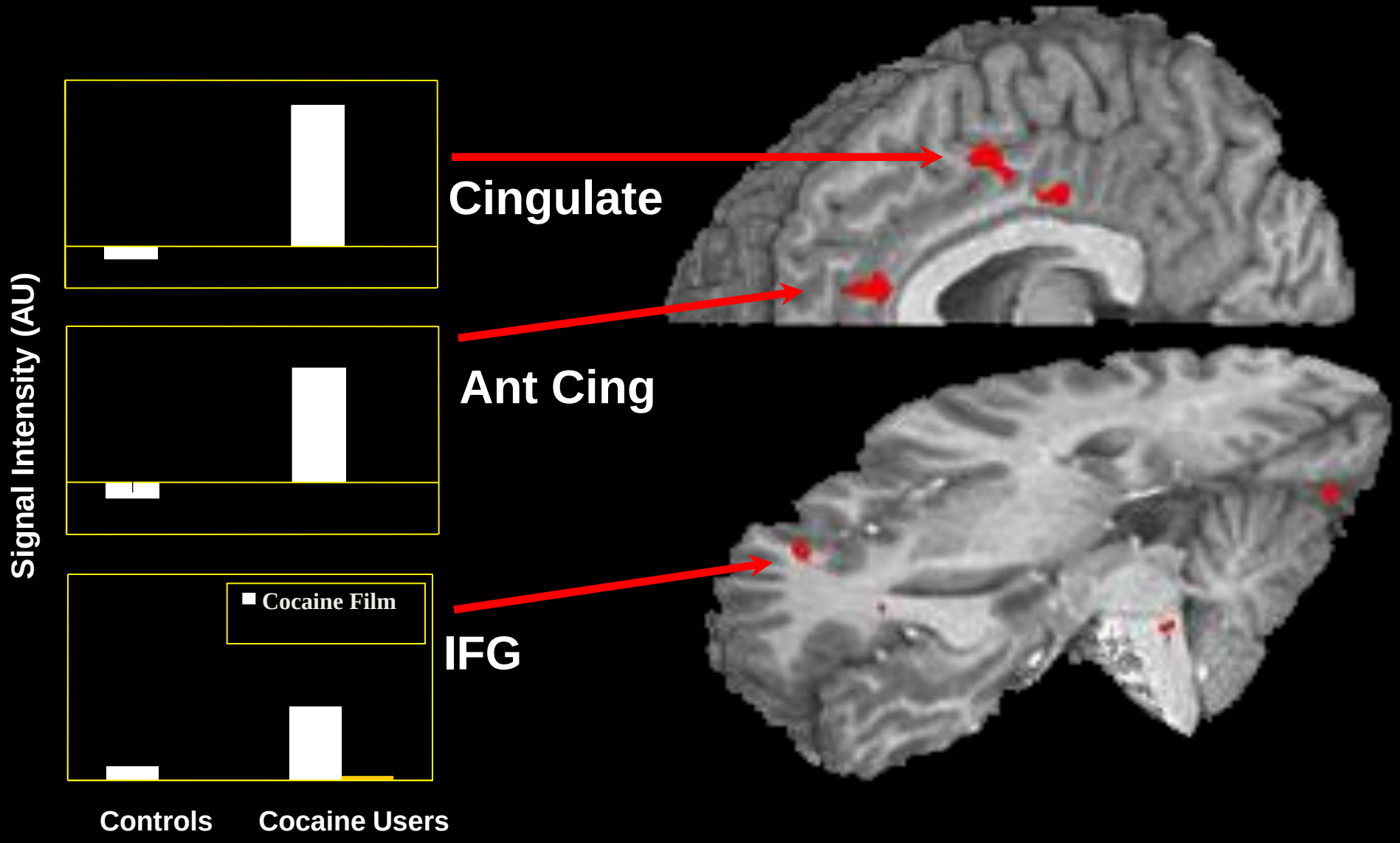
But It's Not Just Memories...

Drugs Usurp Brain Circuits and Alter Motivational Priorities



Cocaine Craving:

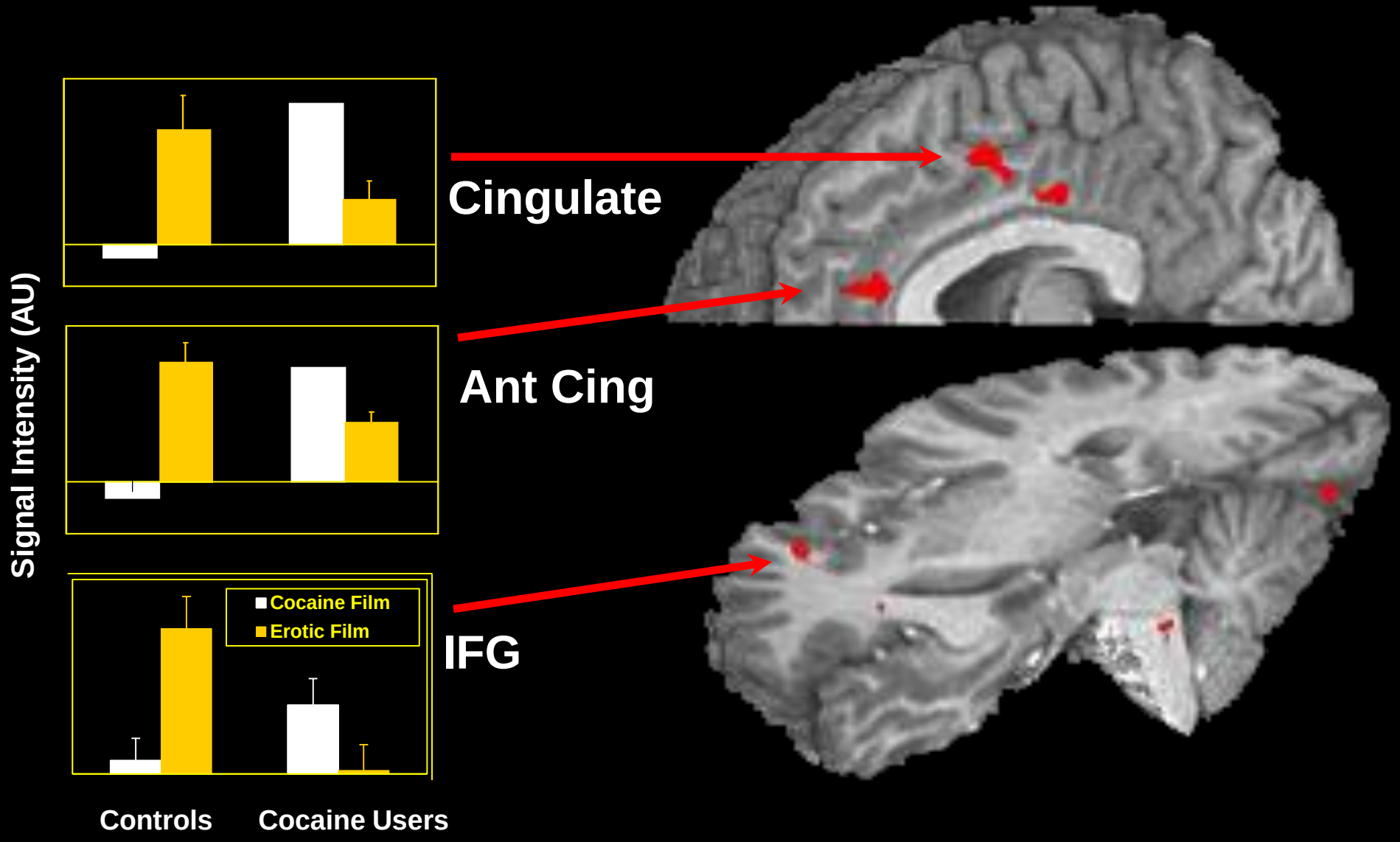
Population (Cocaine Users, Controls) x Film (cocaine)



Garavan et al A .J. Psych 2000

Cocaine Craving:

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



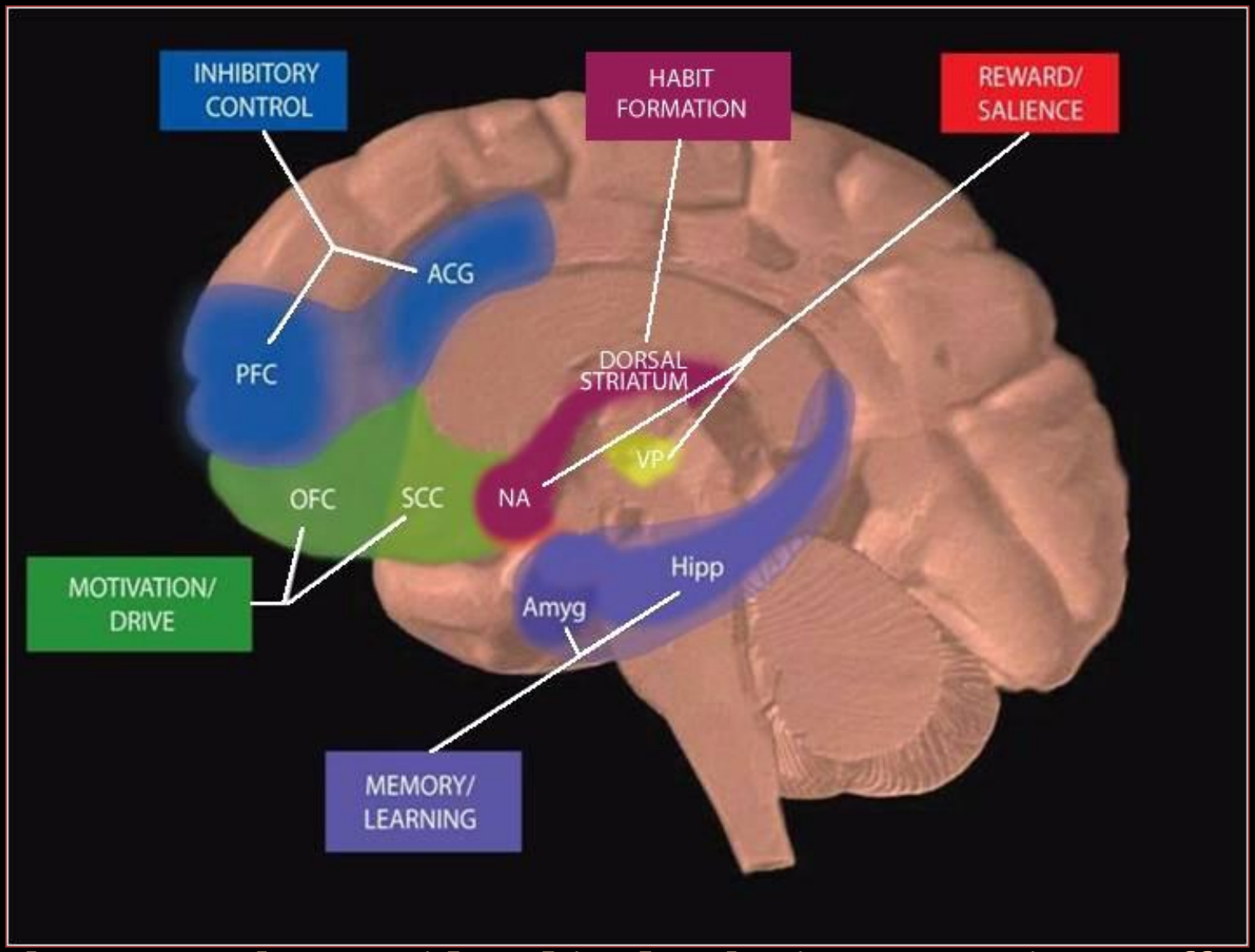
Garavan et al A .J. Psych 2000

This Results in "Motivational Toxicity" and Compulsive Drug Use (Addiction)

So.....

