Methamphetamine: The Science of Addiction

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Department of Health and Human Services

Southwest CAPT Regional Meeting
Dallas, TX
September 26, 2005


Methamphetamine
Speed
Ice
Fire
Crystal
Meth
Crypto
Crank
Chalk
Glass

Methamphetamine

"Meth", "Speed", "Ice", "Glass", "Crystal", "Crank"

Stimulant – potential neurotoxin associated with long-lasting effects on the dopamine and serotonin systems

Who uses methamphetamine?

Tools to Monitor National Drug Trends

- NIDA's Community Epidemiology Workgroup
- SAMHSA's National Survey on Drug Use & Health
- NIDA's Monitoring the Future
- SAMHSA's Drug Abuse Warning Network
- SAMHSA's Treatment Episode Data Set
- NIJ's Arrestee Drug Abuse Monitoring

- Timely information on use patterns
- Identify emerging trends
- Identify who is actually using and vulnerable populations
- Identify risk factors

WHY MONITOR?

- Early 80s - outlaw biker gangs
- Use was concentrated in the West, Southwest and Hawaii in the mid and late-80's
- Early to mid-90s spread to Midwest and South
- Now at epidemic proportions in many regions of the country
- Majority of users 18-34 years old
- Use increasing in rural and suburban communities

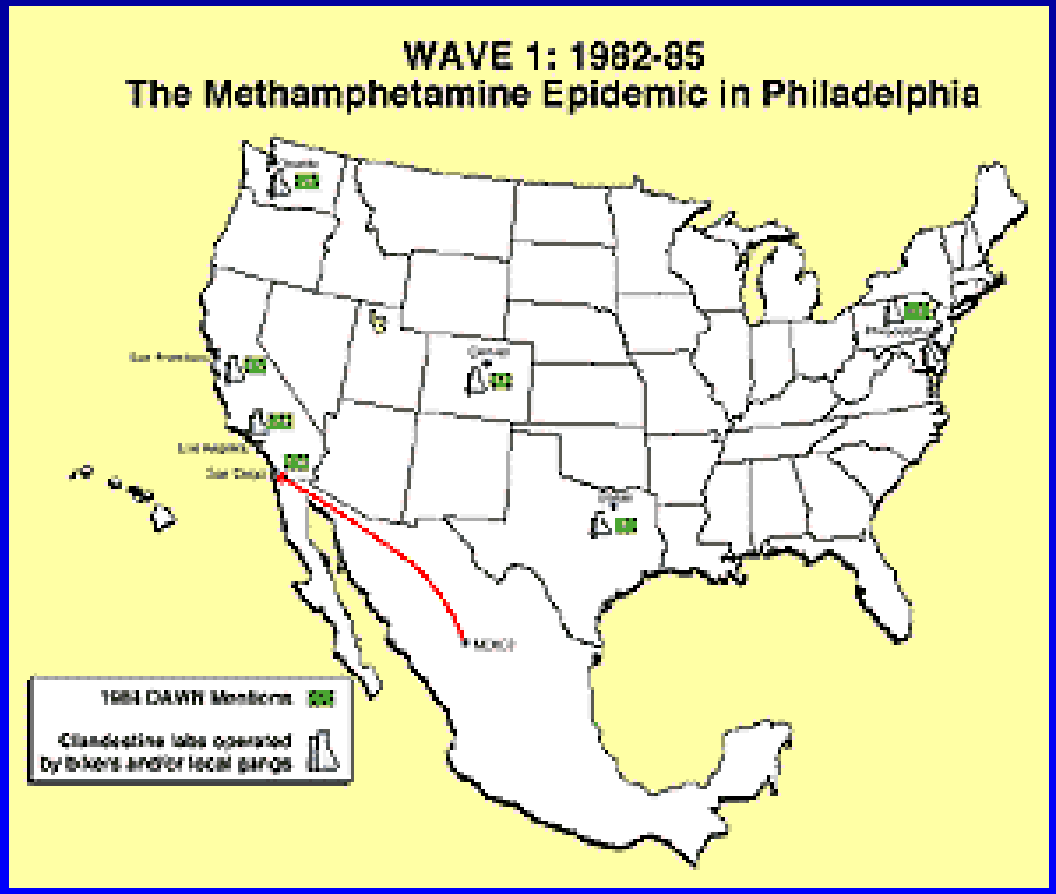
HISTORY OF METH EPIDEMIC

Scope of the Methamphetamine Problem Worldwide

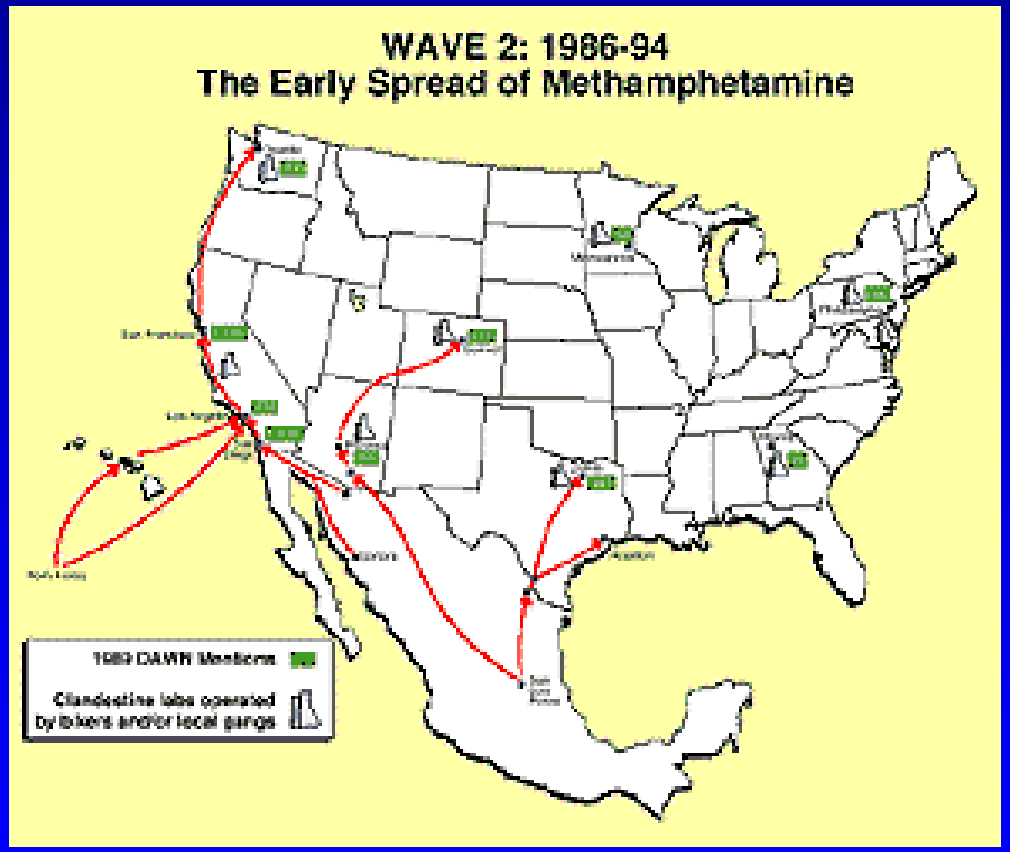
- According to surveys and estimates by WHO and UNDCP, methamphetamine is the most widely used illicit drug in the world except for cannabis.

- World wide it is estimated there are over 42 million regular users of methamphetamine, as compared to approximately 15 million heroin users and 10 million cocaine users

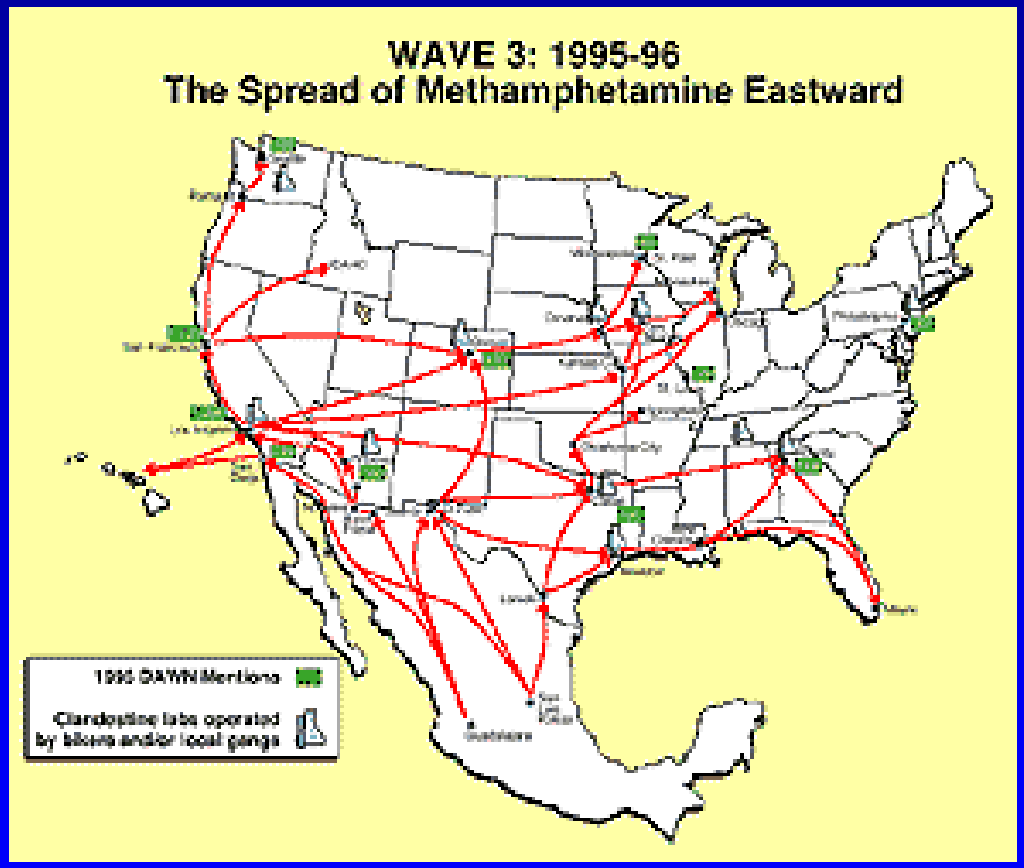
The Emerging Epidemic



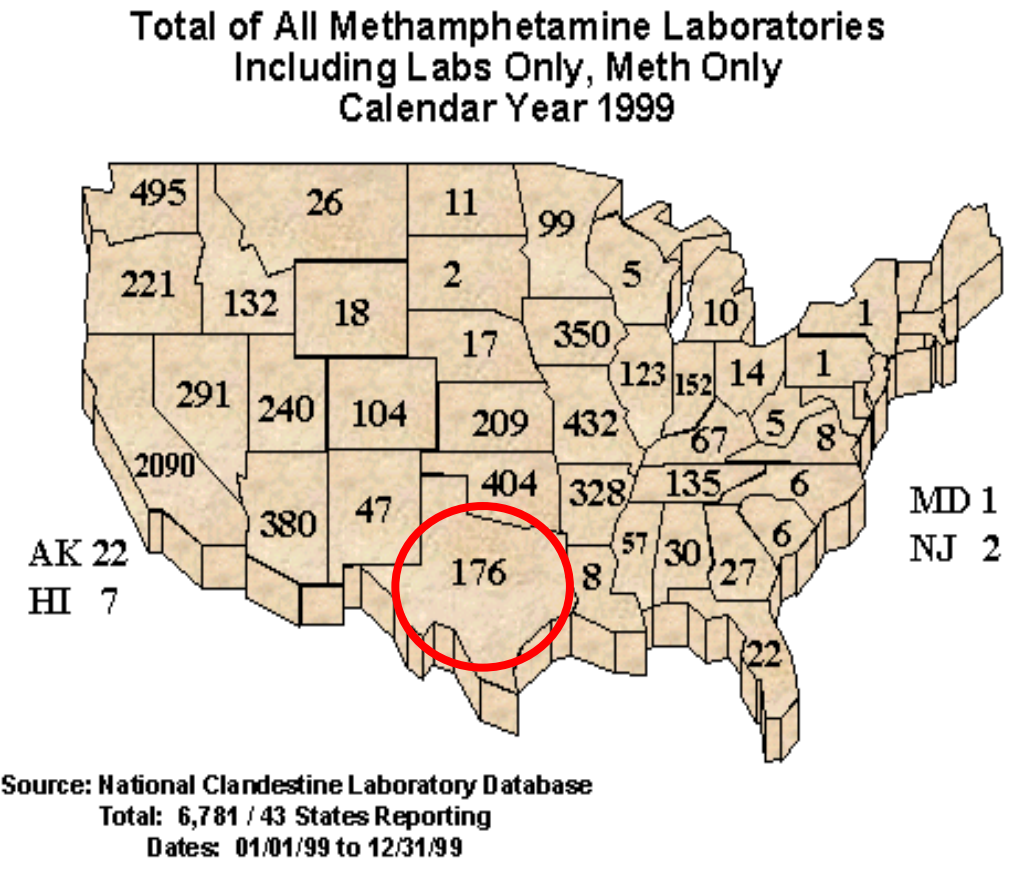
The Emerging Epidemic

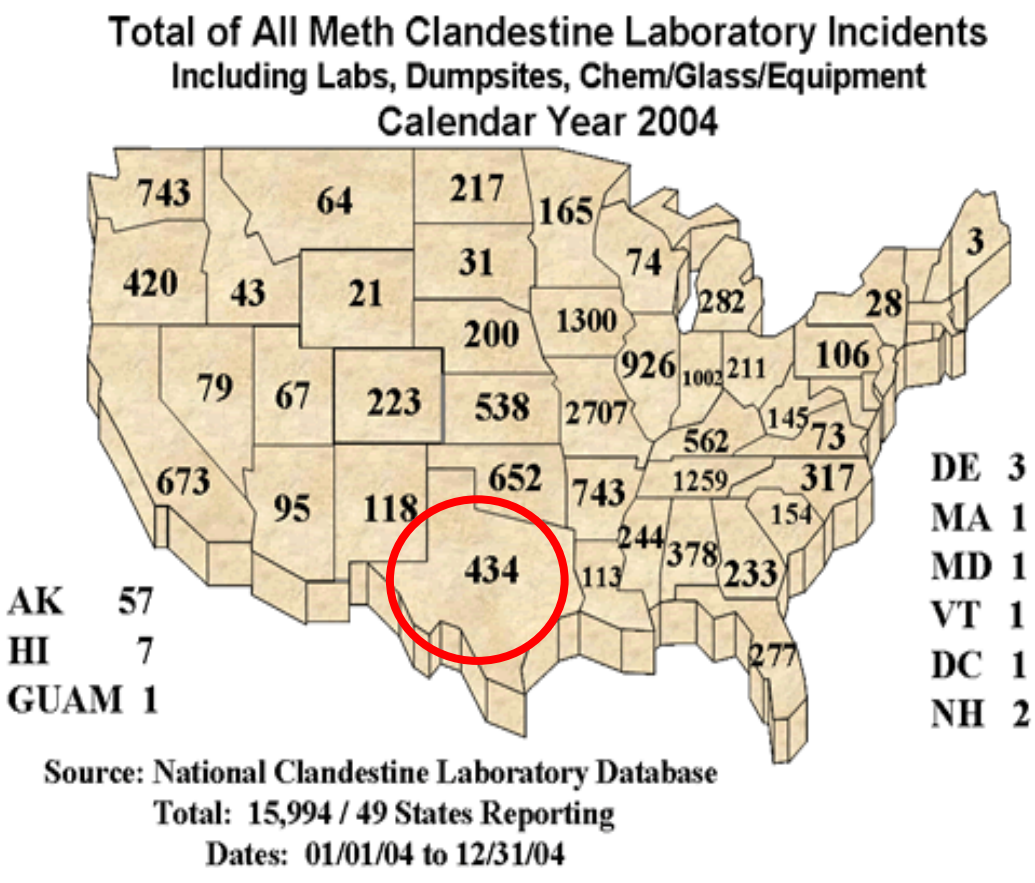


The Emerging Epidemic



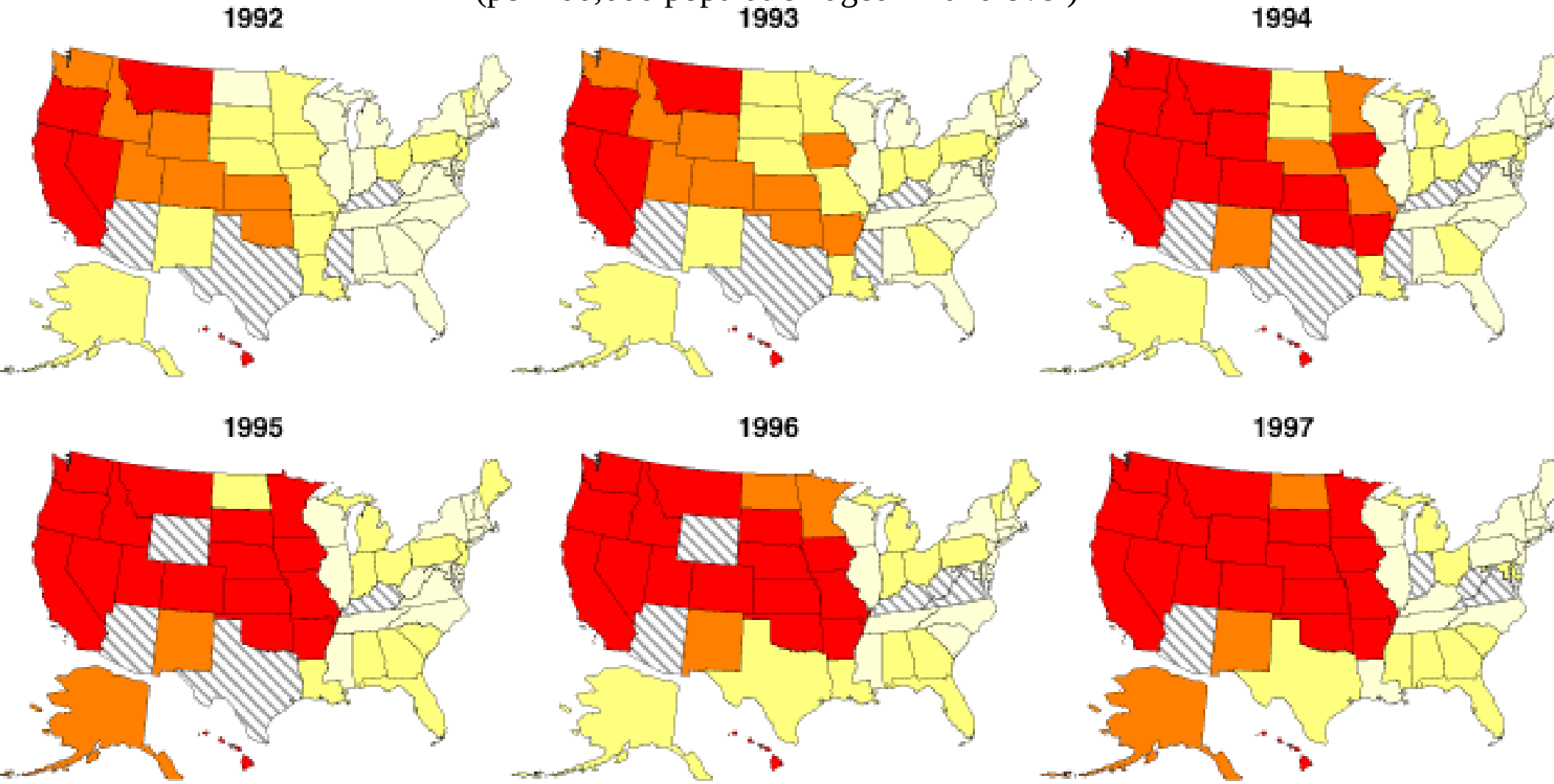
Methamphetamine Lab Seizures: 1999 and 2004





Primary Methamphetamine/amphetamine admission rates

(per 100,000 population aged 12 and over)



NOTES: See Chapter 2.

SOURCE: Office of Applied Studies, Substance Abuse and Mental Health Services Administration, Treatment Episode Data Set (TEDS)– 3.01.04.

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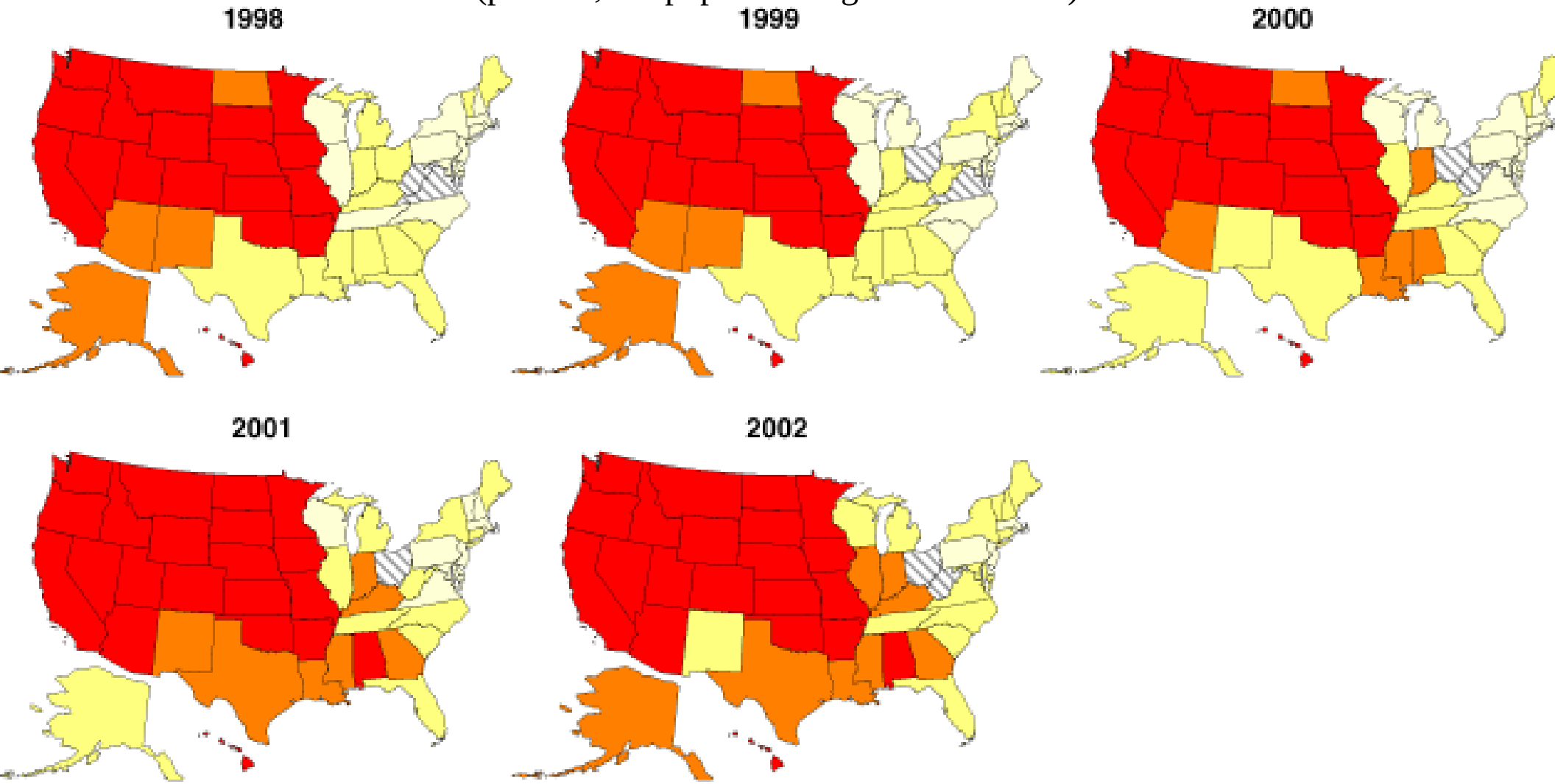


NOTES: See Chapter 2.

SOURCE: Office of Applied Studies, Substance Abuse and Mental Health Services Administration, Treatment Episode Data Set (TEDS)– 3.01.04.

CEWG Areas

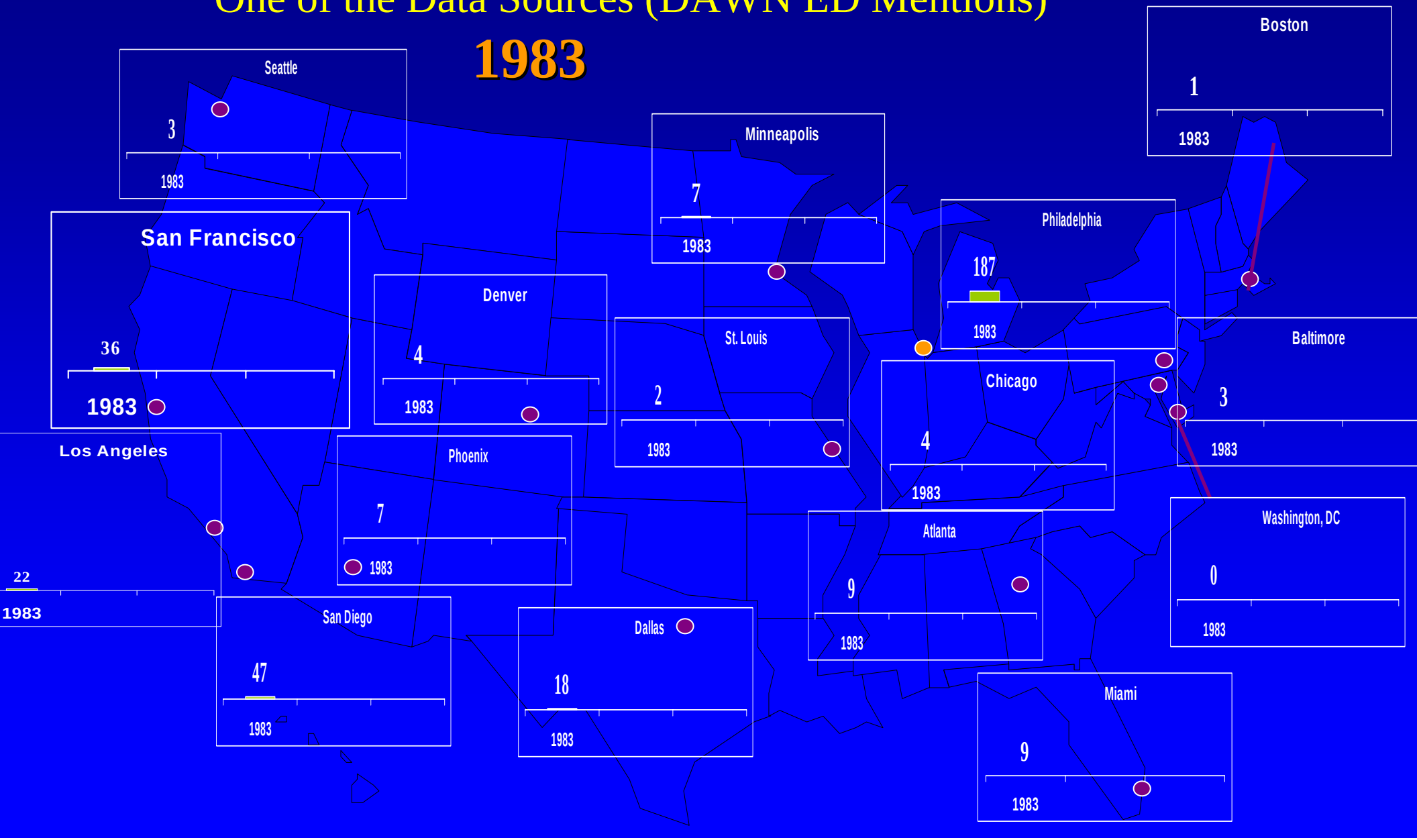

Seattle
Mpls./St. Paul
Boston
Detroit
New York
Phila.
Newark
Chicago
Baltimore
San Francisco
Washington, DC
Denver
St. Louis
Los Angeles
San Diego
Phoenix
Atlanta
State of Texas
Honolulu
New Orleans
Miami

Methamphetamine abuse: June 2004 and January 2005 CEWG Meeting/Reports

- The spread (geographically and into new user groups) of methamphetamine abuse was identified as an issue of great concern by CEWG members
- Abuse indicator remain high in Hawaii, west coast and southwest areas AND, notably,
- **Methamphetamine abuse is spreading eastward**

CEWG: Monitoring Methamphetamine Abuse

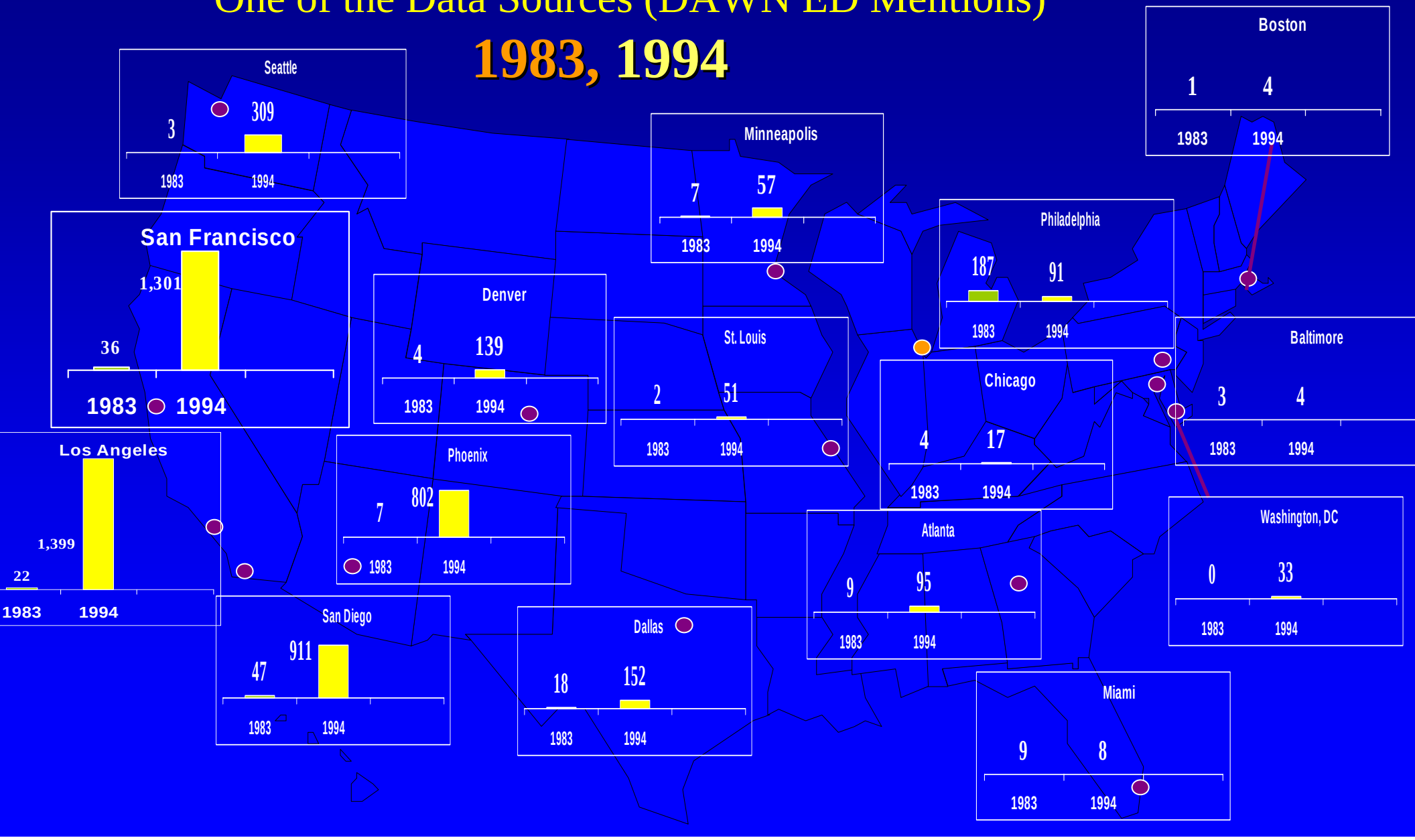
One of the Data Sources (DAWN ED Mentions)



CEWG: Monitoring Methamphetamine Abuse

One of the Data Sources (DAWN ED Mentions)