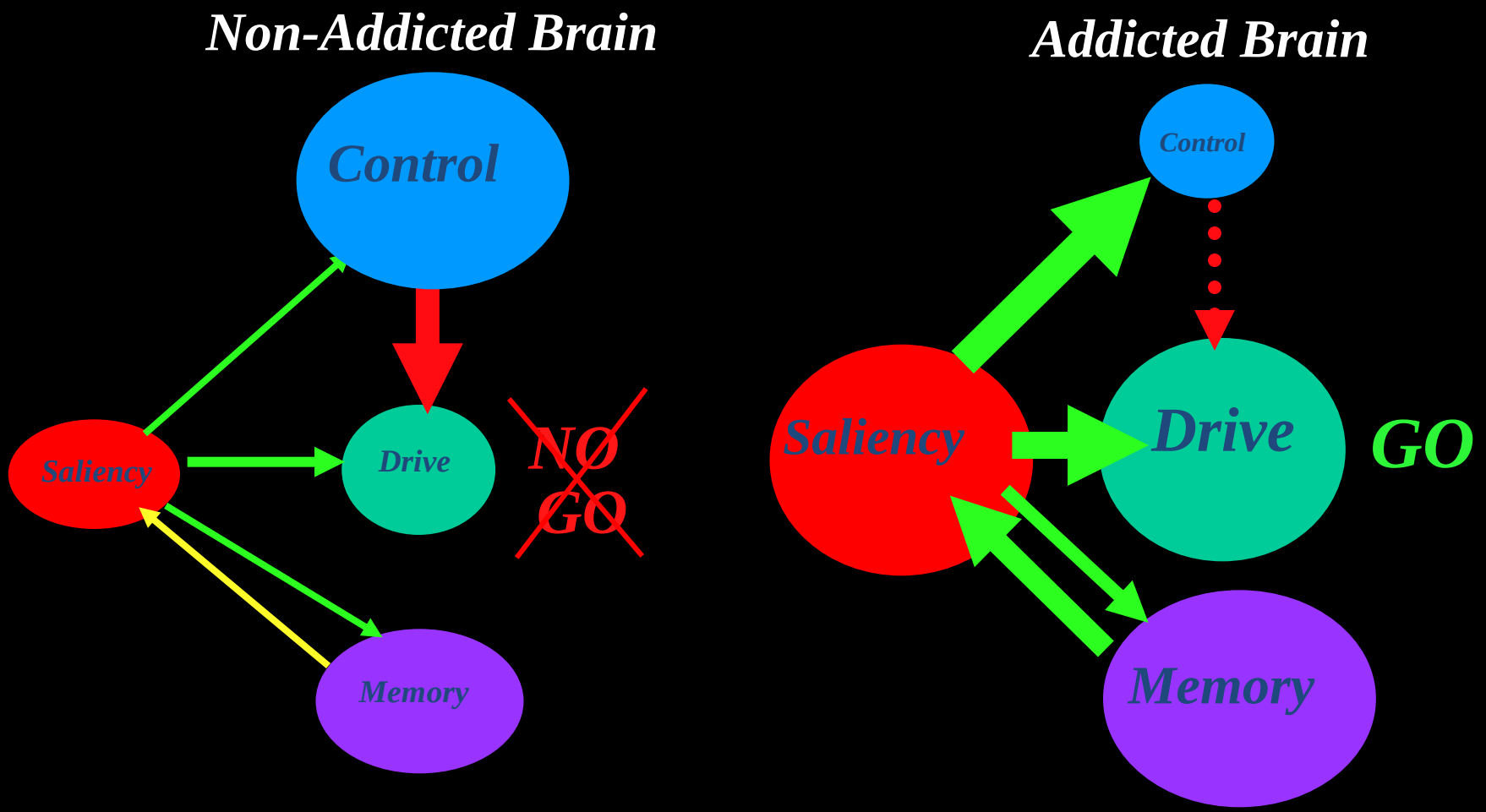
....What Does This Mean For Treatment?

Circuits Involved In Drug Abuse and Addiction



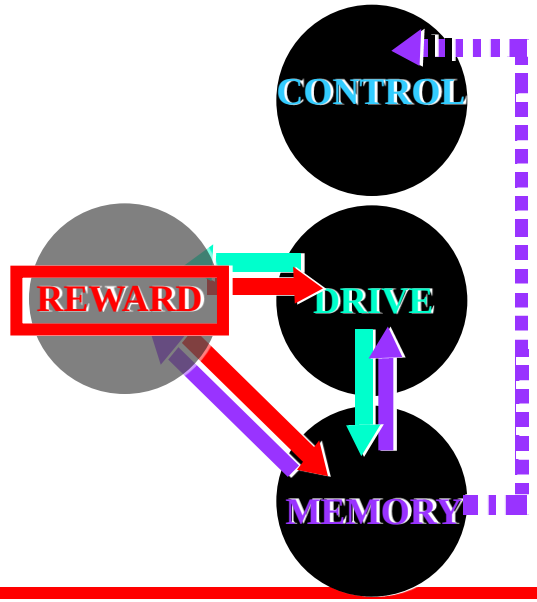
All of these must be considered in developing strategies to effectively treat addiction

Why Can't Patients Just Quit?