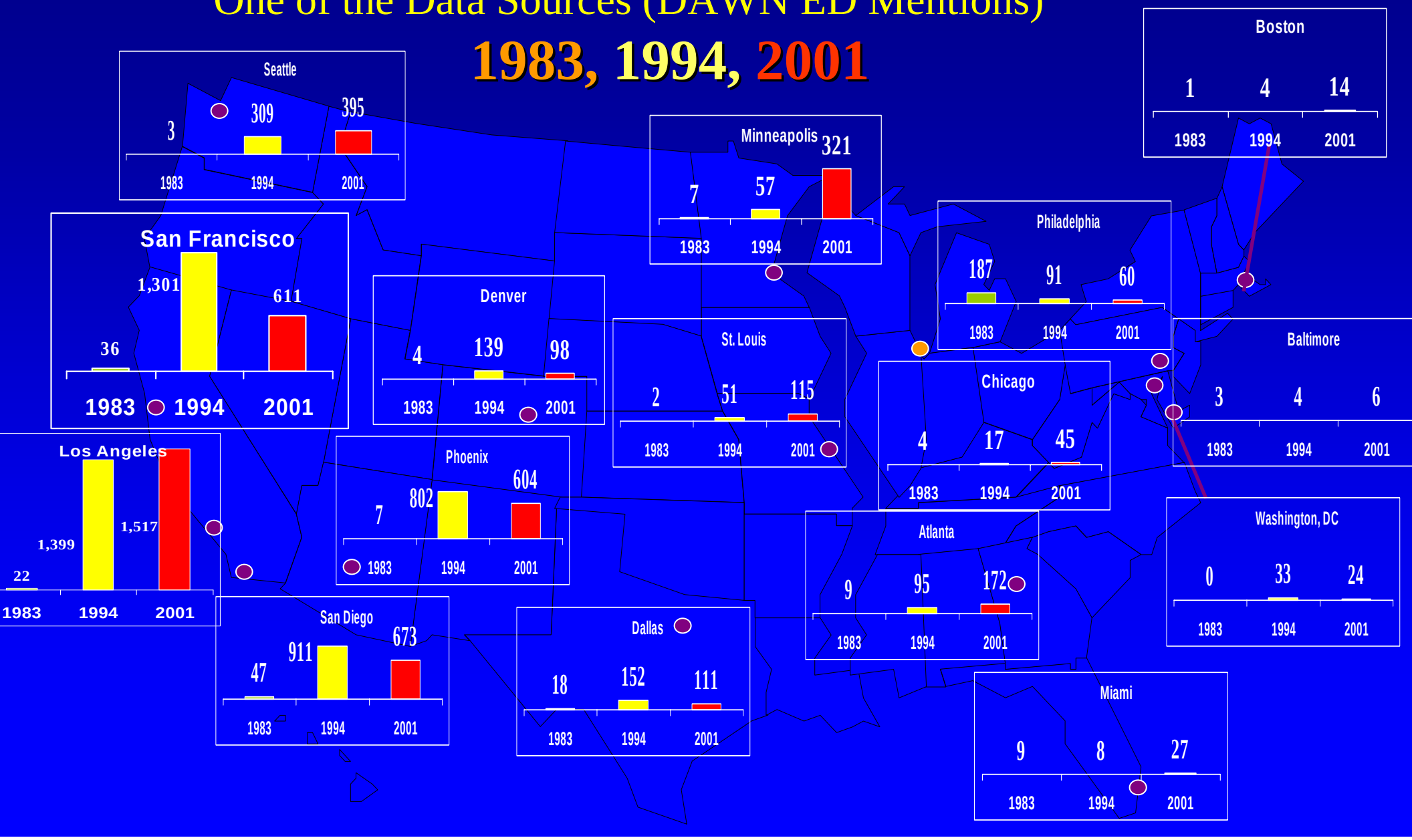
1983, 1994



CEWG: Monitoring Methamphetamine Abuse

One of the Data Sources (DAWN ED Mentions)

1983, 1994, 2001



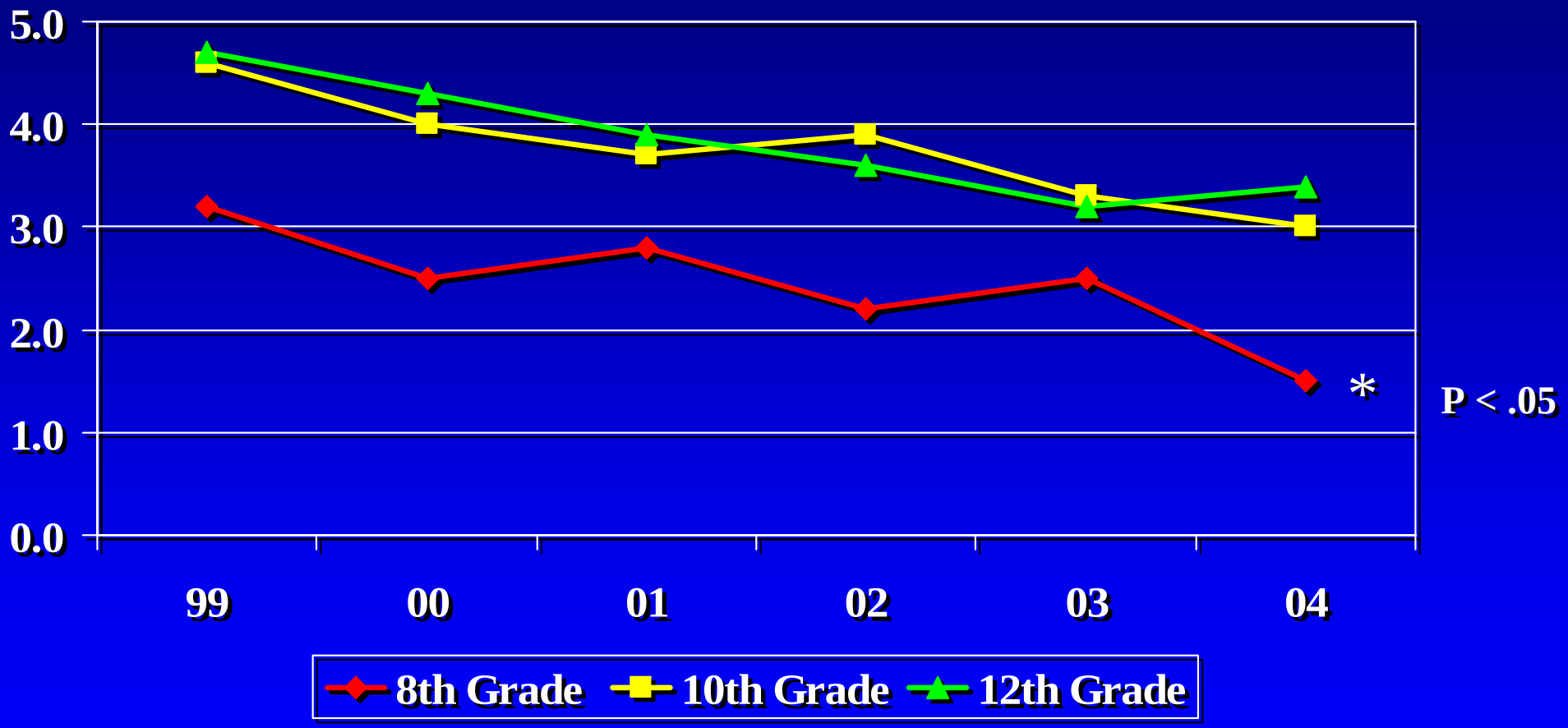
In 2003, over *12.3 million people* age 12 or older reported having used methamphetamine at least once in their lifetime

BUT

Is methamphetamine abuse increasing?

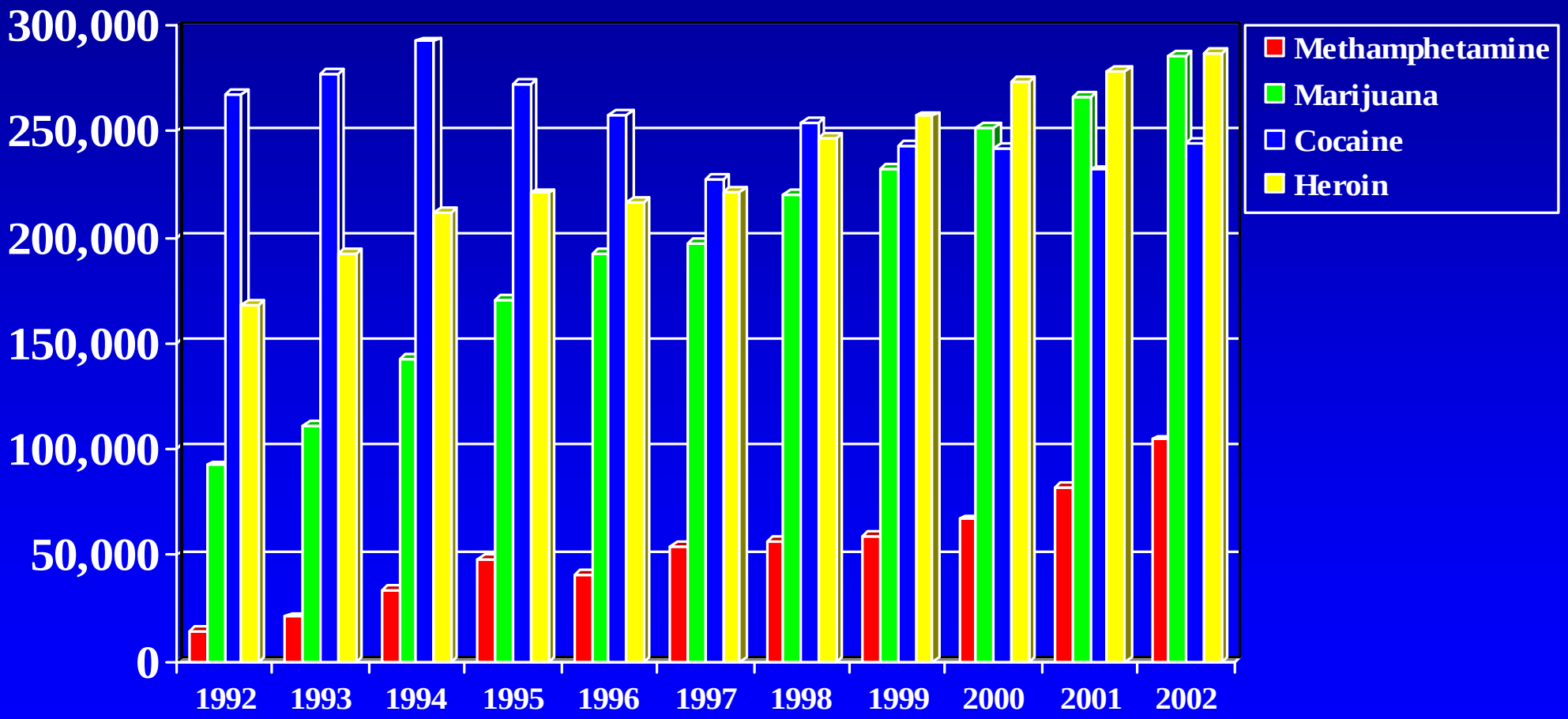
Source: 2003 NSDUH, SAMHSA

According to the Monitoring the Future Study Methamphetamine is not Increasing



Percent of Students Reporting Use of Methamphetamine in Past Year, by Grade

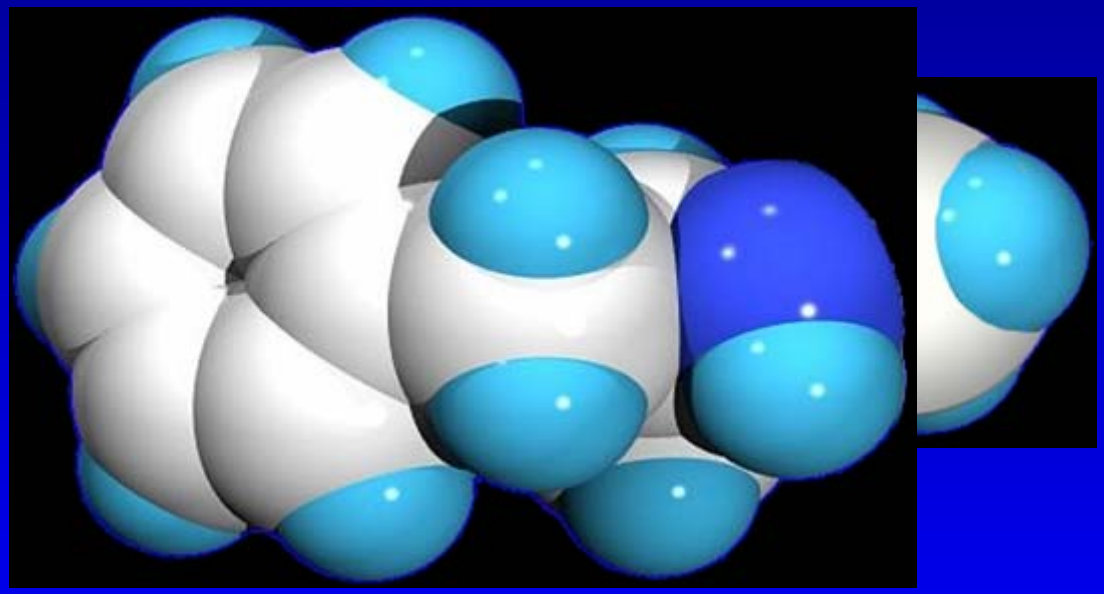
Primary Methamphetamine Treatment Admissions

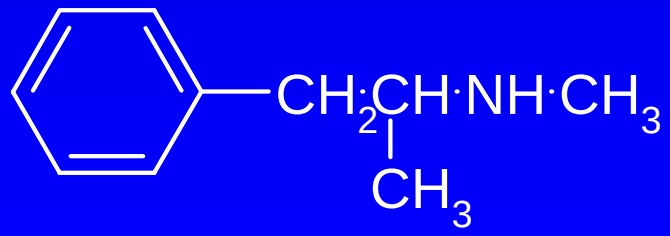


Treatment Episode Data Set (TEDS)

What is methamphetamine?

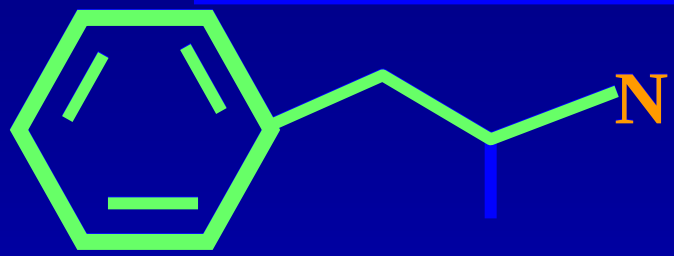
METHAMPHETAMINE



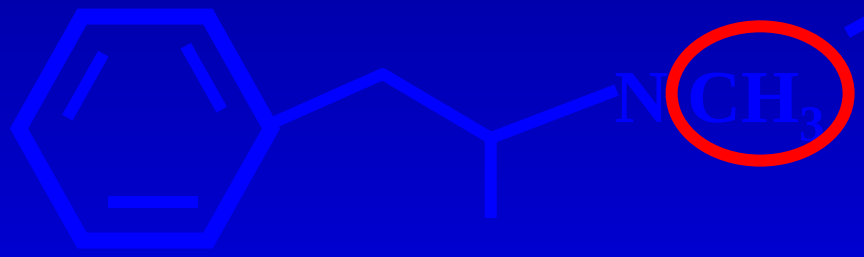


Amphetamine Drugs

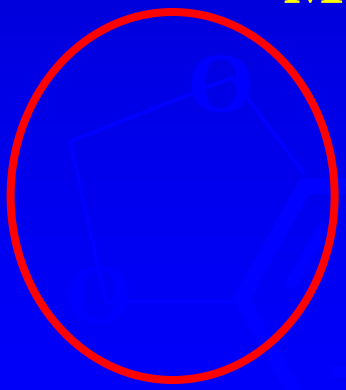
Transmitters



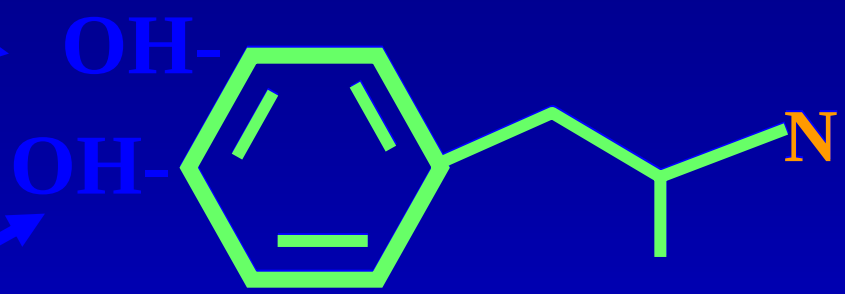
Amphetamine



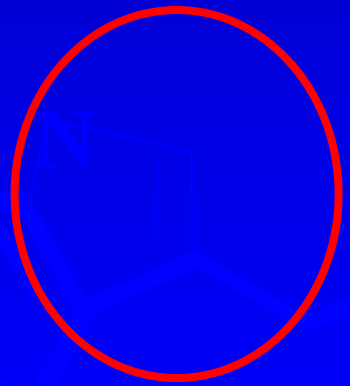
Methamphetamine



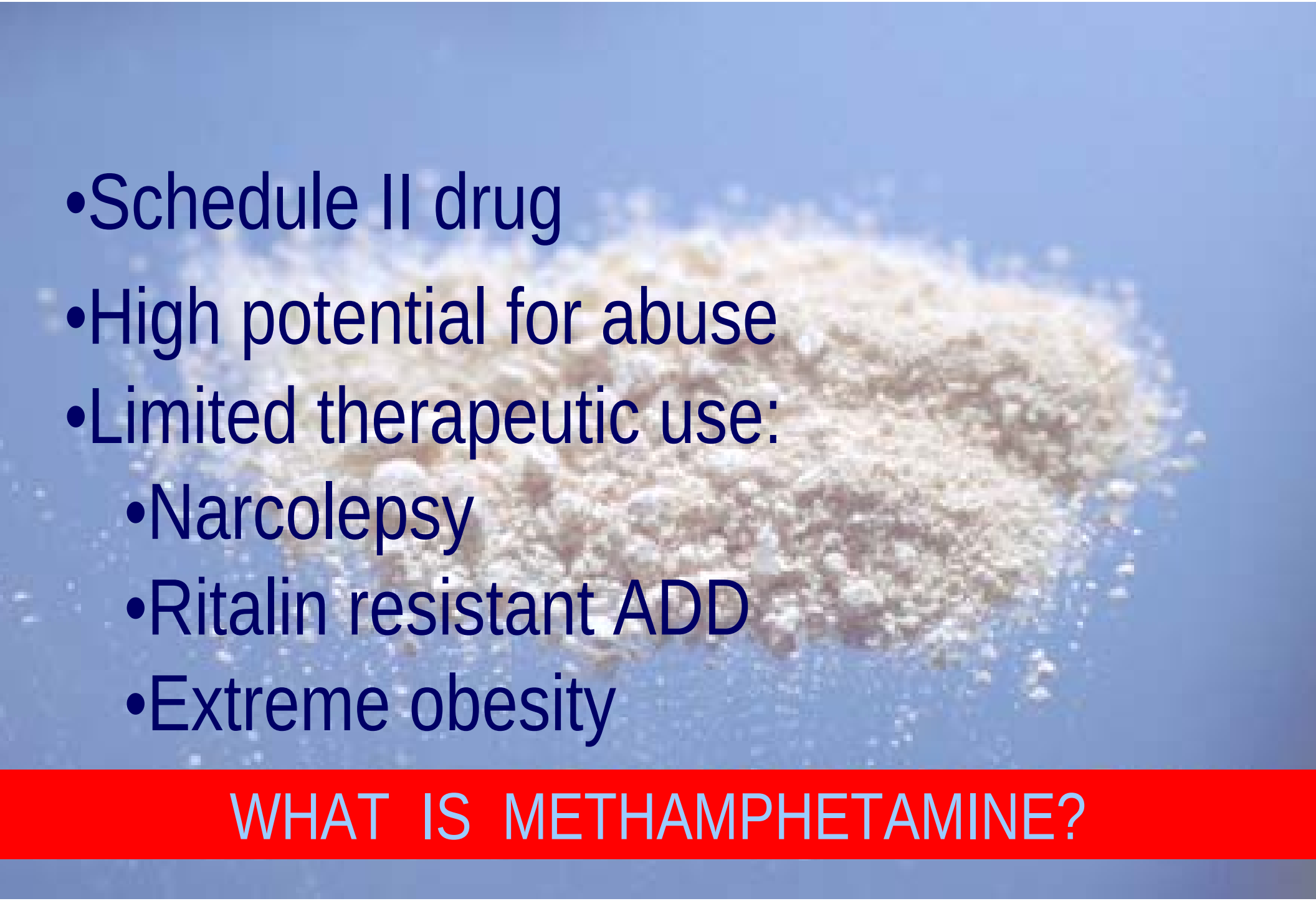
Methylenedioxymethamphetamine
(Ecstasy, MDMA)



Dopamine



Serotonin

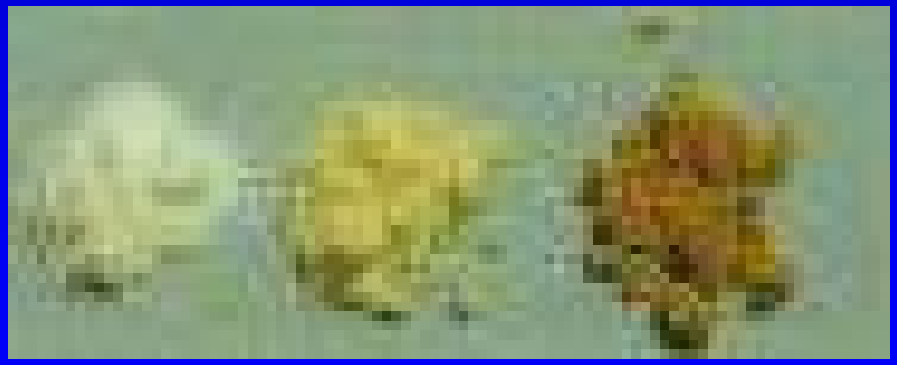

•Schedule II drug
•High potential for abuse
•Limited therapeutic use:
•Narcolepsy
•Ritalin resistant ADD
•Extreme obesity
WHAT IS METHAMPHETAMINE?

Ice

High purity methamphetamine crystals or coarse powder ranging from translucent to white, sometimes with a green, blue, or pink tinge.

Speed

- It is methamphetamine powder ranging in color from white, yellow, orange, pink, or brown.
- Color variations are due to differences in chemicals used to produce it and the expertise of the cooker.
- Other names: shabu, crystal, crystal meth, crank, tina, yaba



What is Yaba?

- Combination of methamphetamine caffeine
- Means crazy medicine in Thai
- Produced in Southeast and East Asia
- Popular in Asian communities in the U.S.
- Increasingly available at raves and techno parties
- Sold as small, brightly colored green or orange-red tablets
- Sometimes flavored like candy, appealing to youth
- Sometimes heated and vapors inhaled (chasing the dragon) or crushed into powder and snorted or injected

National Drug Intelligence Center, DOJ

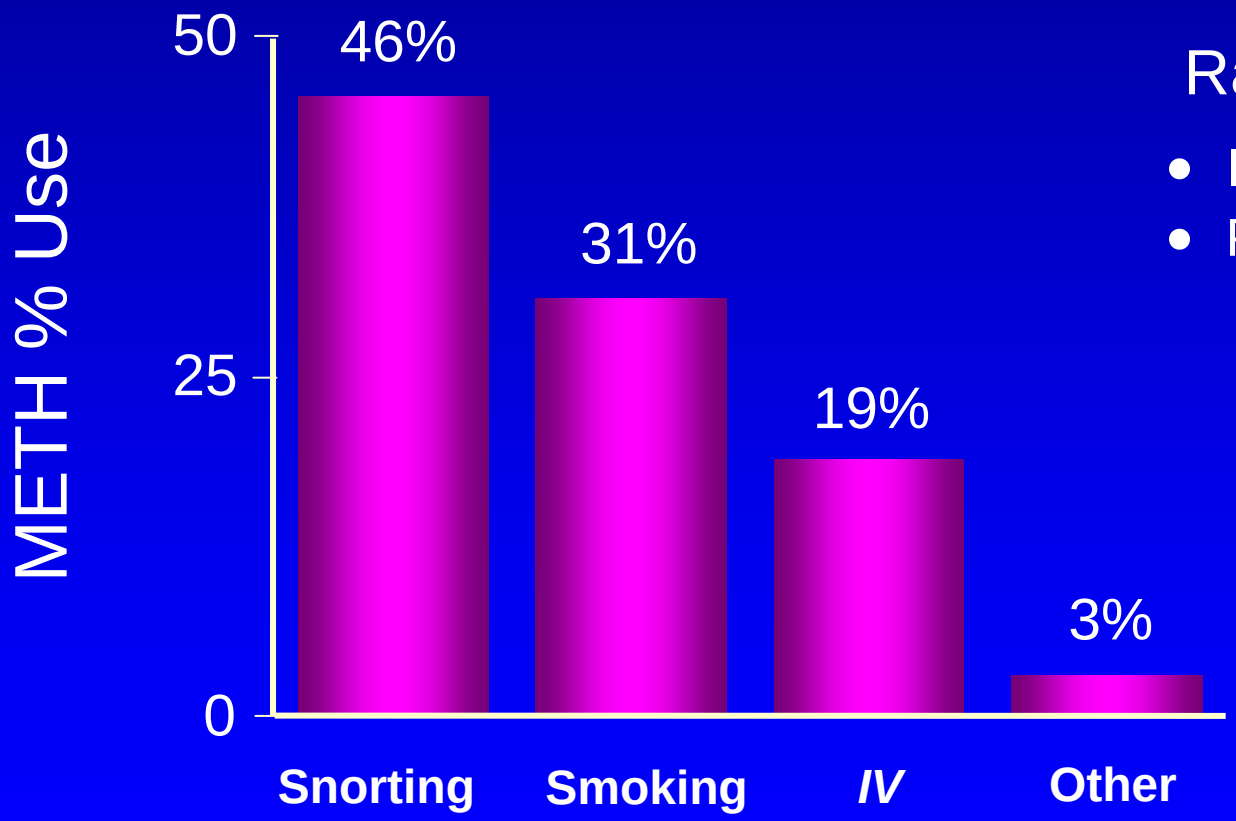
- Synthetic stimulant
- Pills, capsules, powder, and chunks
- Can be made from easily available OTC drugs containing ephedrine, pseudoephedrine, etc.
- “Cookers” in clandestine labs
- Recipe on internet

HOW IS METH MANUFACTURED?

- Intranasal snorting: 5 min. to onset
- Oral ingestion: 20 min. to onset
- Smoked: seconds to onset (euphoric rush)
- IV Injection: seconds to onset (euphoric rush)

HOW IS METH ADMINISTERED?

Human METH Use



Rapid input dominates!

- Immediate euphoric “rush”
- Produces 8 to 24 hr high

Pennell, 1999

- Intranasal snorting: 2-4 hours
- Oral ingestion: 3-5 hours
- Smoked: 1-3 hours
- IV Injection: 1-3 hours; may last 6-12 hours, depending on tolerance and dosage

HOW LONG DO THE EFFECTS LAST?

2002 Methamphetamine Price Ranges

Powdered Meth:

- $3,000-$13,000/pound
- $300-$1,700/ounce
- $40-$125/gram

Ice:

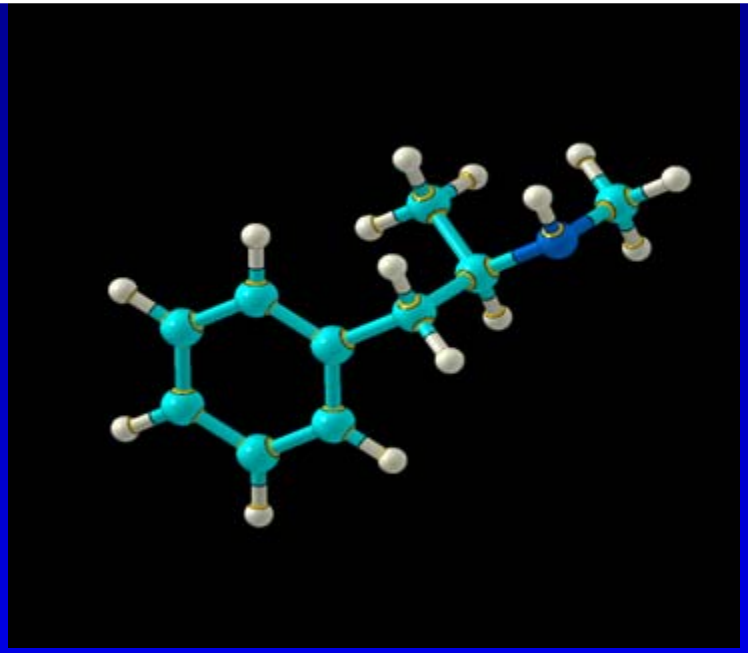
- $1,200-$70,000/pound
- $350-$2,300/ounce
- $120-$500/gram

HOW MUCH DOES METH COST?

What are the effects of methamphetamine?