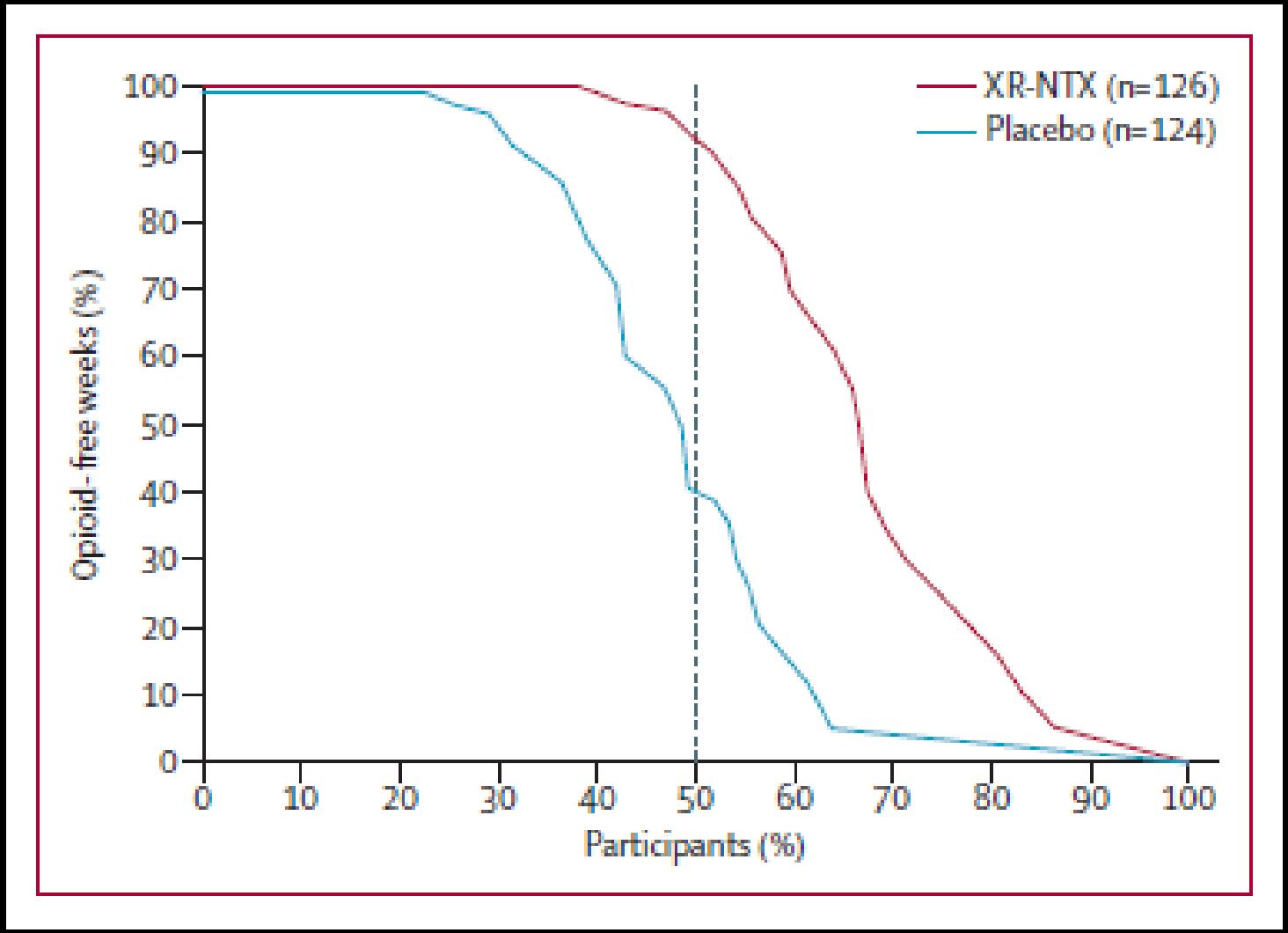
NIDA

Treating the Addicted Brain

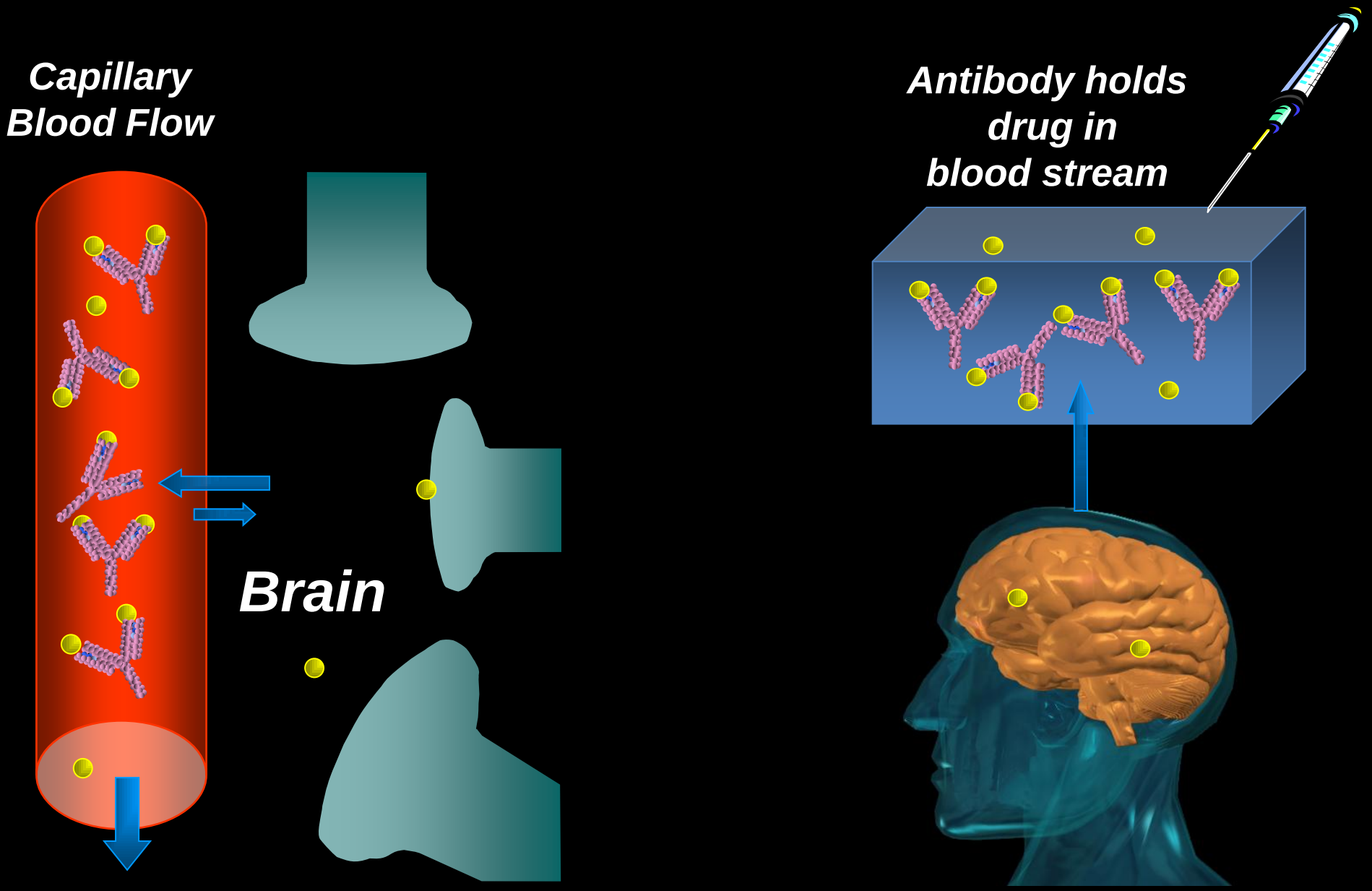


Decrease the rewarding value of drugs

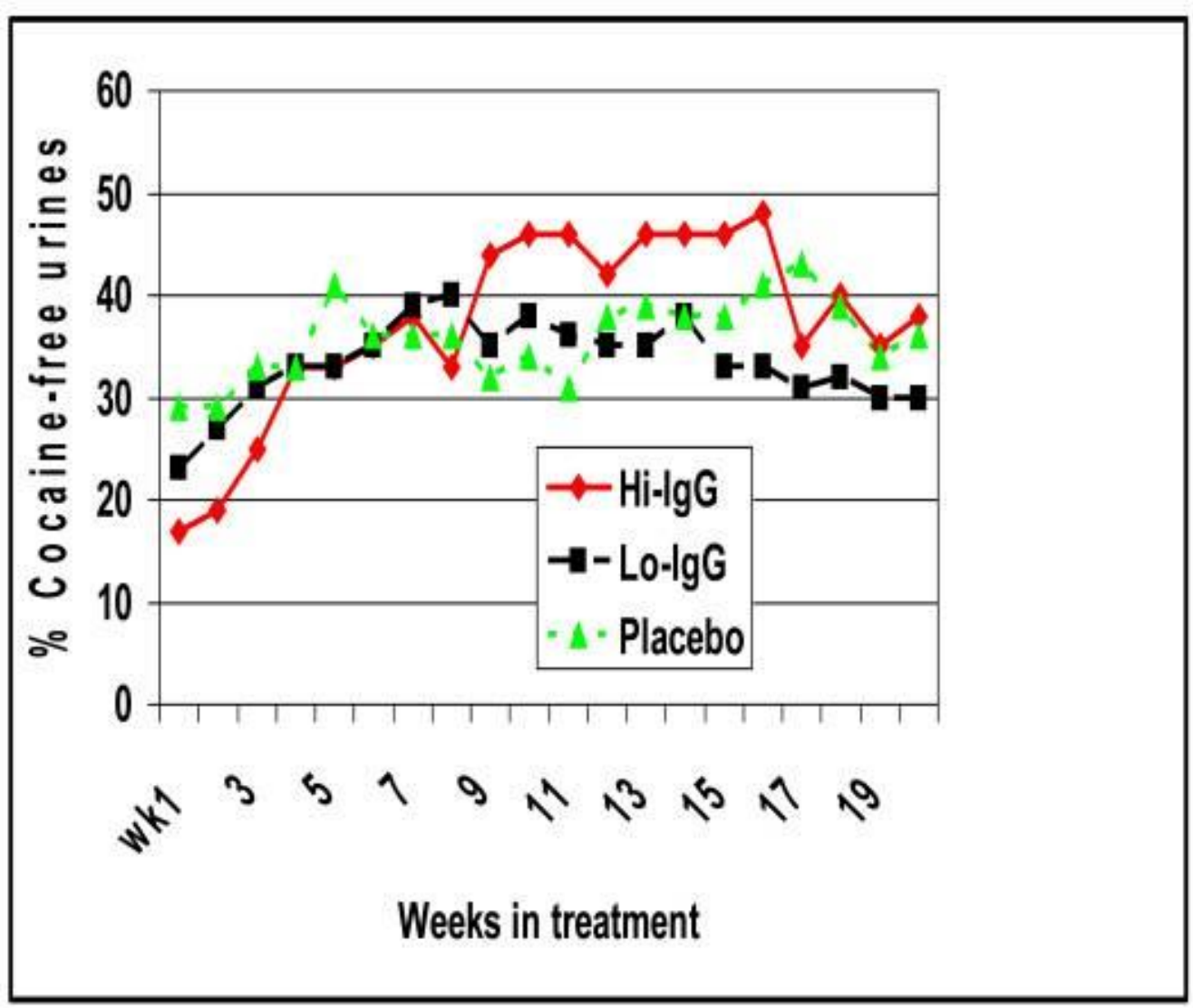
Vivitrol (an opioid antagonist) significantly increases percentage of patients with opioid-free weeks