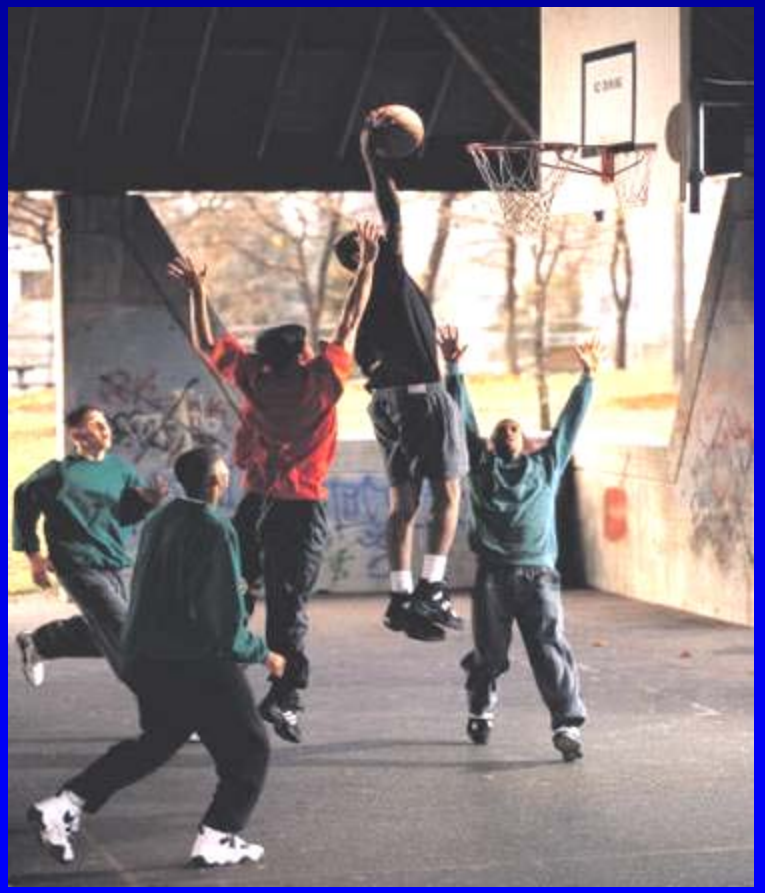
Concerns with Methamphetamine

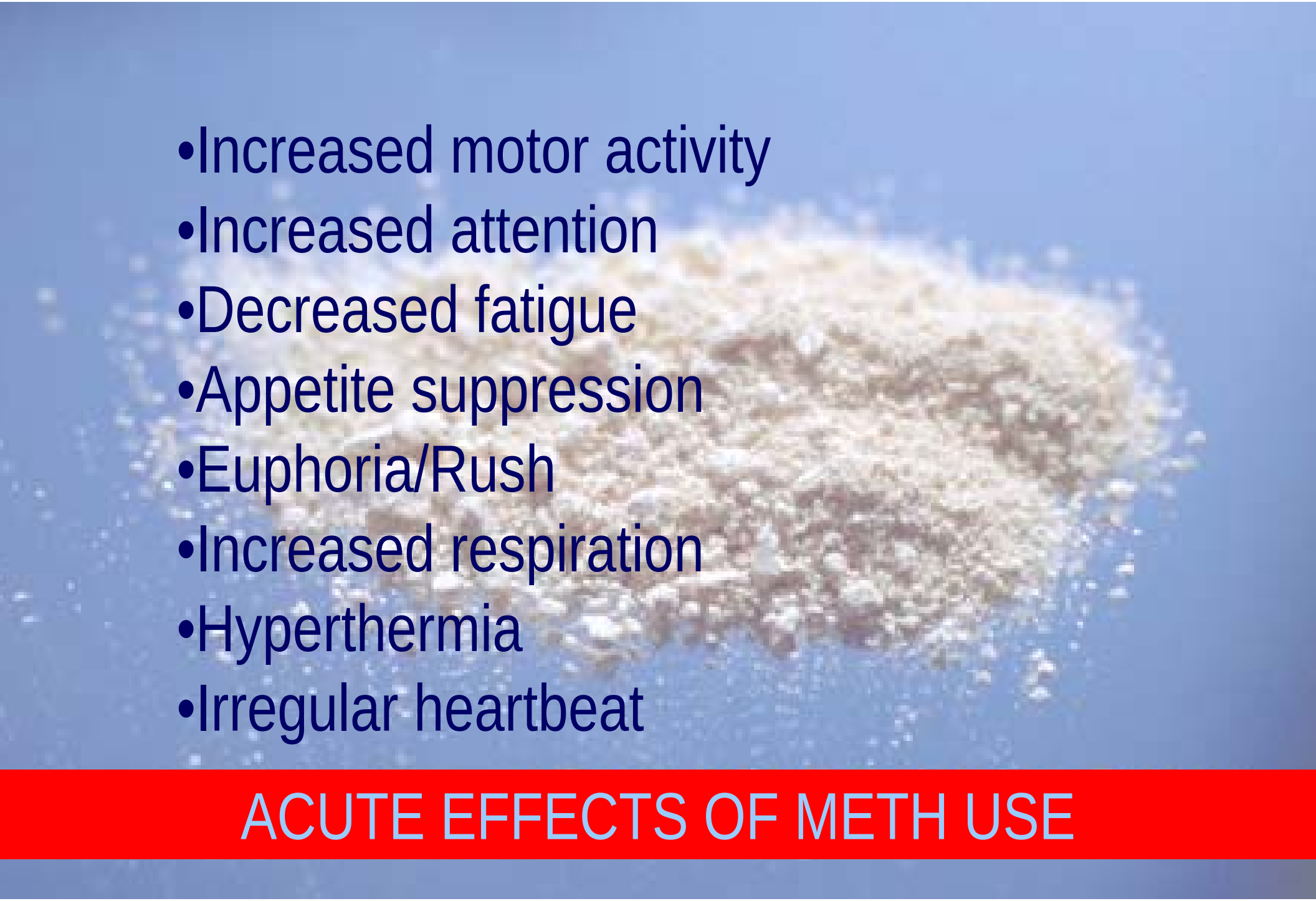
- Neurotoxic in animal models of drug self administration
- Highly addictive
- Intoxication associated with behaviors that increase risks for infection with HIV and HCV
- Can be easily manufactured by small clandestine laboratories

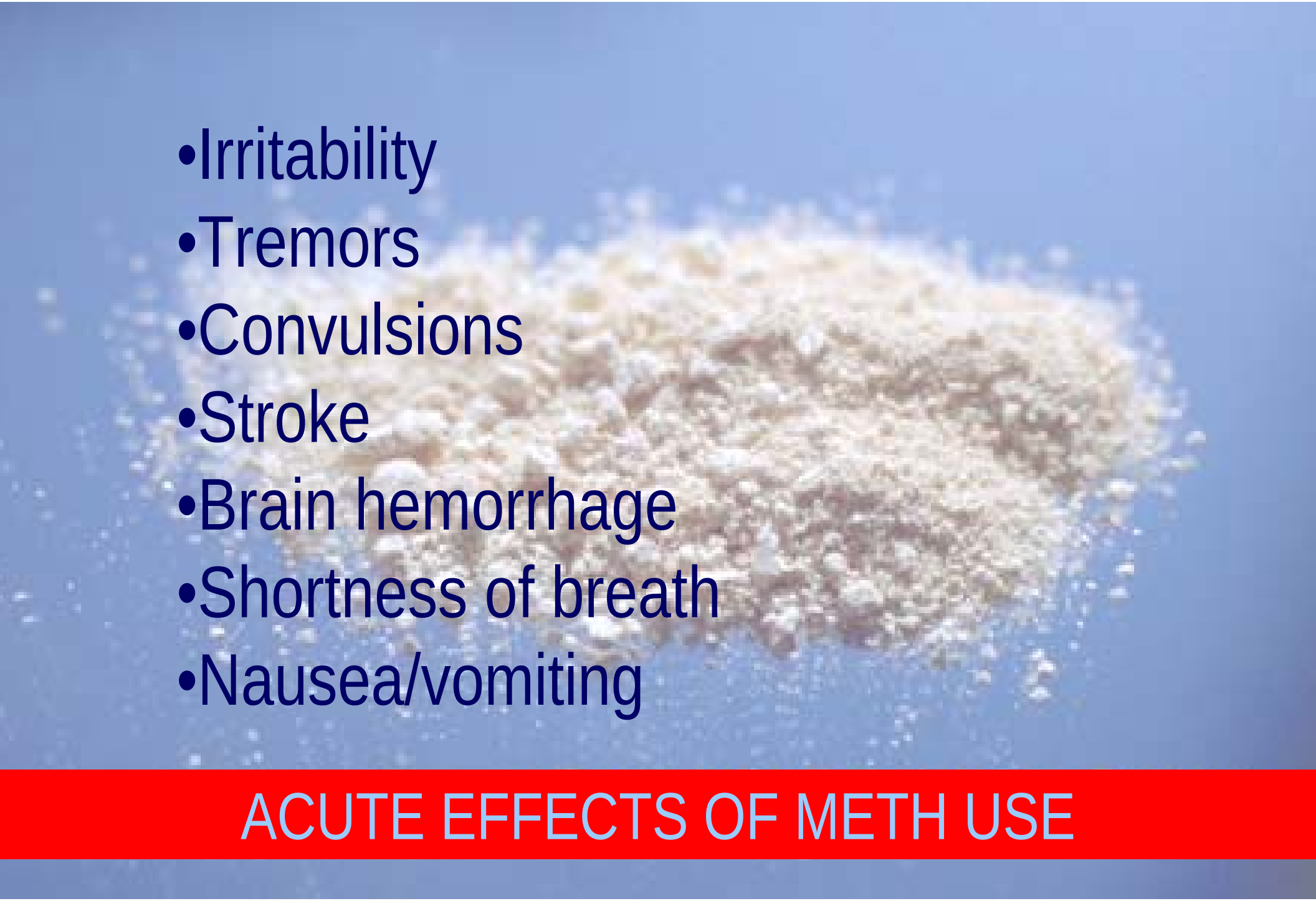


Does methamphetamine affect the way you function?

- *speed and motor coordination*
- *attention and alertness*
- *cognitive function*
- *mood*
- *motivation*




•Increased motor activity
•Increased attention
•Decreased fatigue
•Appetite suppression
•Euphoria/Rush
•Increased respiration
•Hyperthermia
•Irregular heartbeat
ACUTE EFFECTS OF METH USE


•Irritability
•Tremors
•Convulsions
•Stroke
•Brain hemorrhage
•Shortness of breath
•Nausea/vomiting
ACUTE EFFECTS OF METH USE

- Addiction
- Psychosis/paranoia
- Hallucinations
- Anxiety
- Depression
- Anorexia/malnutrition
- Aggression/violence
- For*m*ication & skin infections

LONG TERM EFFECTS OF METH USE


• Drug craving
• Depression
• Sleep disturbances
• Hunger
METHAMPHETAMINE WITHDRAWAL SYNDROME

- Sores/abscess at injection site
- Infection of heart valves and lining
- *HIV/AIDS*
- *HEP C & other infectious diseases*

CONSEQUENCES OF IV METH USE

METH Use Leads to Severe Tooth Decay

Source: Richards, JR and Brofeldt, BT, J Periodontology, August 2000.

"METH Mouth"

Source: *The New York Times*, June 11, 2005

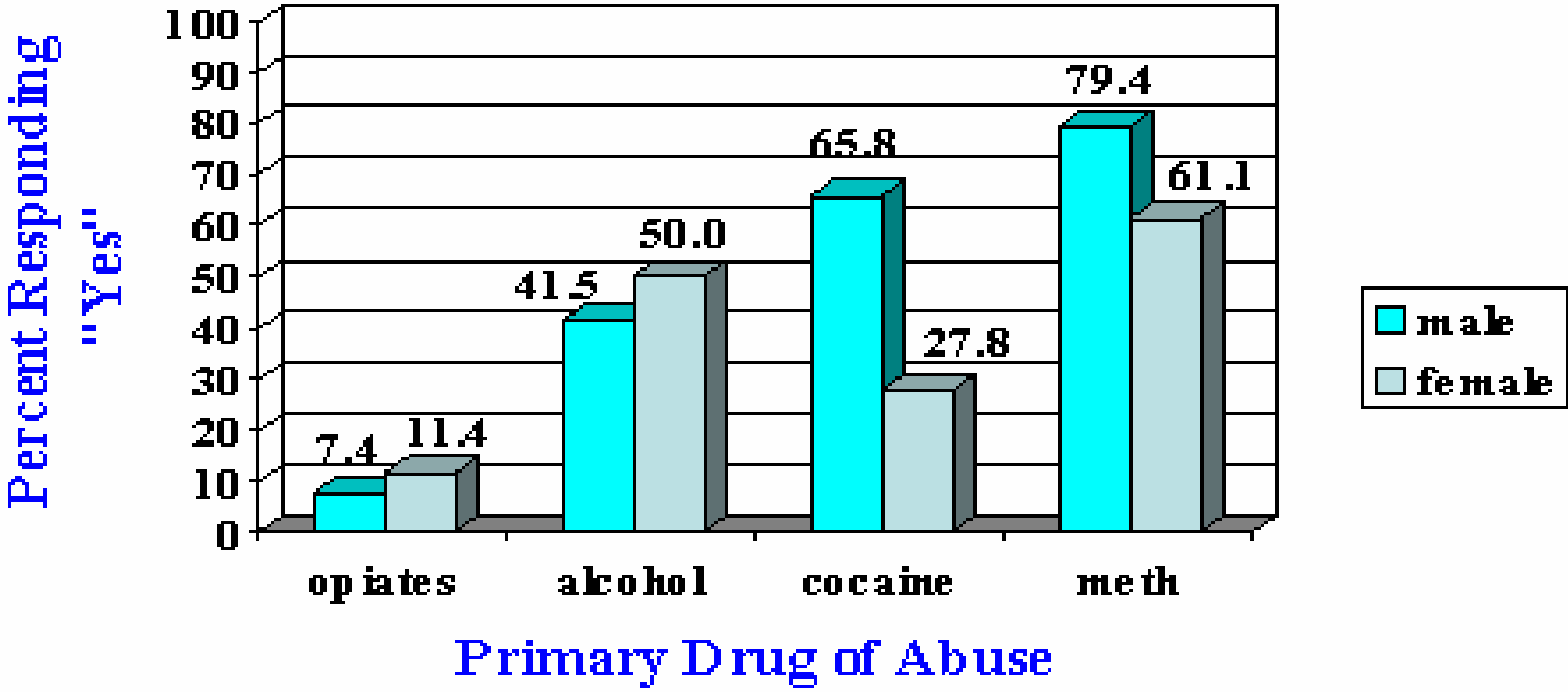
Meth and AIDS

What is the Role of Methamphetamine in the HIV Epidemic?

- Does it disrupt immunological function?
- What is the neurobiology that underlies the risky sexual behavior that occurs during METH intoxication
- What physiological changes resulting from METH use may increase level of infectivity (e.g., erosion of normal protective epithelial layer)