Antibodies can reduce brain concentrations

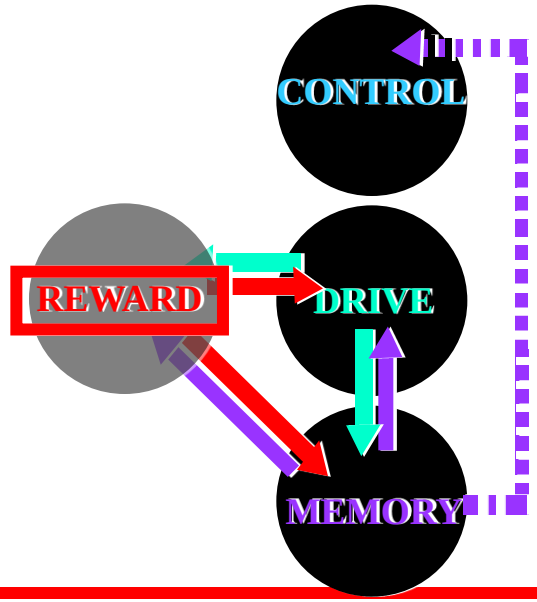


Fewer cocaine urines at higher vaccine dose

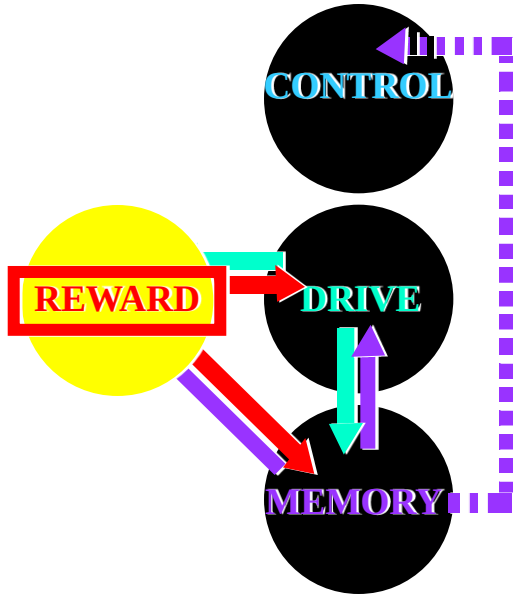


Kosten, et al, 2010 Arch Gen Psych

Treating the Addicted Brain

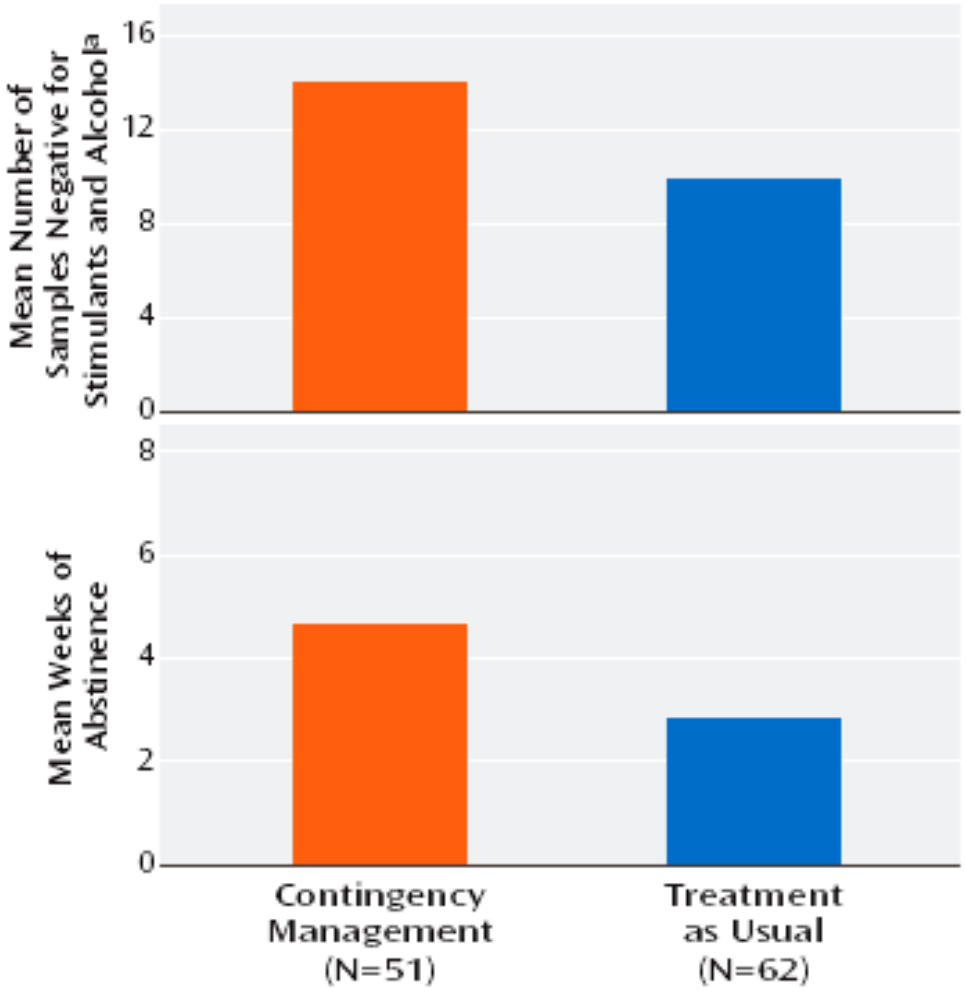


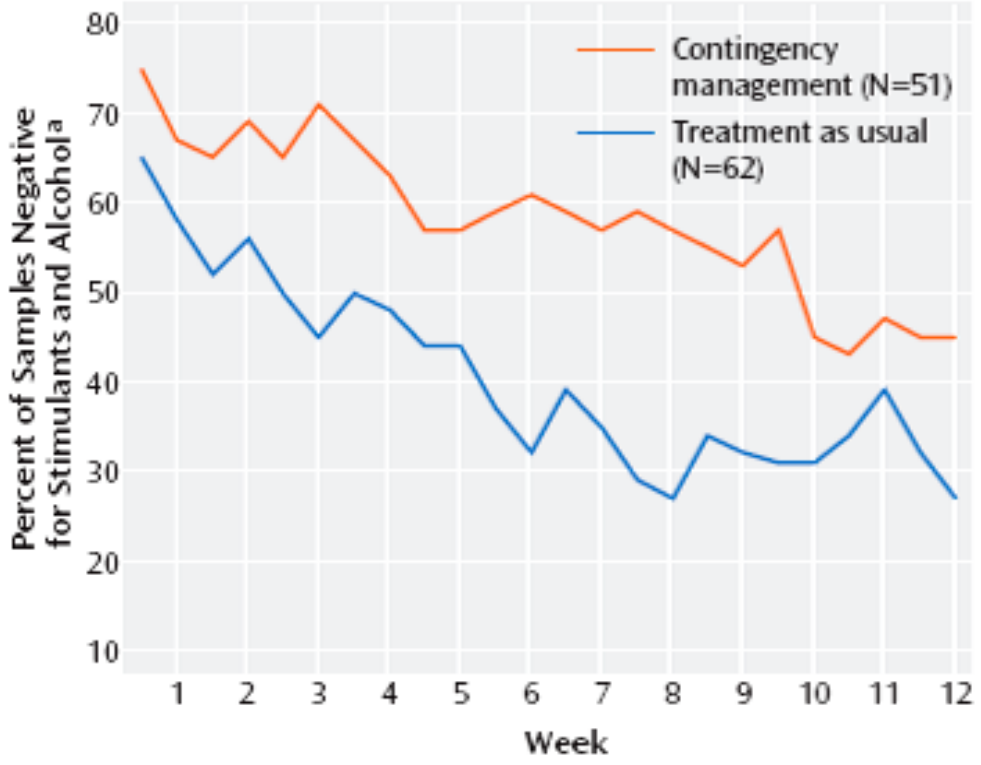
Decrease the rewarding value of drugs



Increase the rewarding value of non-drug reinforcers

Contingency Management for the Treatment of Methamphetamine Use Disorders

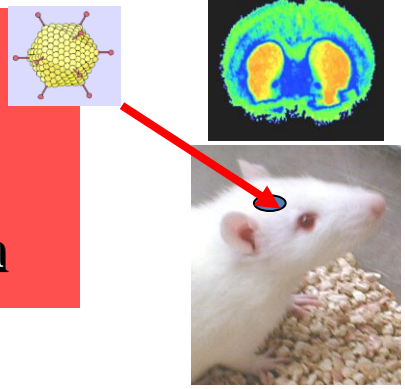


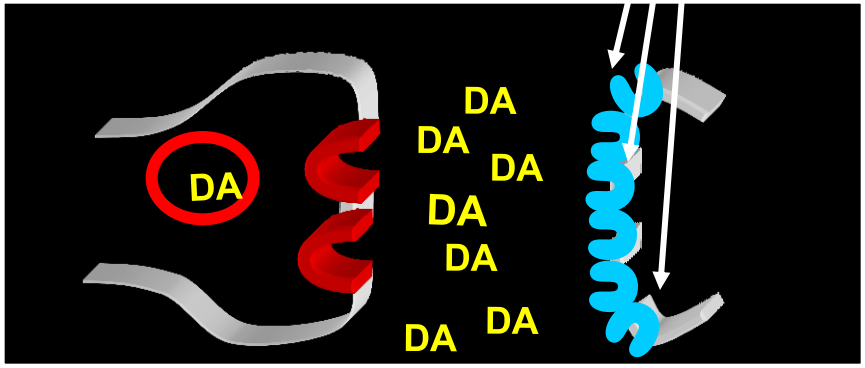


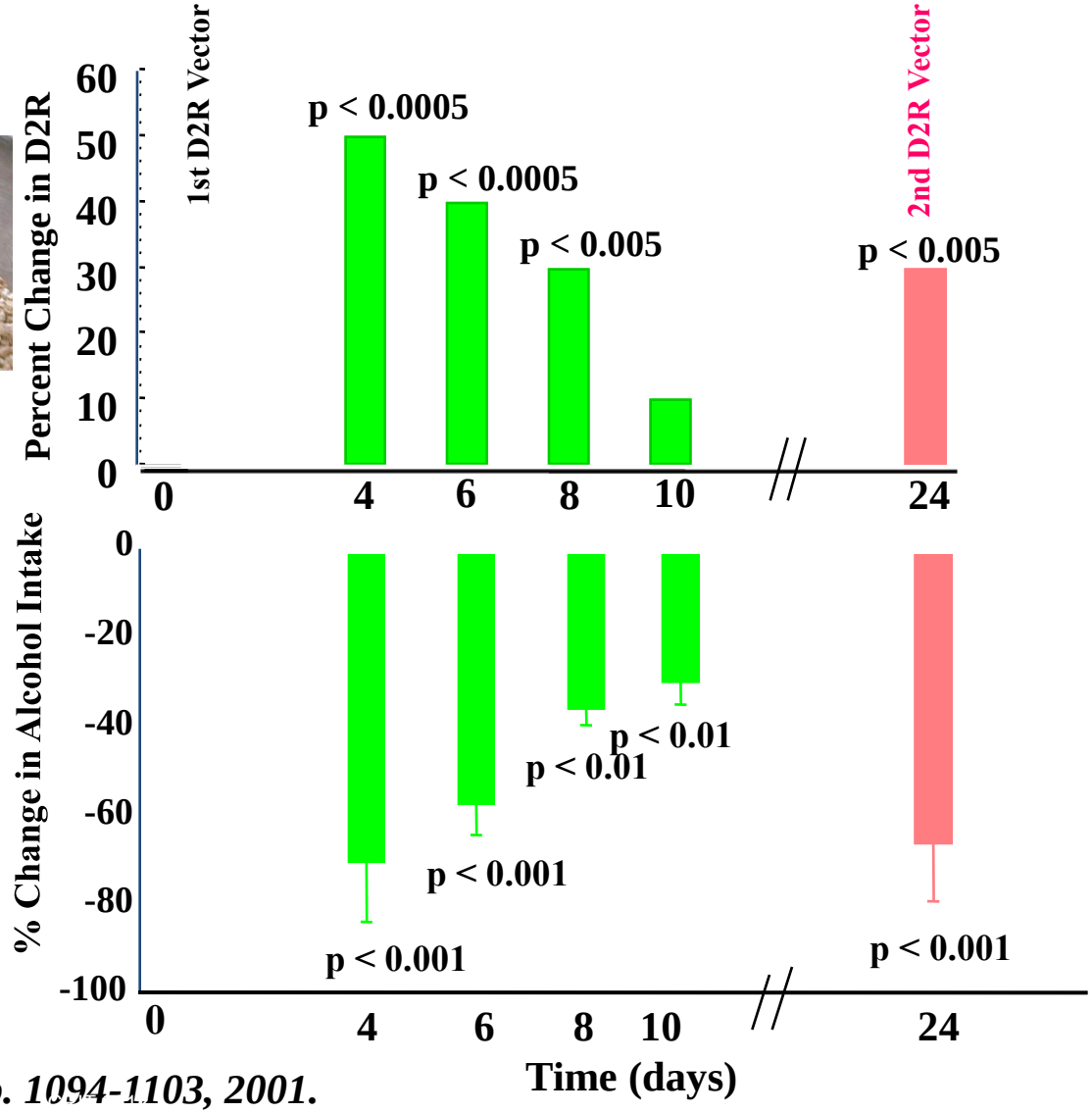
Roll, J.M. et al., AJP 163(11) pp. 1993-1999, November 2006.

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

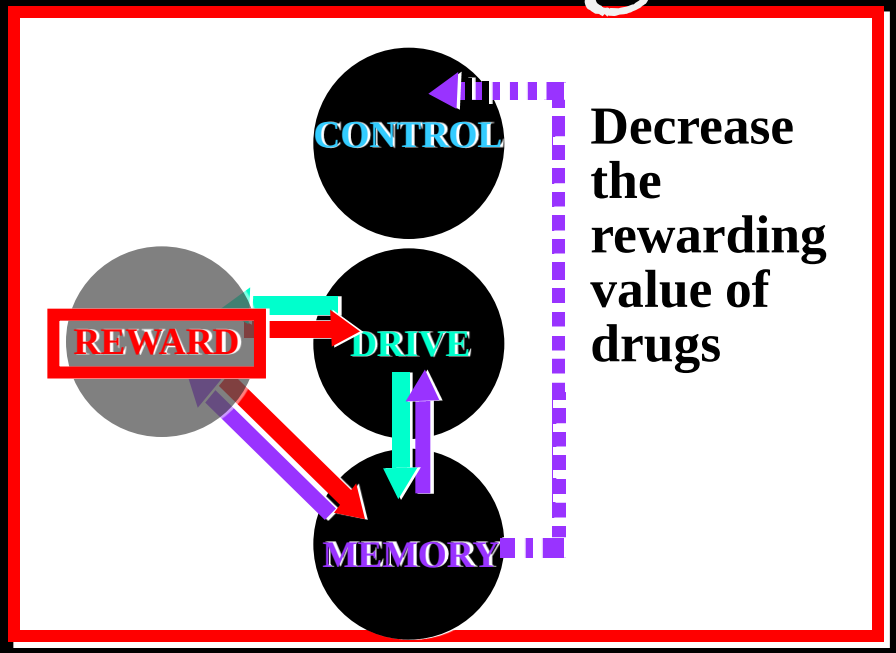




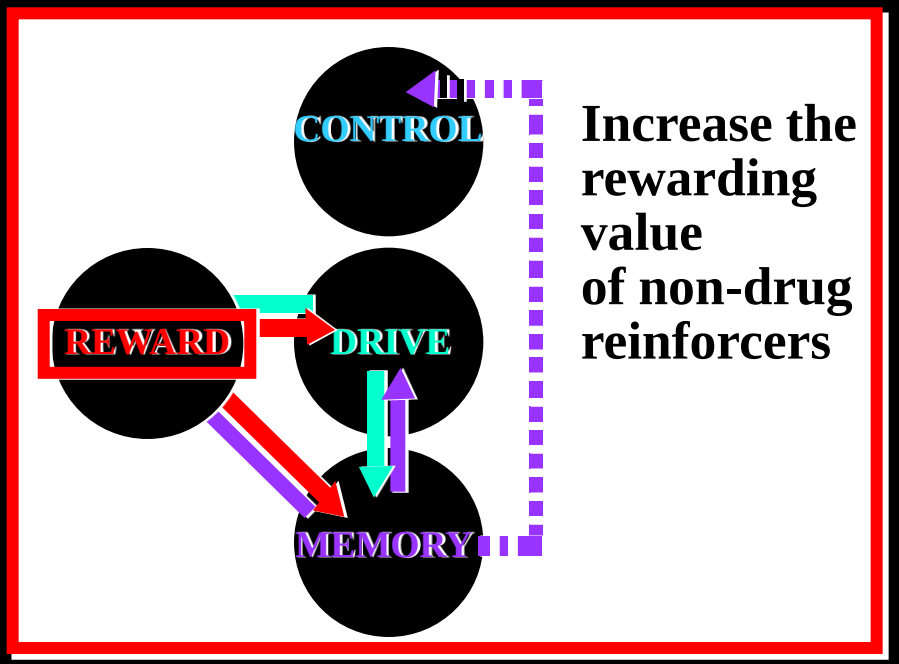


Thanos, PK et al., J Neurochem, 78, pp. 1094-1103, 2001.