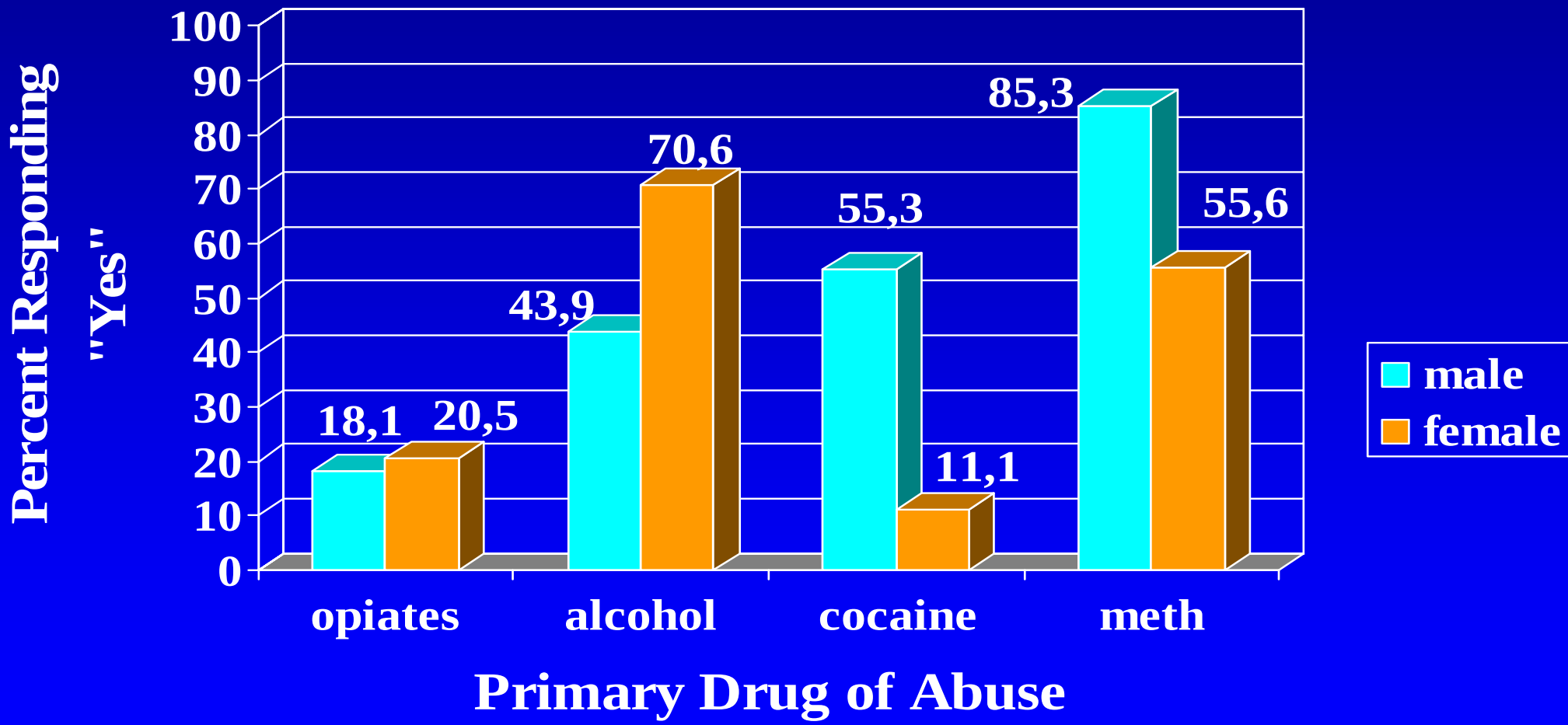
Methamphetamine and Sex

I am more likely to have sex when using …



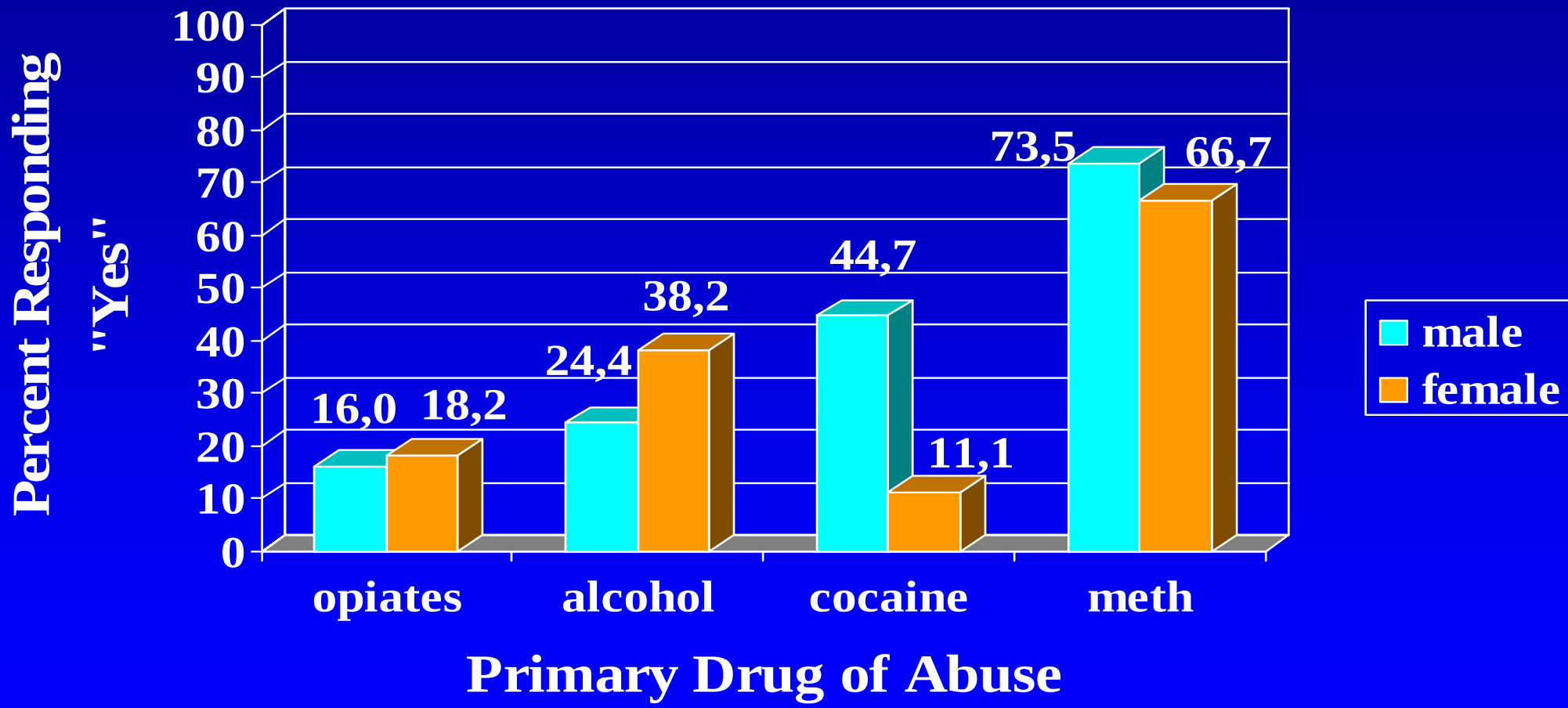
(Rawson et al., 2002)

My sexual *drive* is increased by the use of …



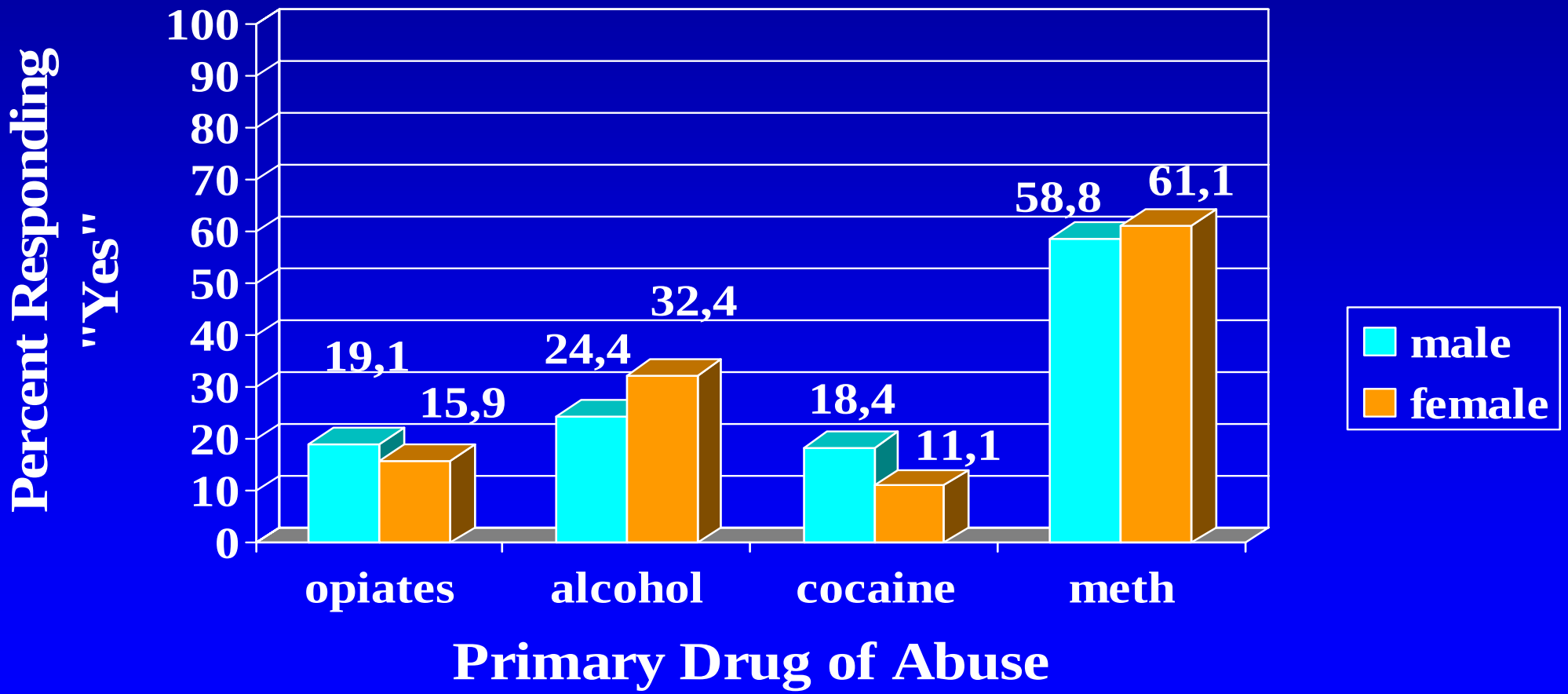
(Rawson et al., 2002)

My sexual *pleasure* is enhanced by the use of …



(Rawson et al., 2002)

My sexual *performance* is improved by the use of …

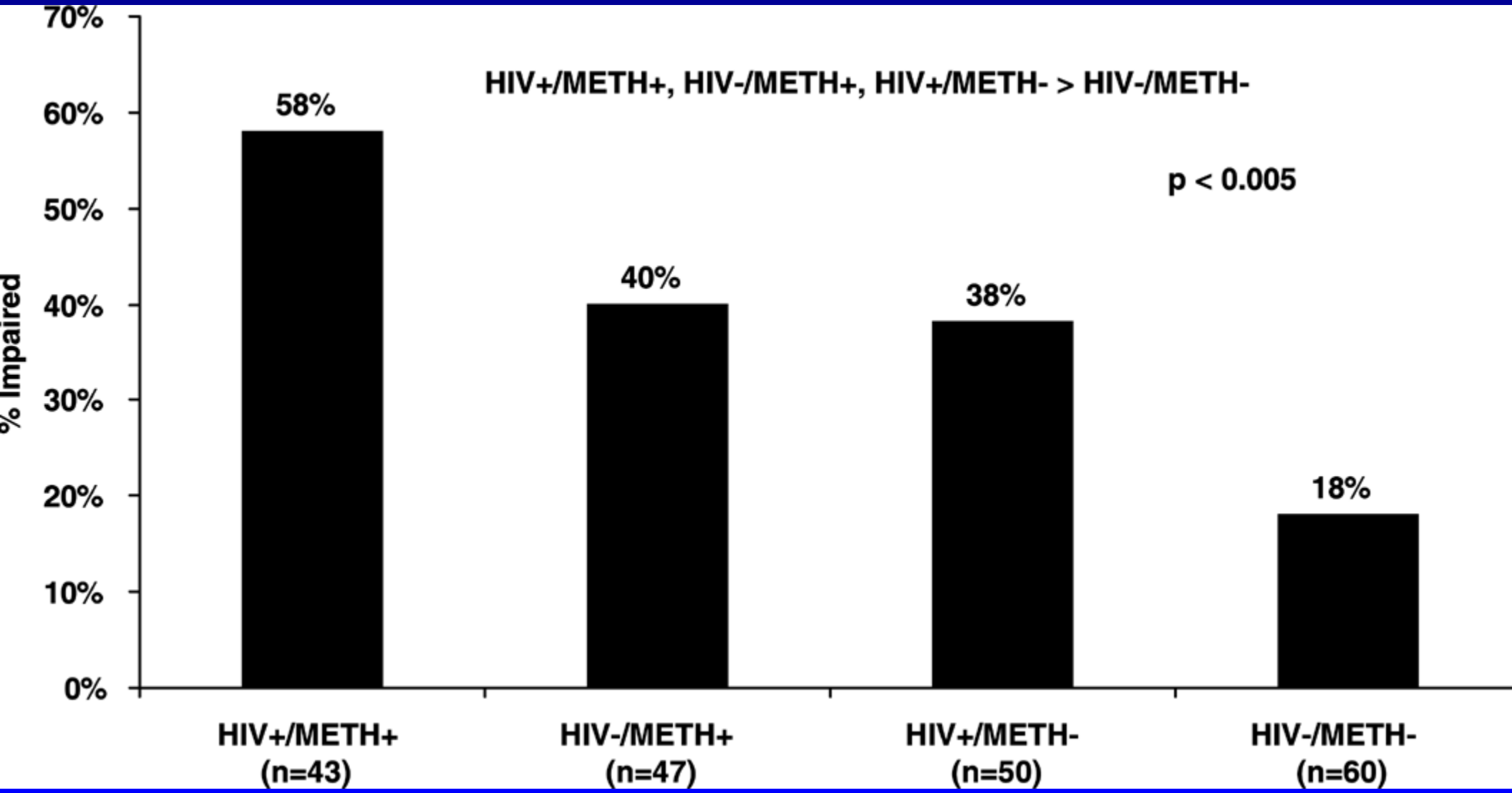


(Rawson et al., 2002)

Methamphetamine Impacts the Spread and Course of HIV/AIDS:

- Increases risky sexual behavior, especially among men who have sex with men (MSM)
- Reduces medication adherence to HAART
- Increases replication of FIV in brain cells (the feline equivalent of HIV)
- Meth dependence increases the risk of HIV-related cognitive problems

Methamphetamine Dependence Increases Risk of Neuropsychological Impairment in HIV+ Persons



Grant et al, J Intl Neuropsychological Society V 10, pg 1, 2004

What about prenatal exposure to methamphetamine?

Animal Studies

- Limited studies of prenatal exposure to methamphetamine
- Variable results: Some decreases in neurotransmitters; some increases; different sites
- May result from differing dose levels, variable gestational exposure, and postnatal ages at which offspring are assessed.
- More studies needed.

Infant Development, Environment, And Lifestyle Study (IDEAL)
Multi-Site Study of Prenatal Methamphetamine

- "Hotbeds" of Methamphetamine Use
  - Iowa
  - Oklahoma
  - Southern California
  - Hawaii
- Over 13,000 deliveries screened
- Subjects: 200 Meth exposed and 200 control infants
- Three-year longitudinal study
- Preliminary data available for newborn and one month

Multi-Site Study of Prenatal Methamphetamine

- Child Outcomes
  - Arousal regulation
  - Cognition
  - Social relationships
  - Neuromotor development
  - Neuroendocrine function
  - Medical status
- Overall goal: To determine how drug effects and effects of psychosocial risk characteristics of the environment combine to affect child outcome

Fetal Effects of Methamphetamine

Preliminary evidence suggests that prenatal methamphetamine exposure is associated with subtle physical and neurobehavioral effects including:

- Lower arousal
- Poorer self-regulation
- Poorer quality of movement
- Increased central nervous system stress
- Small for gestational age
- Long-term consequences???

Clinical observations suggest that prenatal Methamphetamine exposure is associated with increased incidence of:

Short-term effects

- Abnormal sleep patterns
- Poor feeding
- Tremors

Delayed Effects

- Attention deficit disorder
- Poor School Performance
- Language delays

So…

Why Do People Take Methamphetamine In The First Place?

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

- Sense of well-being, euphoria
- Increased energy
- Release of social inhibitions
- Feelings of cleverness/competence
- Magnification of pleasurable sensations
- Appetite suppression

WHY DO PEOPLE TAKE METH?

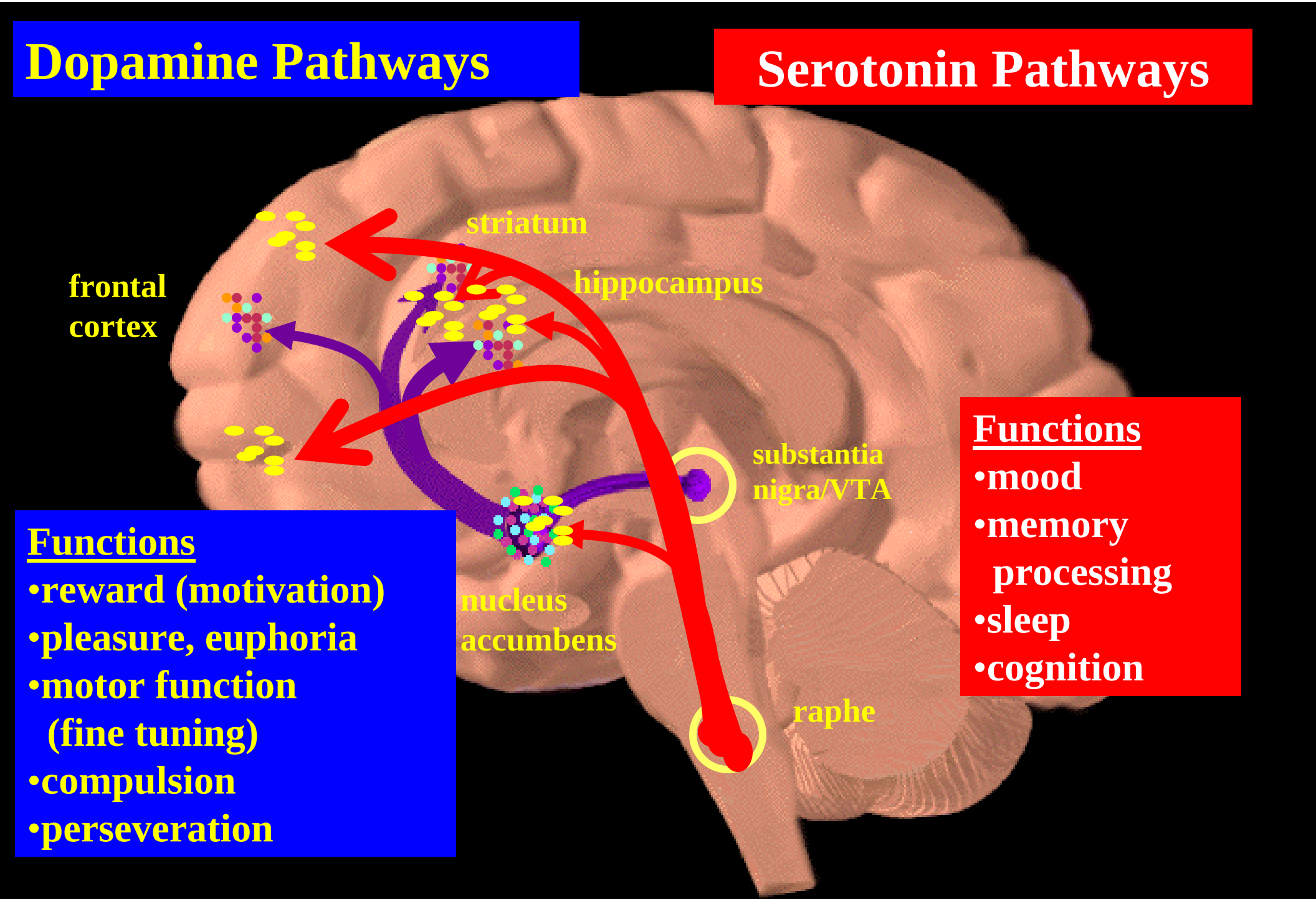

People Take Methamphetamine
Because They Like What
it Does to Their Brains
WHY DO PEOPLE TAKE METH?