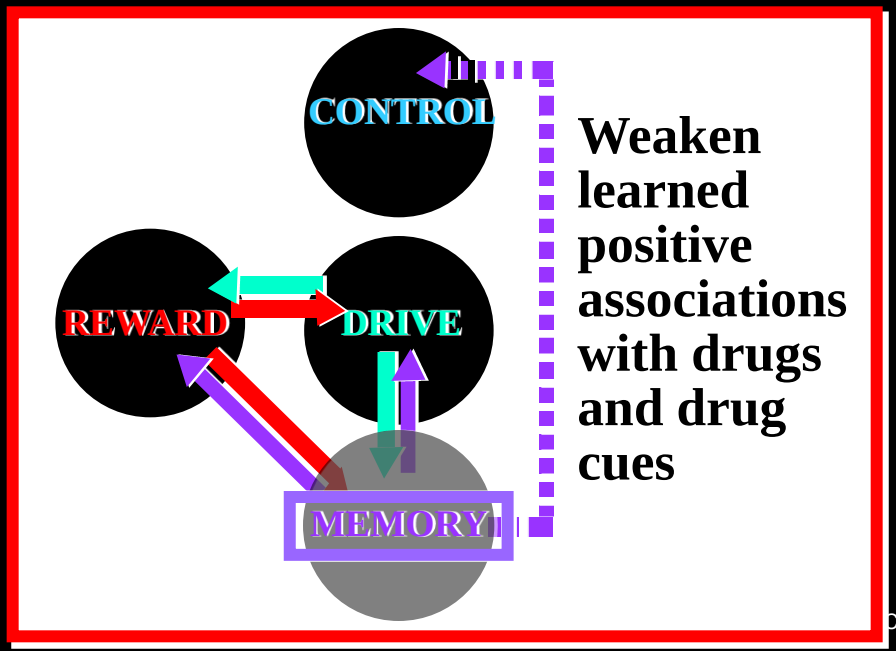
Treating the Addicted Brain



Decrease the rewarding value of drugs

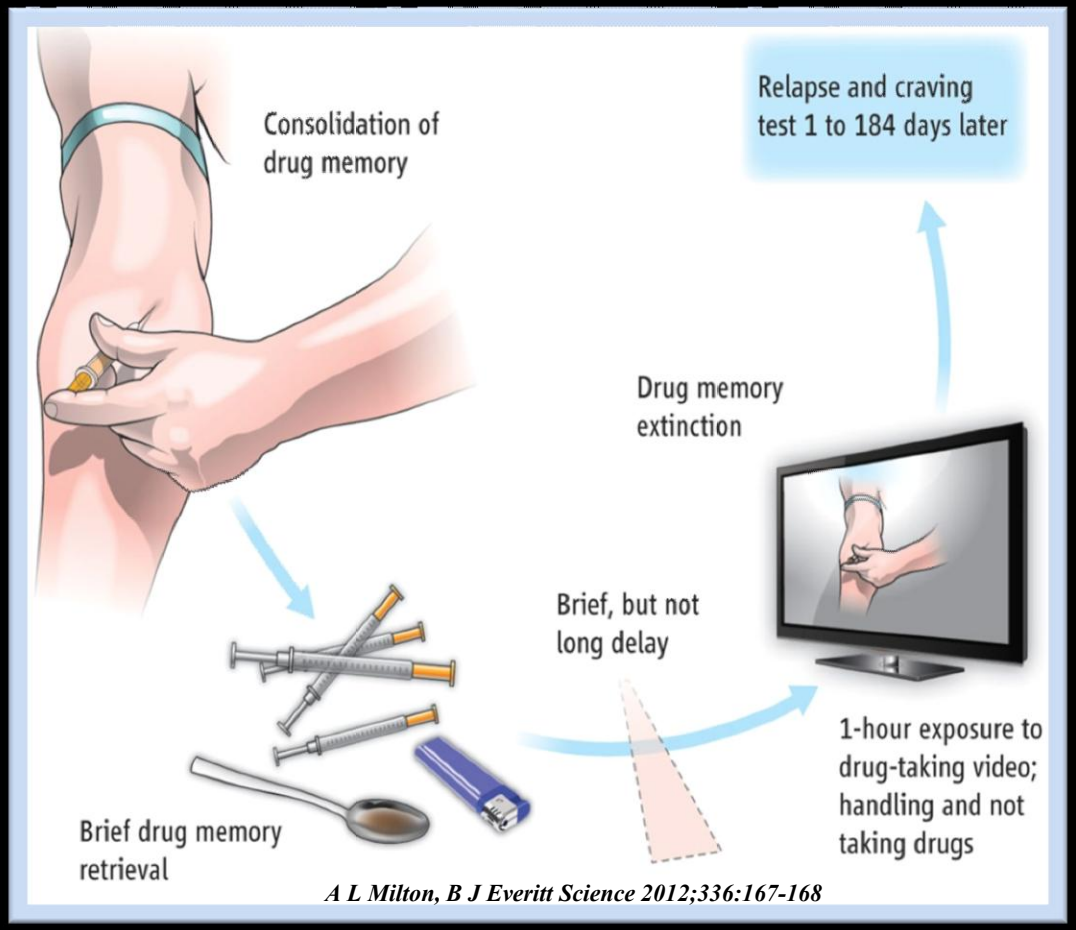


Increase the rewarding value of non-drug reinforcers

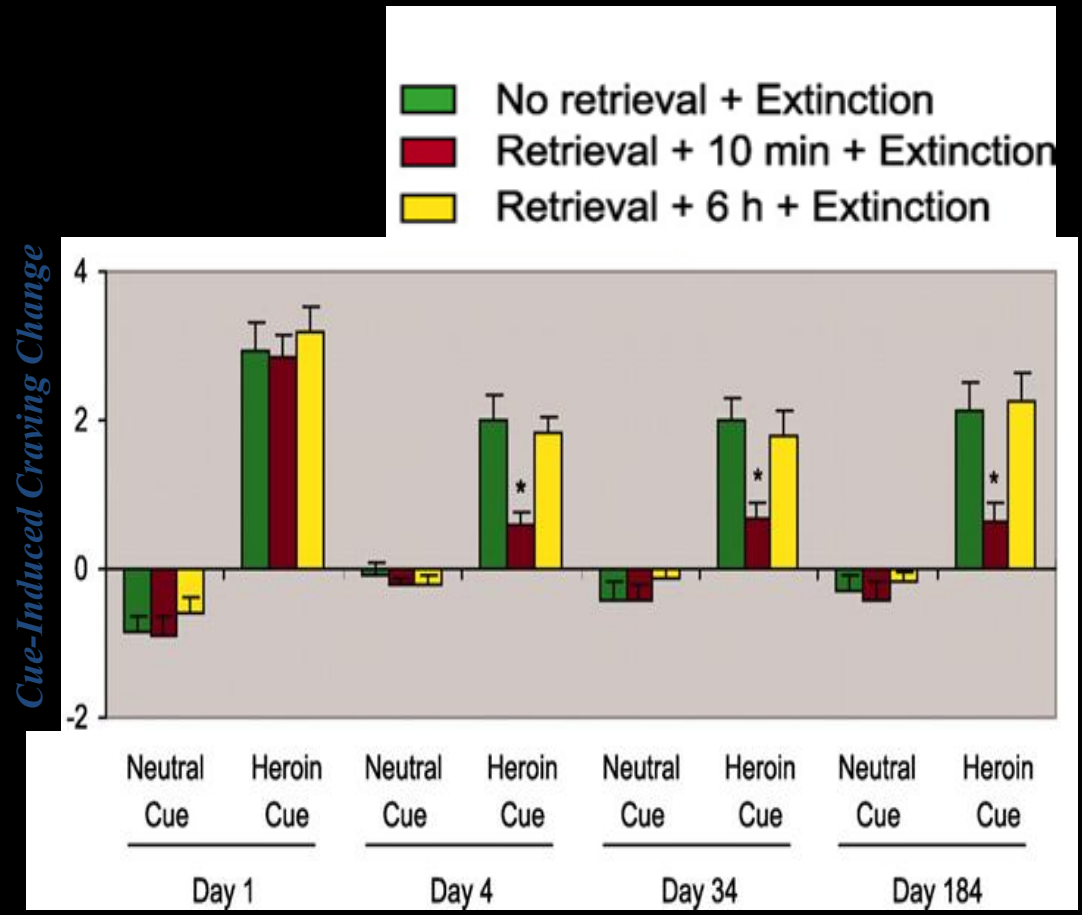


Weaken learned positive associations with drugs and drug cues

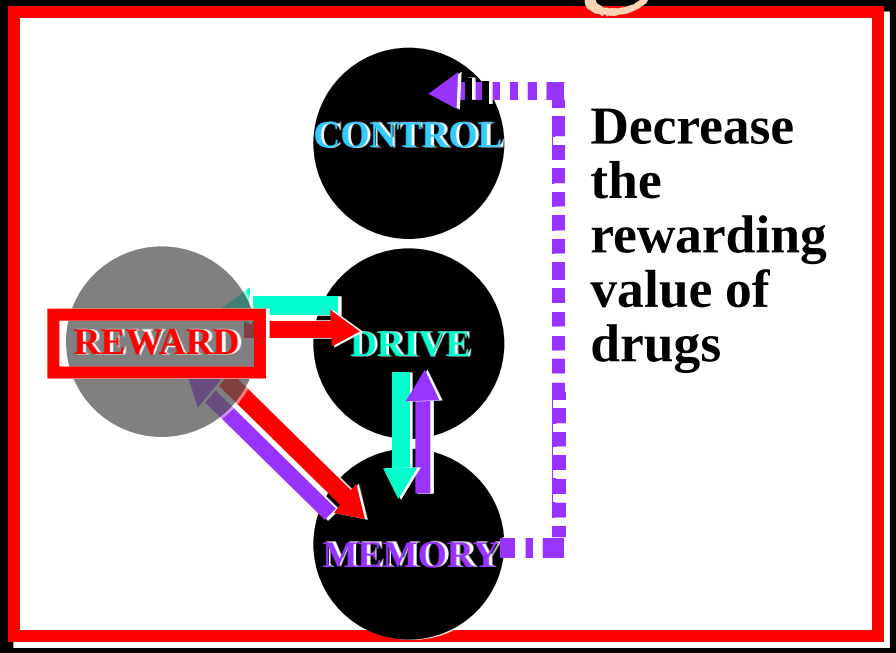
A Method that Weakens Cue-drug Memories Decreases Drug Craving



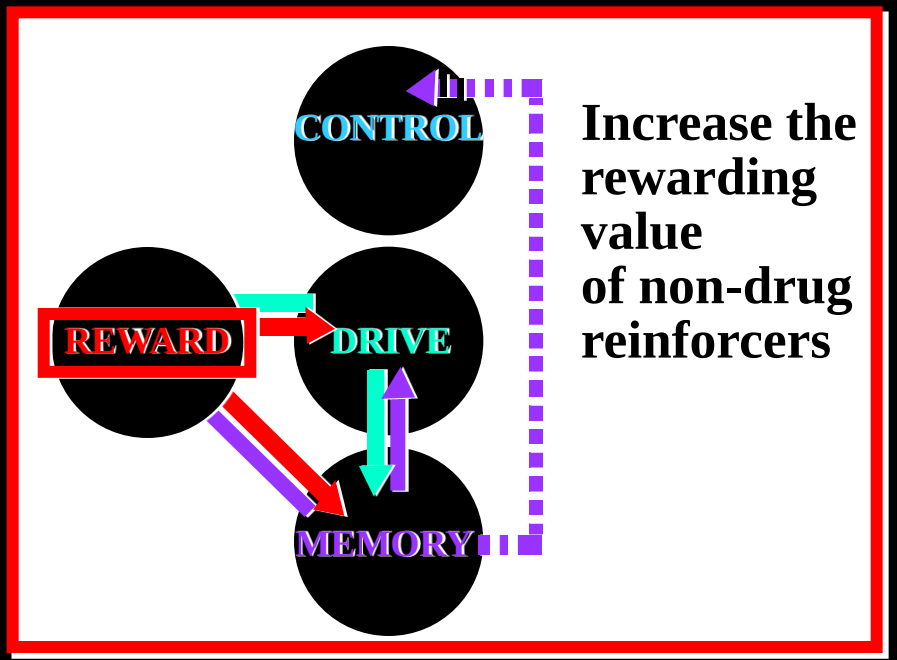
A L Milton, B J Everitt Science 2012;336:167-168