How does Methamphetamine exert its behavioral effects?

We Know That Despite Their Many Differences, most Abused Substances Enhance the Dopamine and Serotonin Pathways

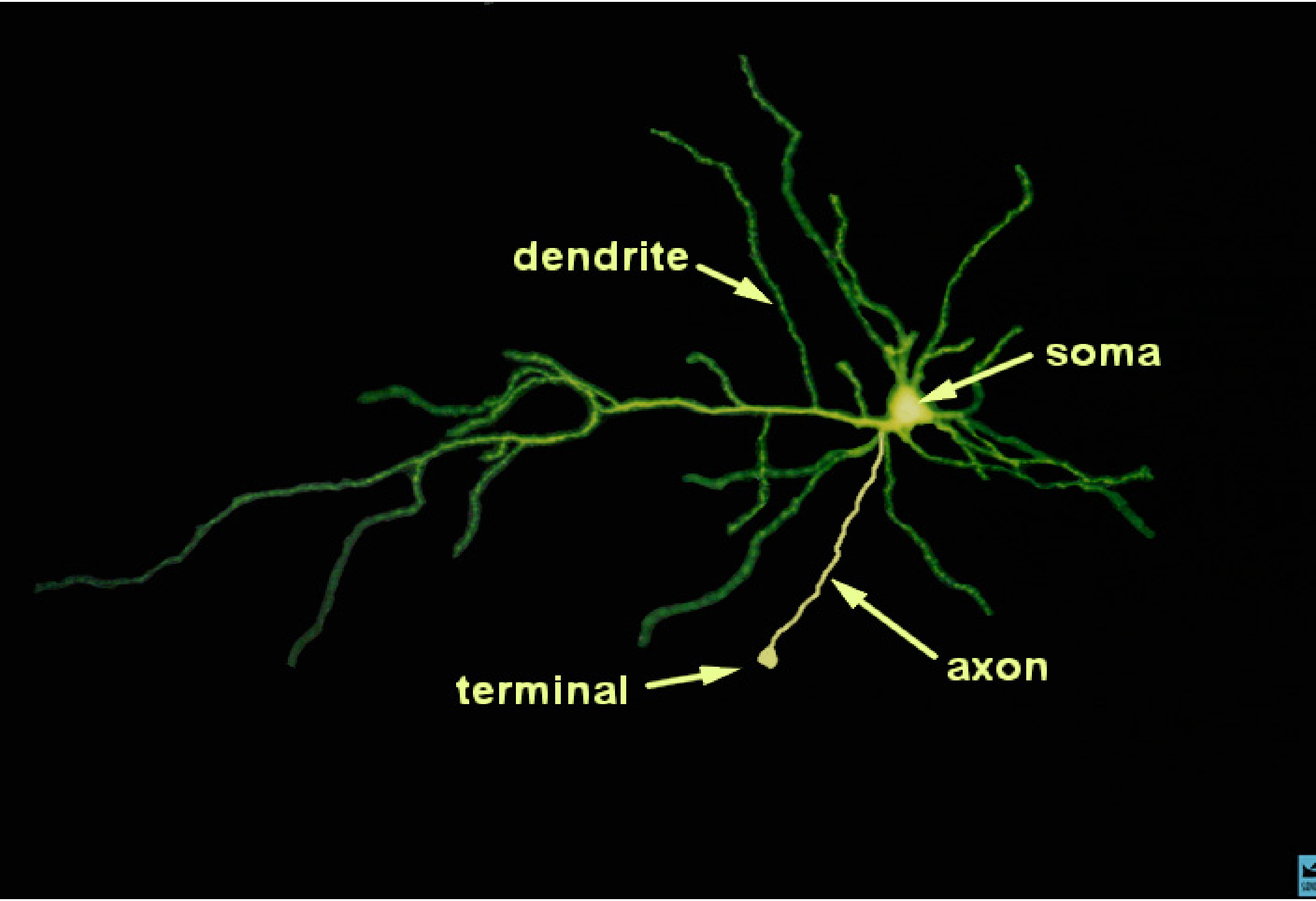
Dopamine Pathways

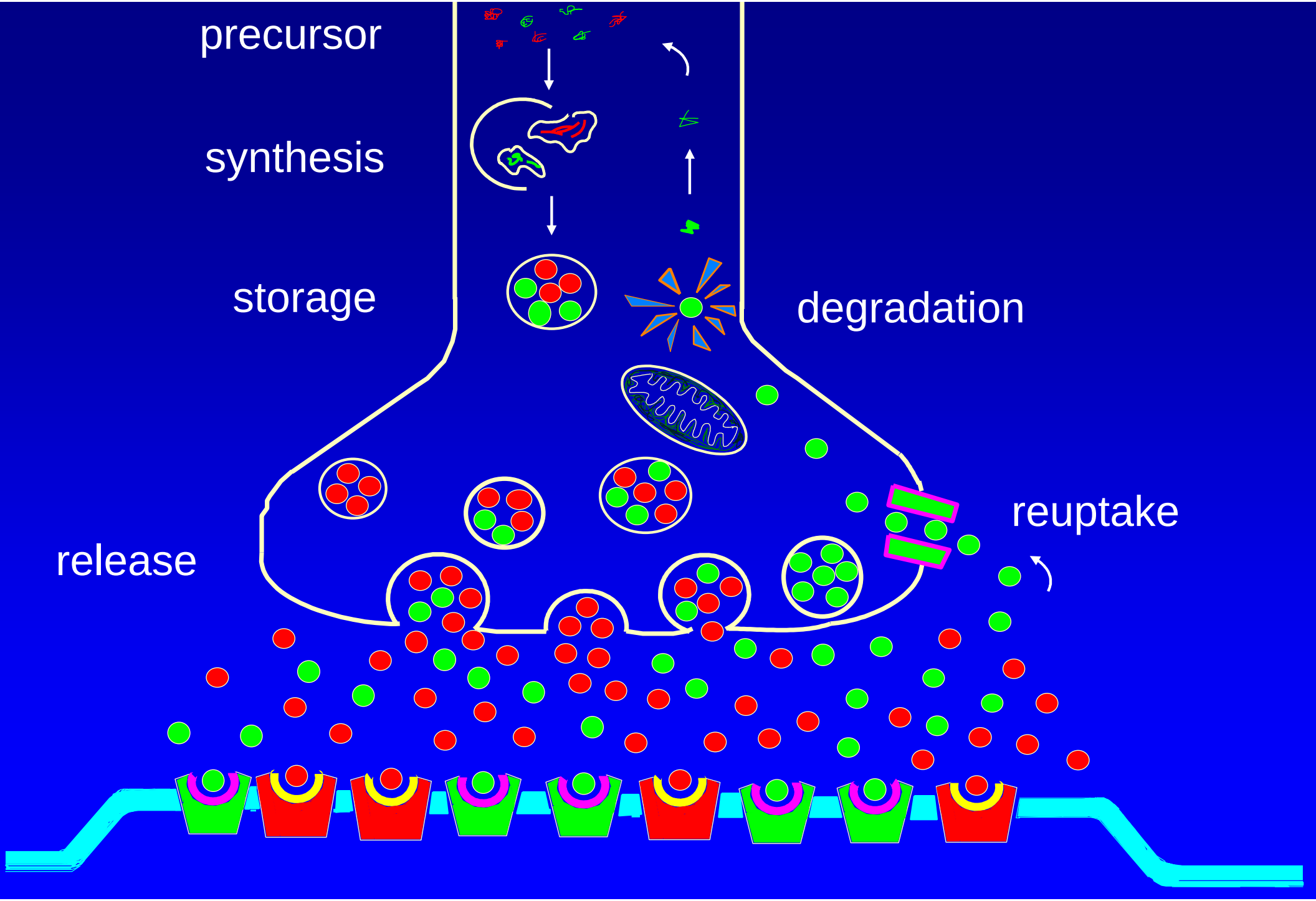
Serotonin Pathways

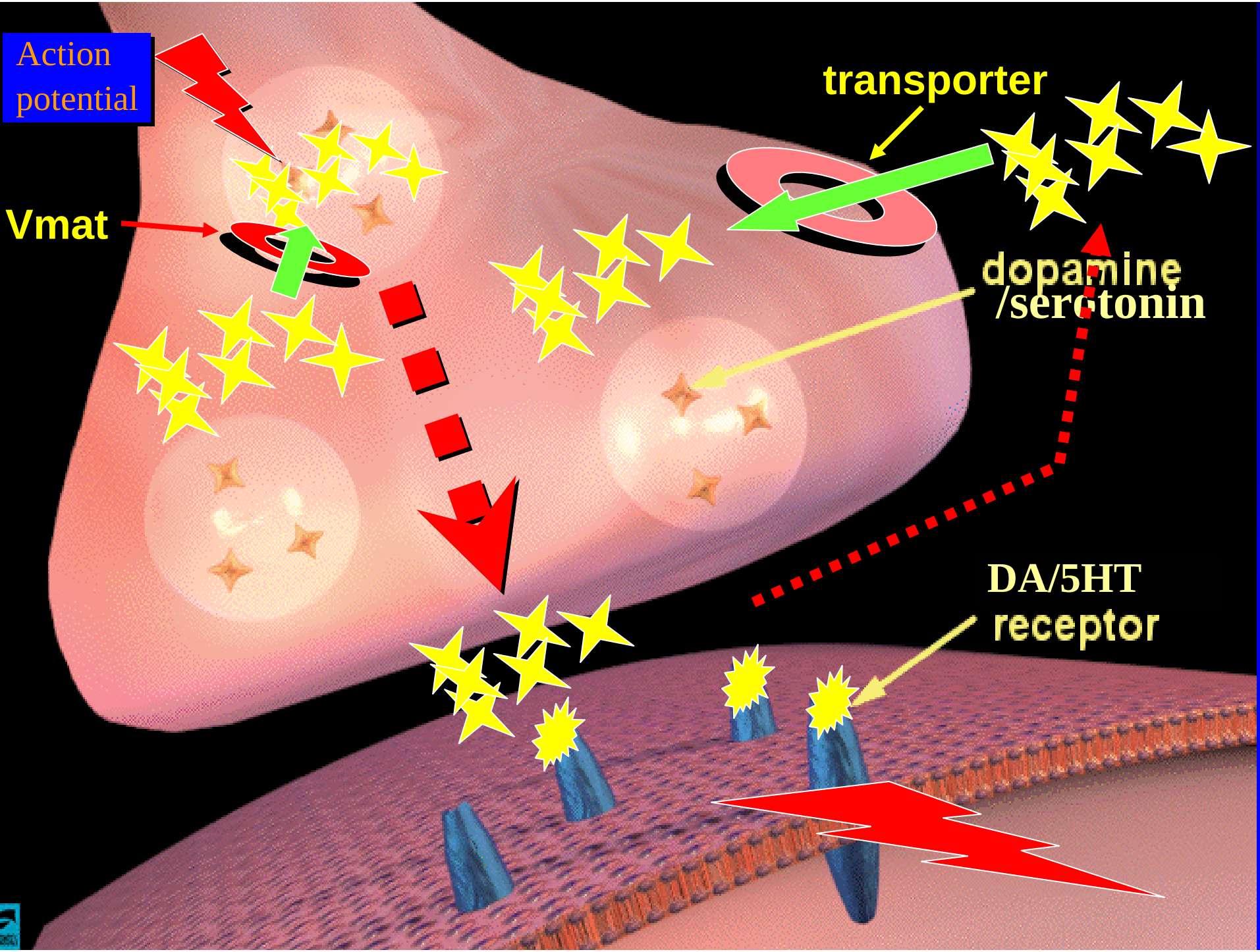


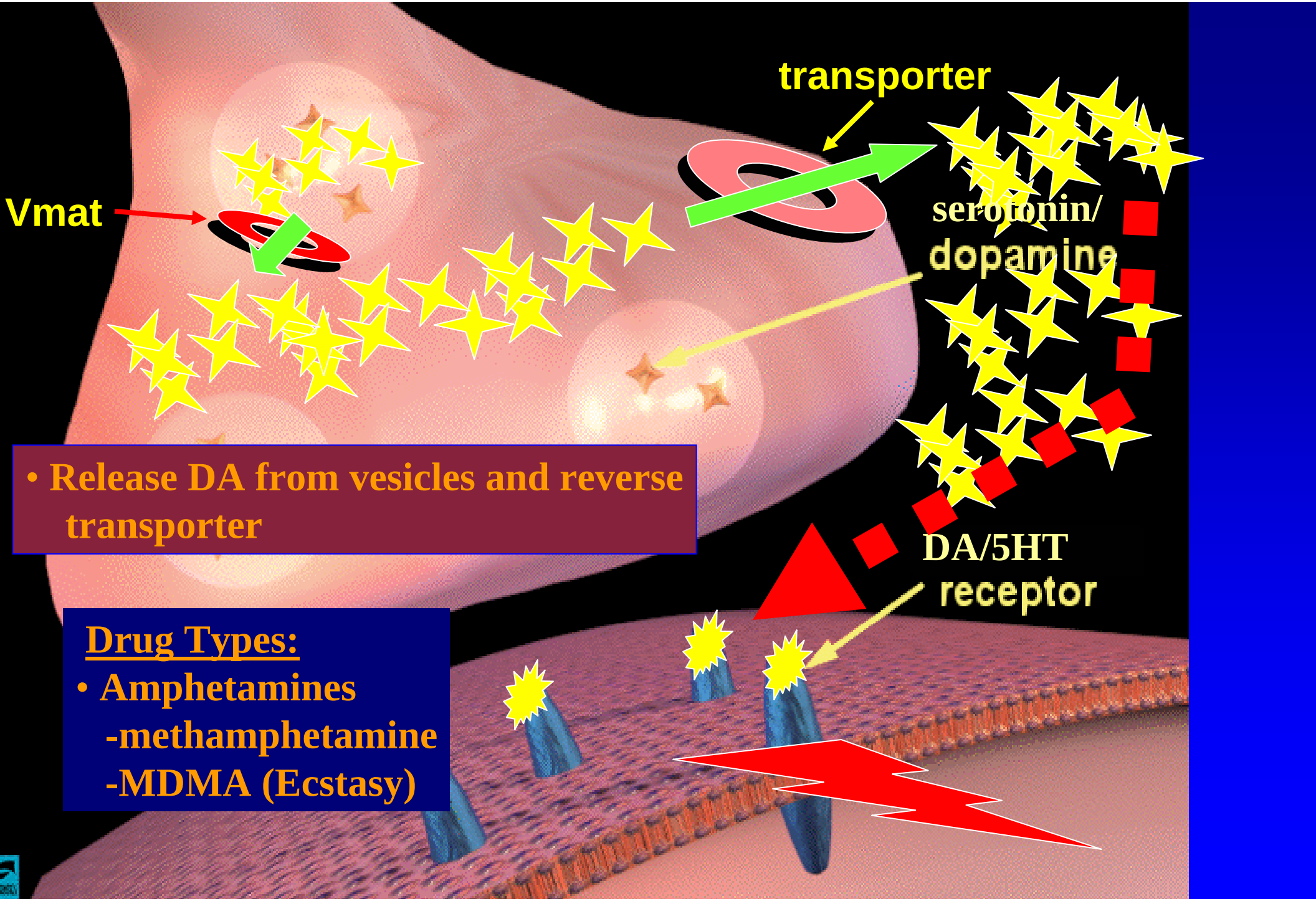
Functions
- reward (motivation)
- pleasure, euphoria
- motor function (fine tuning)
- compulsion
- perseveration