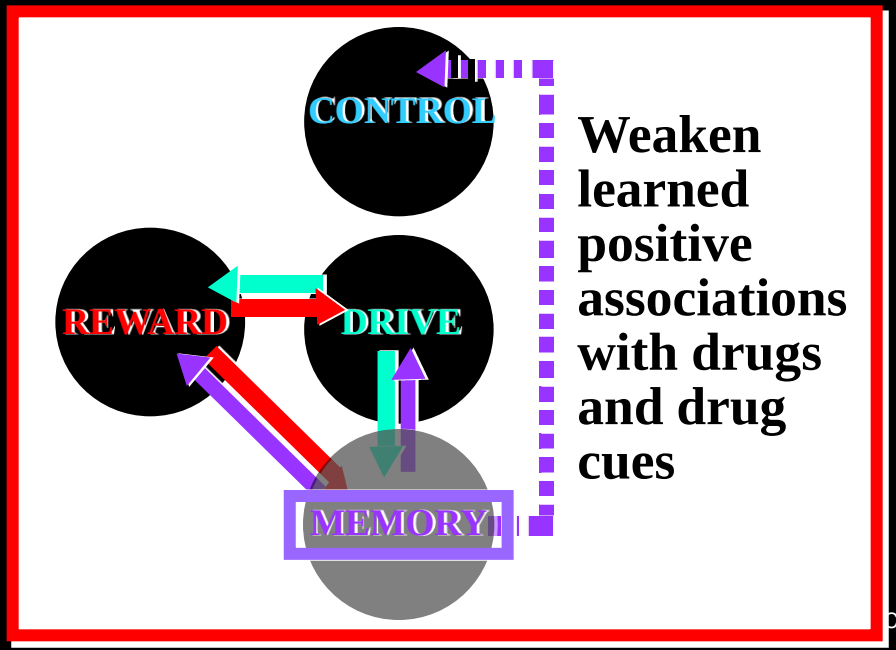
Treating the Addicted Brain



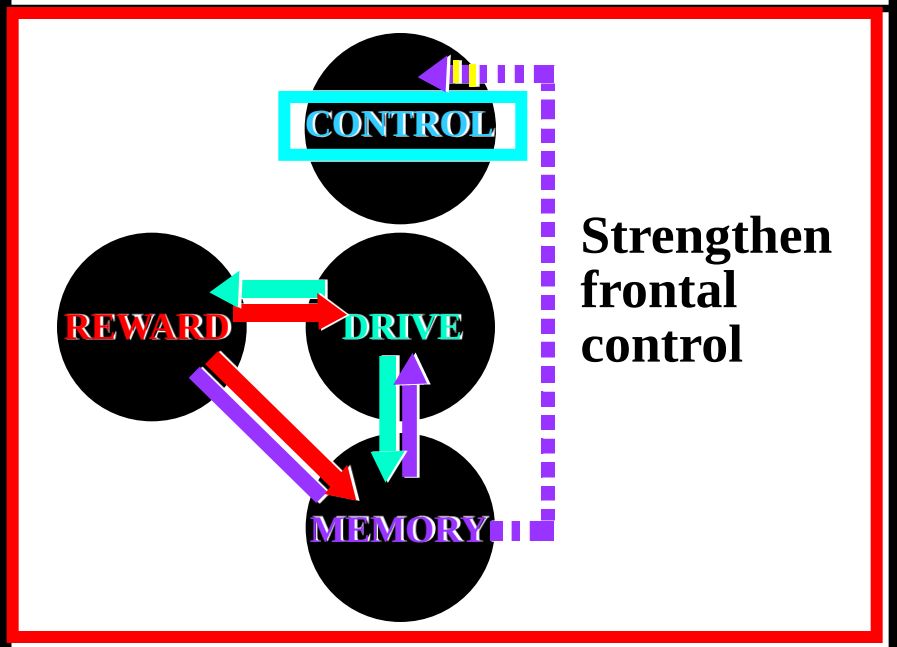
Decrease the rewarding value of drugs



Increase the rewarding value of non-drug reinforcers

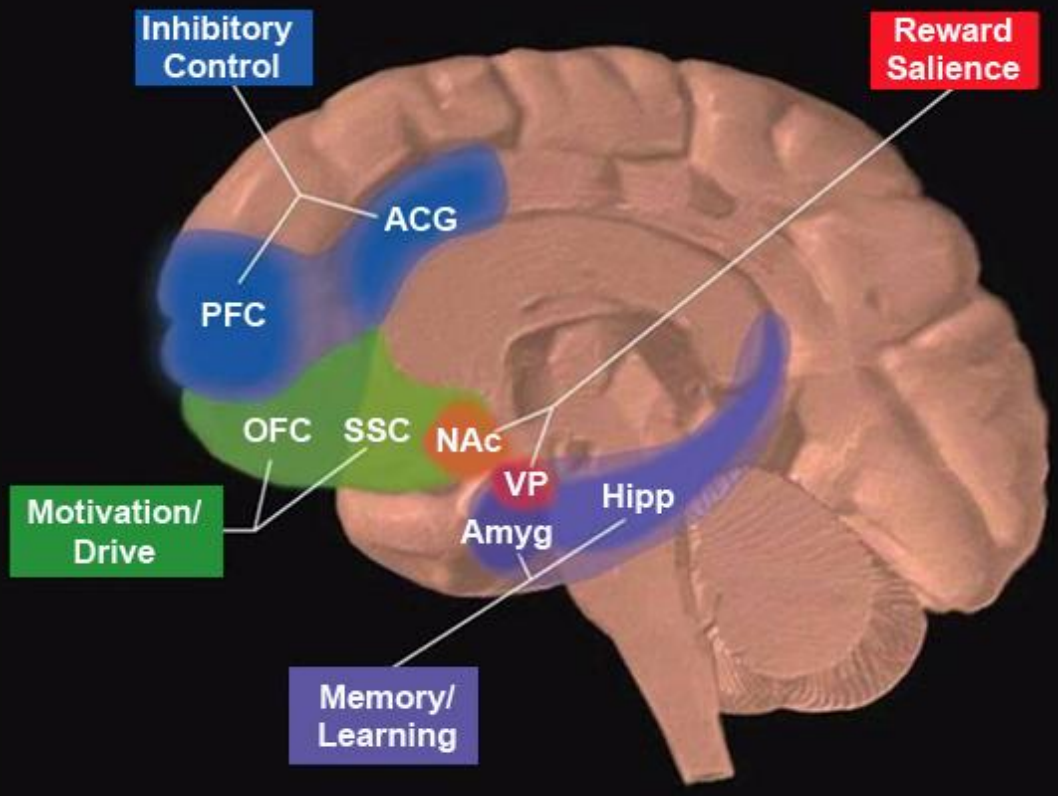


Weaken learned positive associations with drugs and drug cues



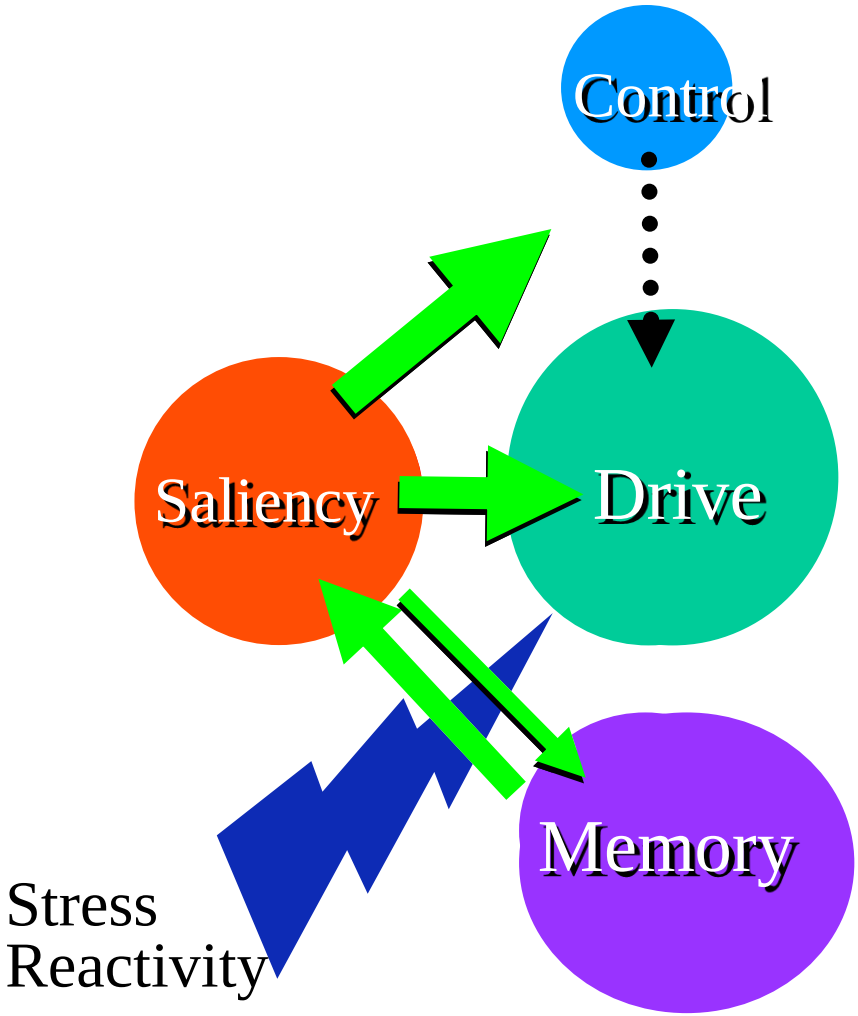
Strengthen frontal control

Addiction Circuitry and Drug Development: Preventing Relapse



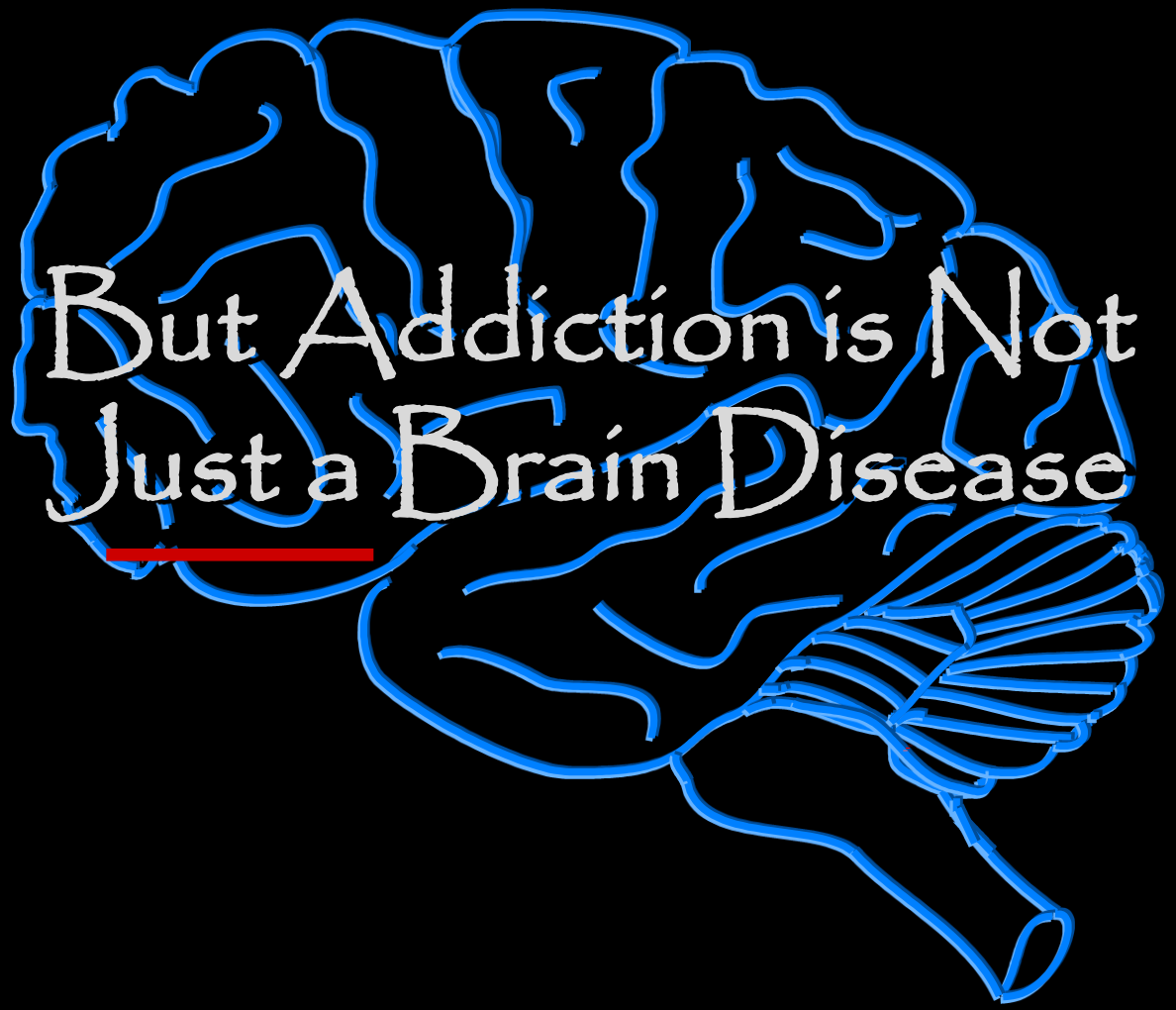
Block drug's rewarding effects	Vaccines,Enzymatic degradation Naltrexone CB_1 antagonists
Interfere with conditioned learning (craving)	Antiepileptic GVG N-acetylcysteine
Promote new learning	D-Cycloserine
Counteract stress response	CRF antagonists
Strengthen communication between limbic and cortical areas	Adenosine A2 Dopamine D3 antagonists
Strengthen executive function/ Inhibitory control	Modafinil Stimulant medications

Psychotherapy for Relapse Prevention

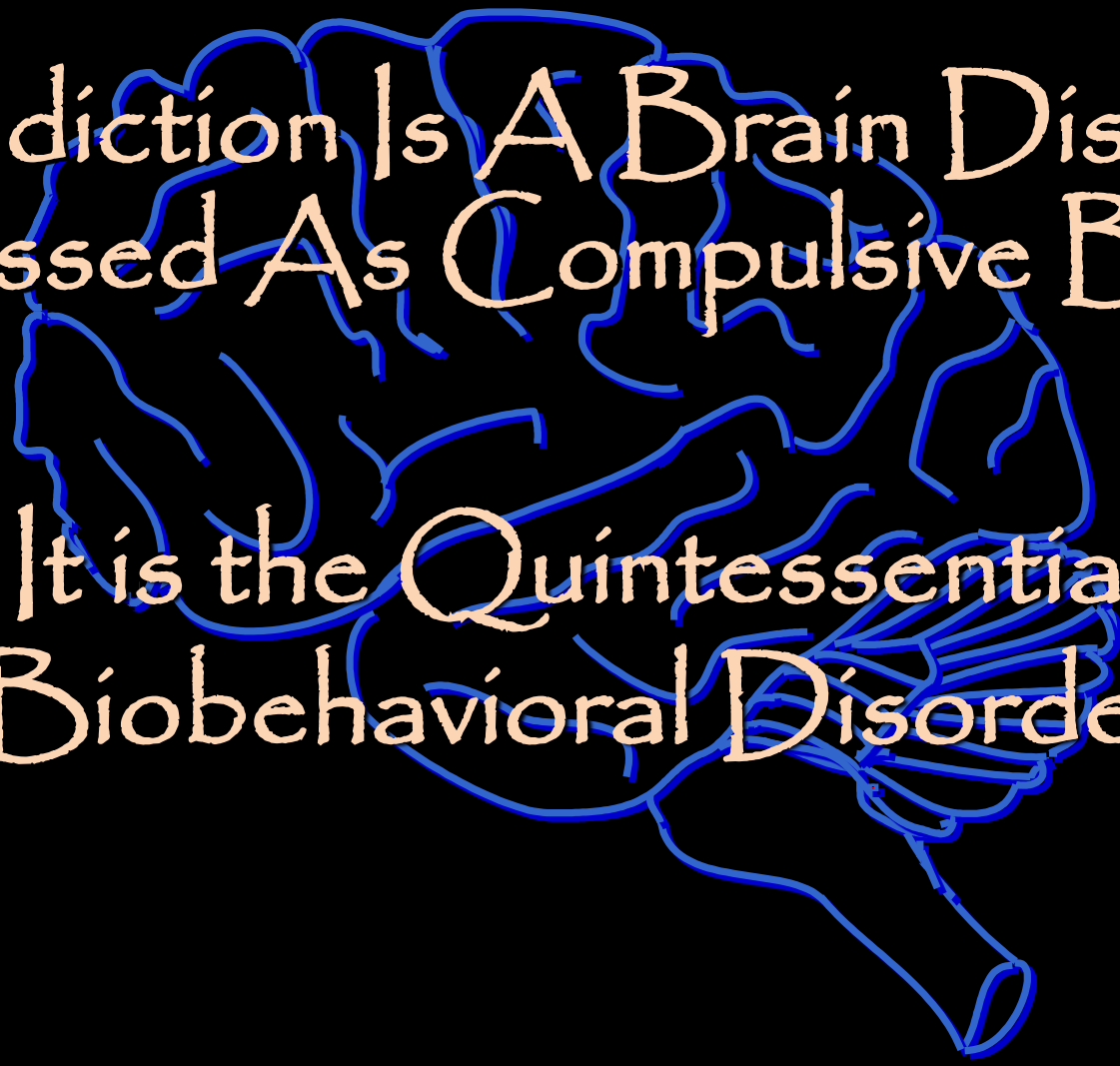


Interfere with Drugs Reinforcing Effects	Contingency Management
Executive Function Inhibitory Control	Cognitive Therapy
Strengthen Cortical/ Limbic Connections	Motivational Therapy
Interfere with conditioned memories/craving	Neurofeedback Desensitization
Promote new learning	Conditioning
Counteract stress responses that lead to relapse	Relaxation Behavioral Therapy


Addiction is Fundamentally
a Brain Disease


But Addiction is Not
Just a Brain Disease

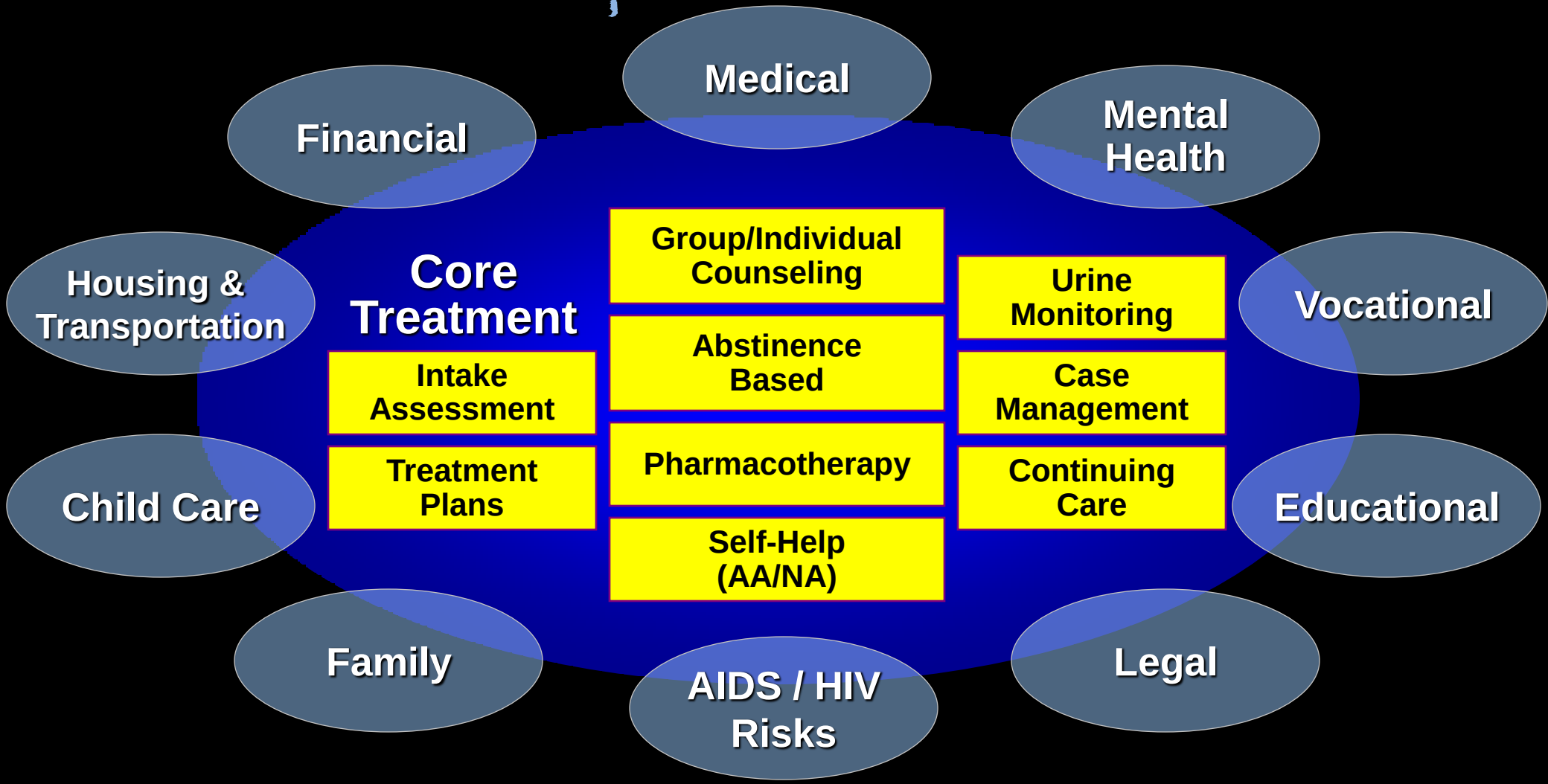
Addiction Is A Brain Disease Expressed As Compulsive Behavior



It is the Quintessential Biobehavioral Disorder

Treating A Biobehavioral Disorder Must Go Beyond Just Fixing The Chemistry

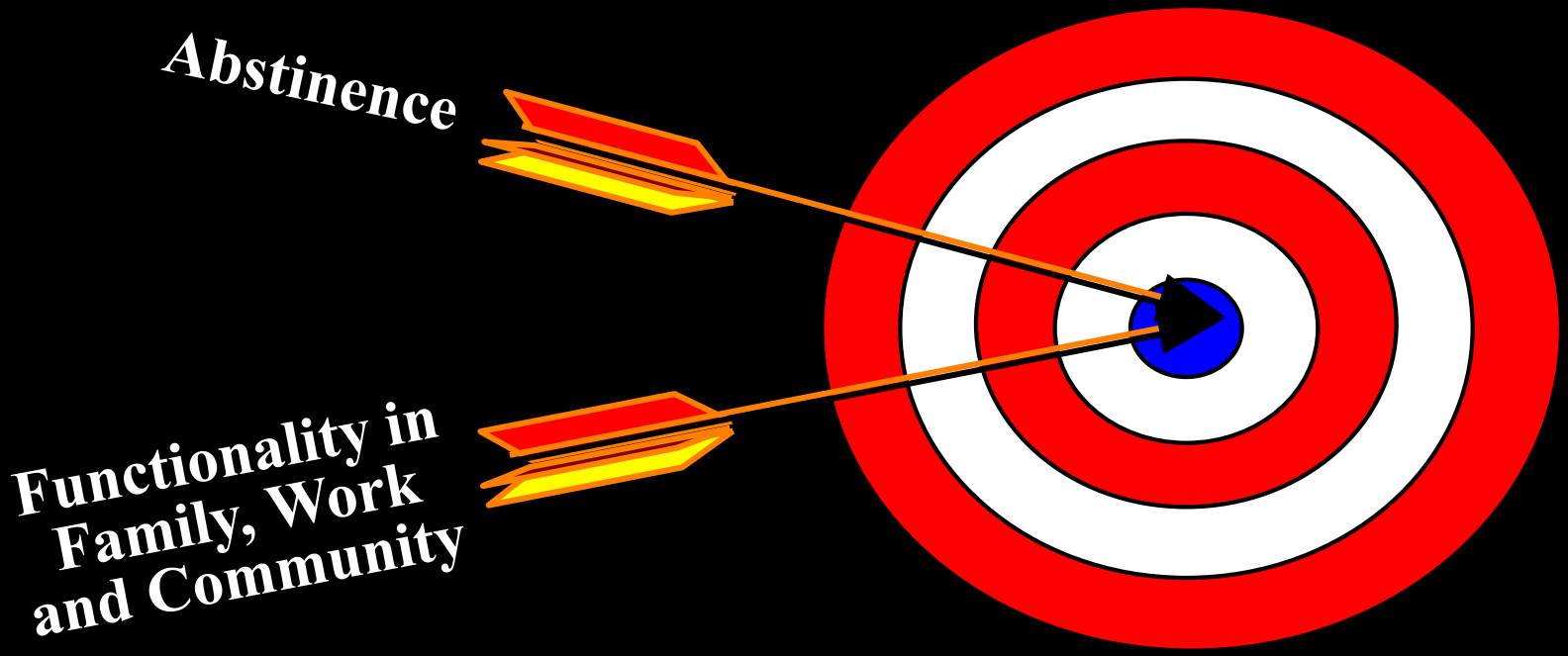
Drug Abuse Treatment Core Components and Comprehensive Services



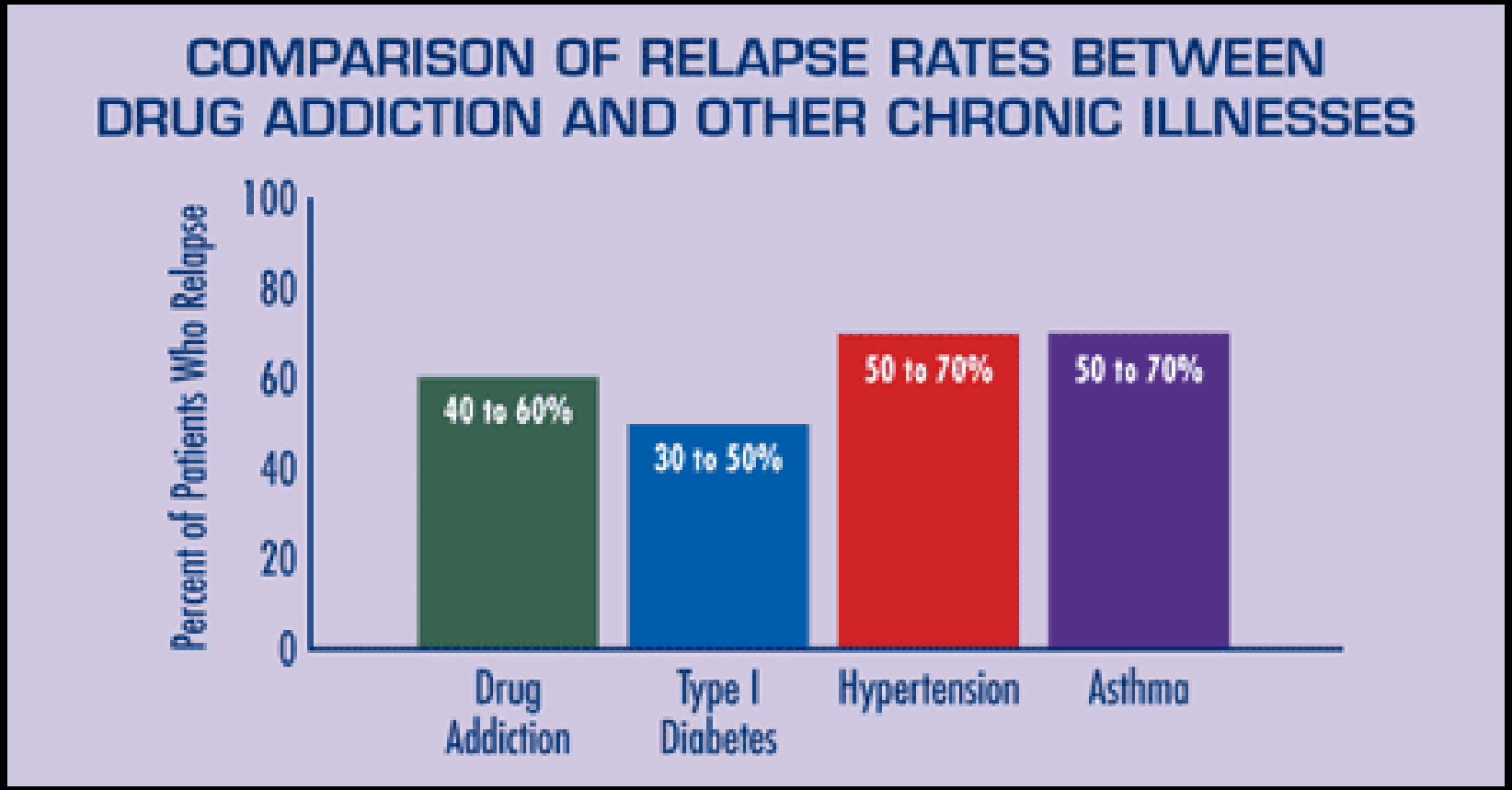
Etheridge, Hubbard, Anderson, Craddock, & Flynn, 1997 (PAB)

In Treating Addiction...

We Need to Keep Our Eye on the Real Target



But, drug addiction is a chronic disease with relapse rates similar to those of other chronic illnesses

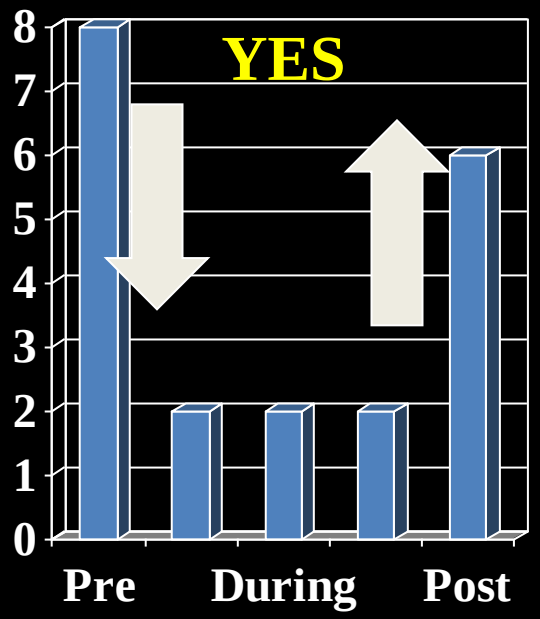


Source: McLellan, A.T. et al., JAMA, Vol 284(13), October 4, 2000.

We Need to View and Treat Addiction As A Chronic, Relapsing Illness

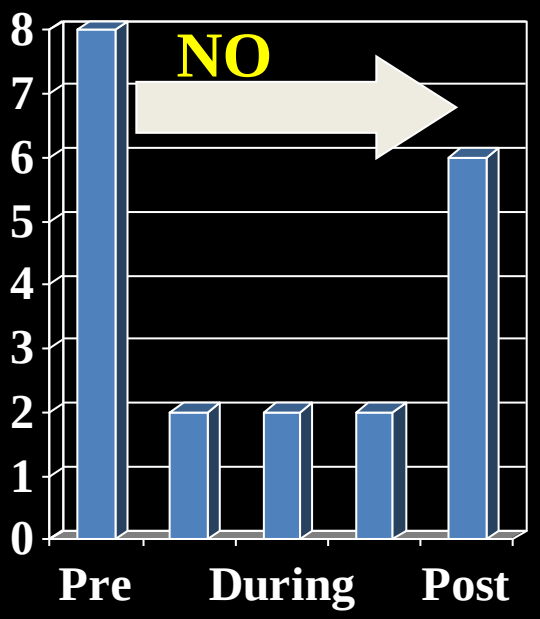
How Do We Evaluate If a Treatment is Effective?

Hypertension Tx



Stage of Treatment

Addiction Tx



Stage of Treatment

If we treat a diabetic and symptoms don't subside….what do we do?

Would we increase the dose?
Would we change medications?
Would we change treatment approaches?

Would we fail to provide ongoing treatment for a diabetic?

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**

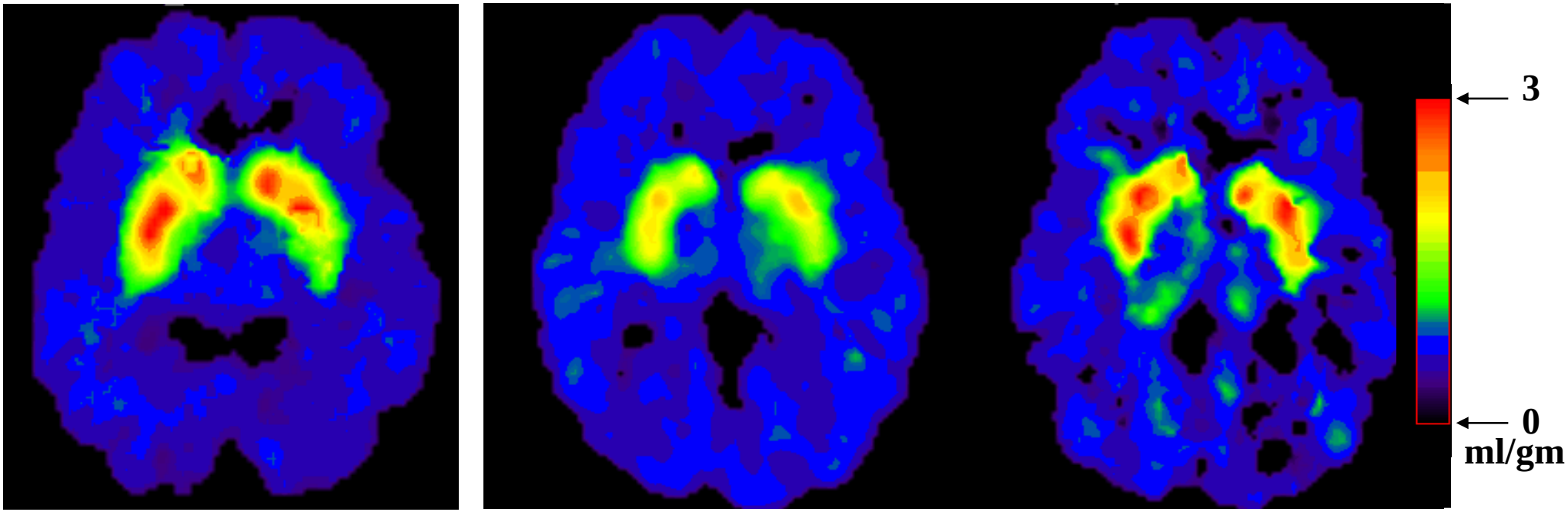
Therefore…

NIDA

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

ADDICTION CAN BE TREATED

Partial Recovery of Brain Dopamine Transporters in Methamphetamine (METH) Abuser After Protracted Abstinence



Normal Control

METH Abuser (1 month detox)

METH Abuser (14 months detox)

Source: Volkow, ND et al., Journal of Neuroscience 21, 9414-9418, 2001.