Functions
- mood
- memory processing
- sleep
- cognition


dendrite
soma
terminal
axon


precursor
synthesis
storage
degradation
reuptake
release


Action potential
transporter
Vmat
dopamine /serotonin
DA/5HT receptor



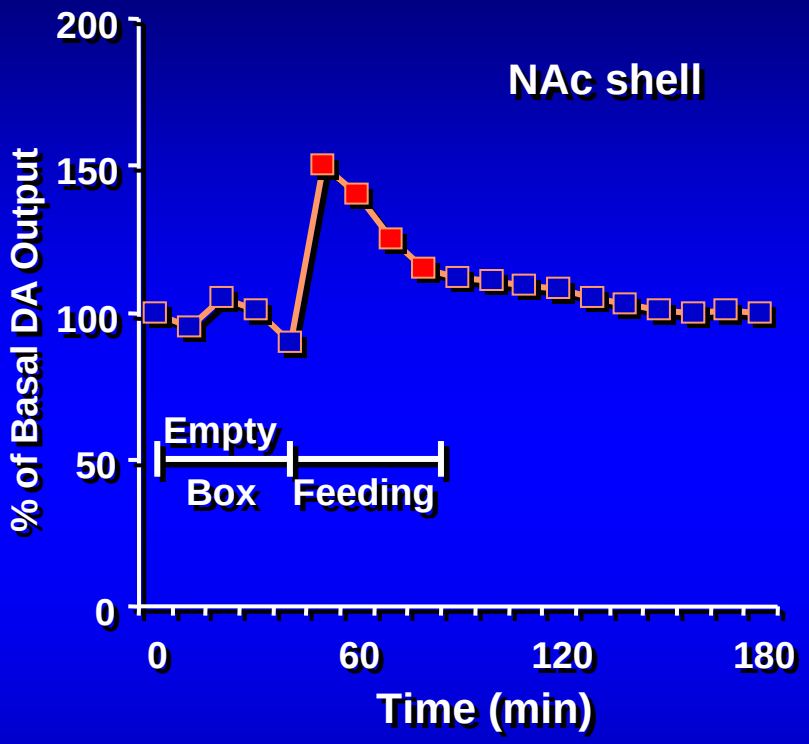
- Release DA from vesicles and reverse transporter

Drug Types:

- Amphetamines
  - -methamphetamine
  - -MDMA (Ecstasy)

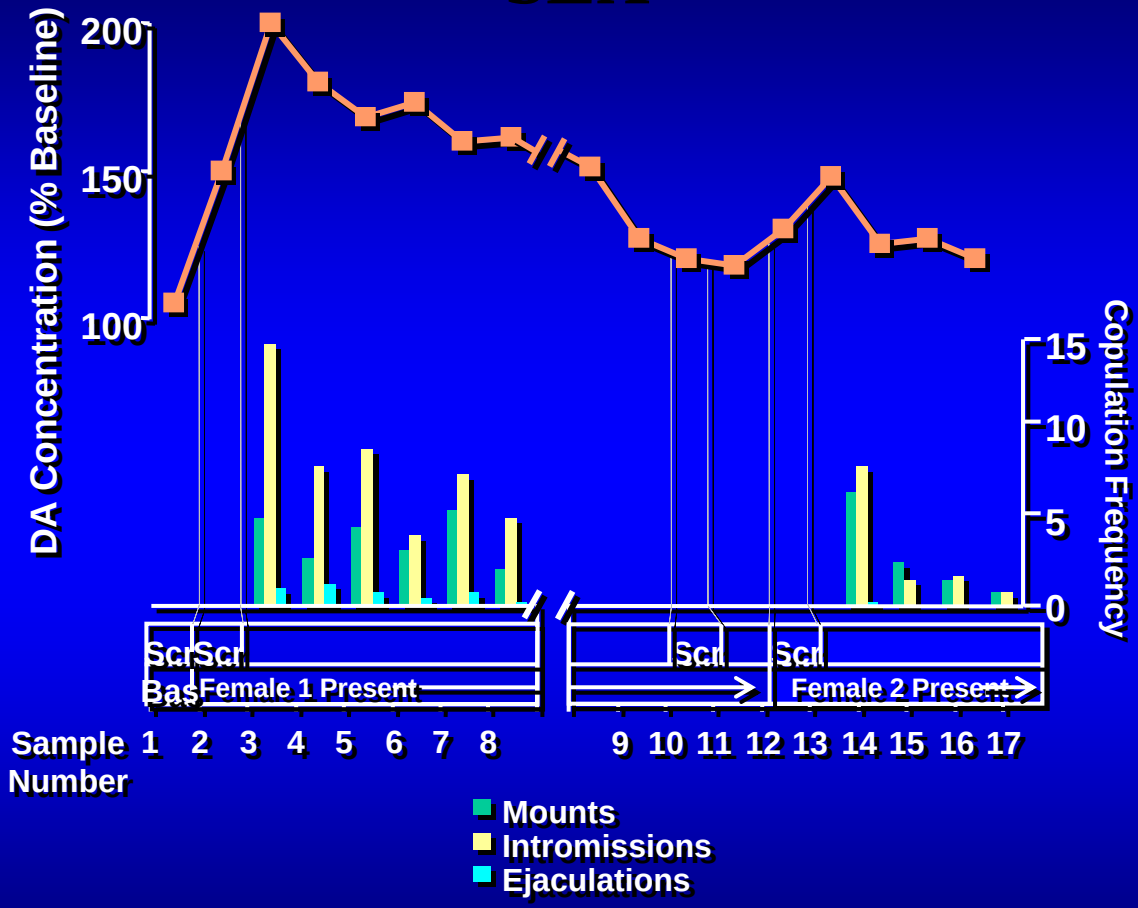
Natural Rewards Elevate Dopamine Levels

FOOD



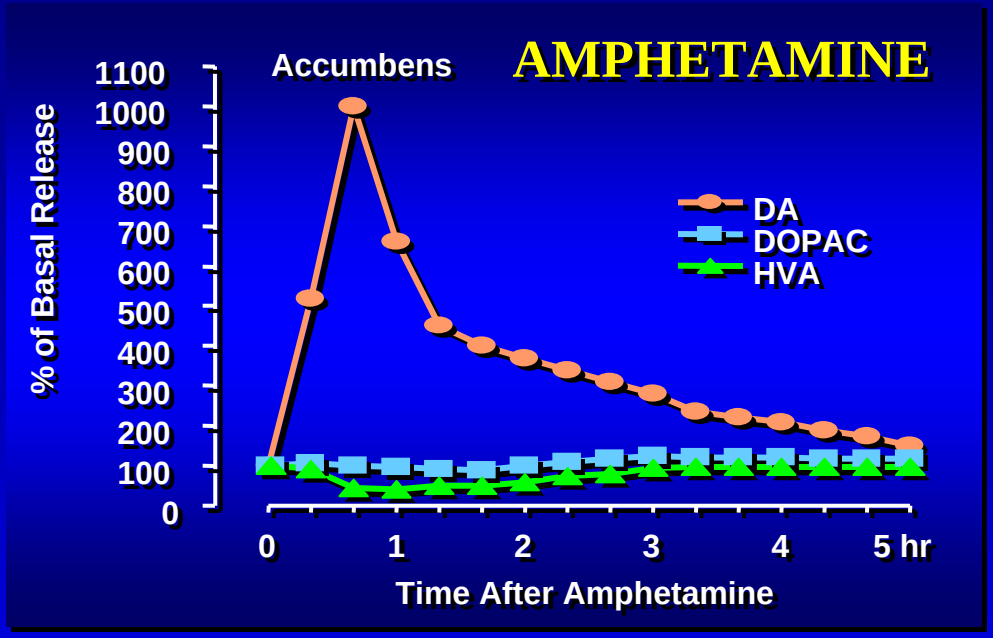
Source: Di Chiara et al.

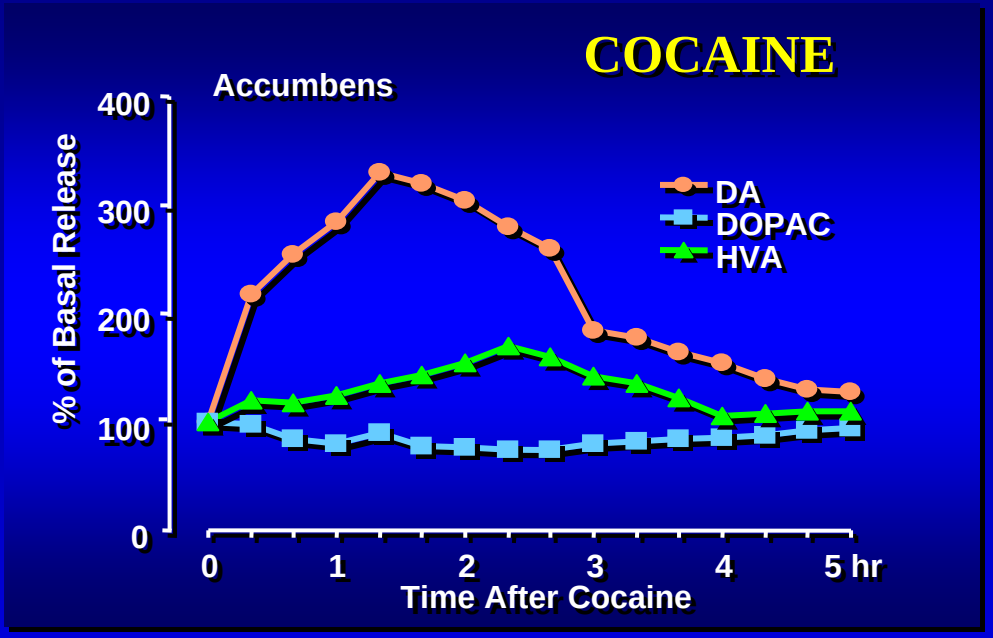
SEX

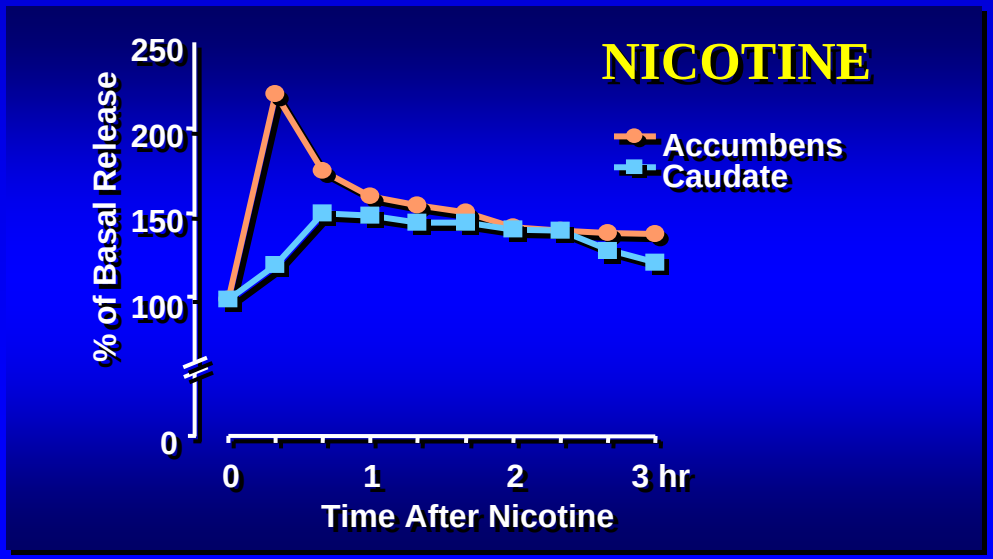


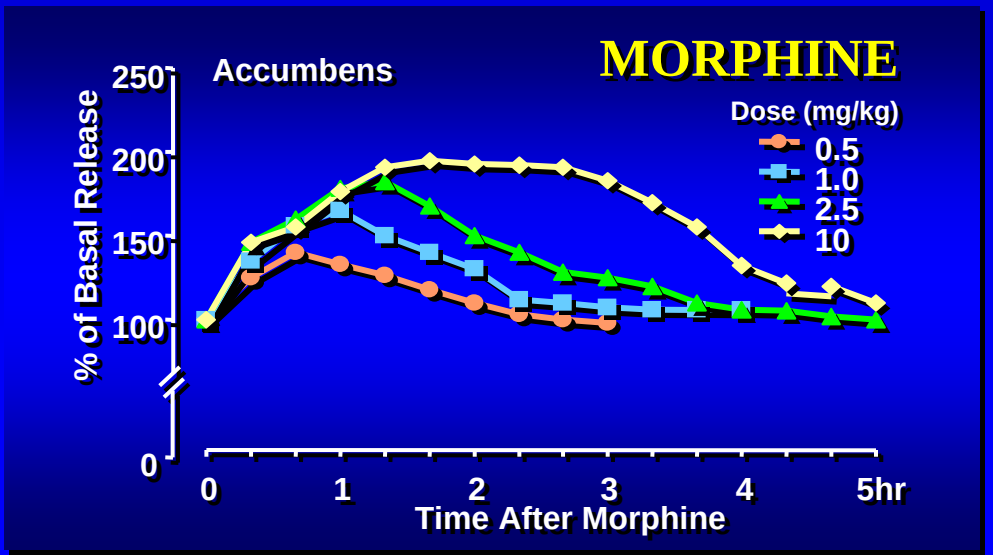
Source: Fiorino and Phillips

Effects of Drugs on Dopamine Levels





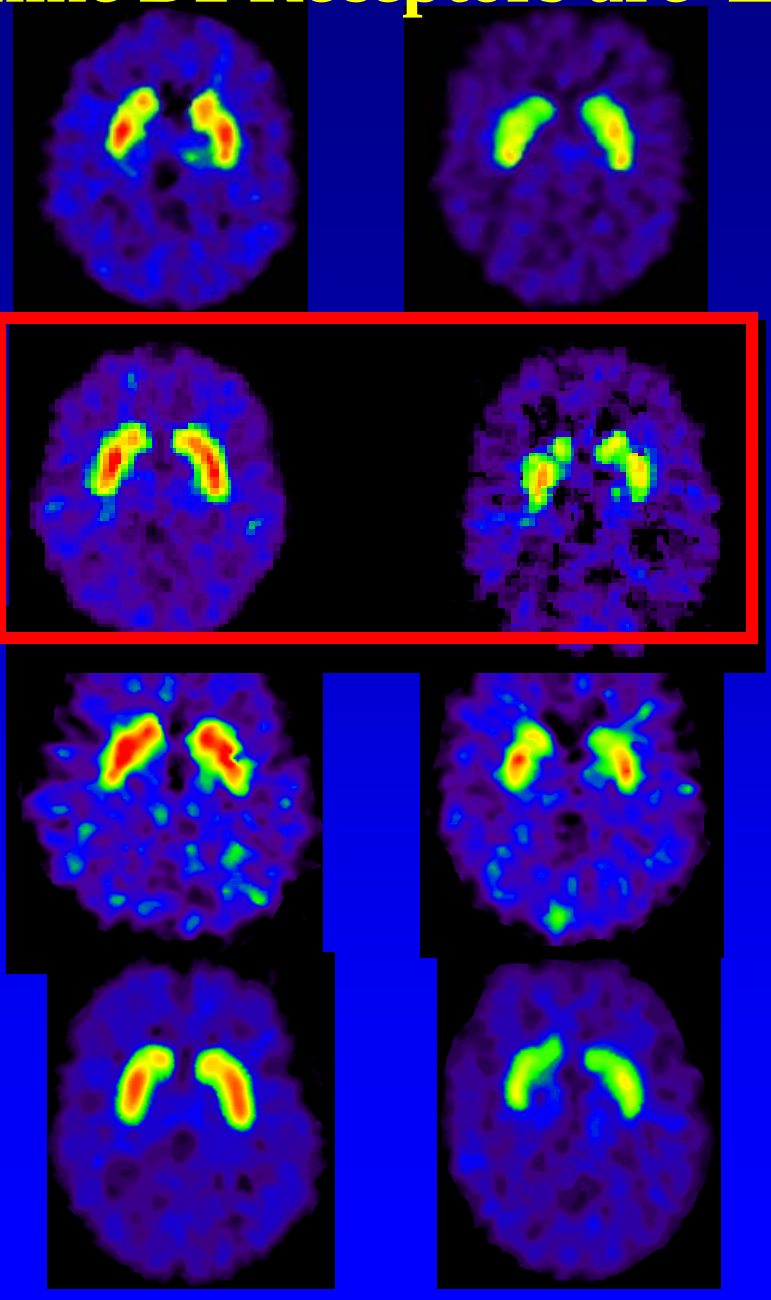




Source: Di Chiara and Imperato

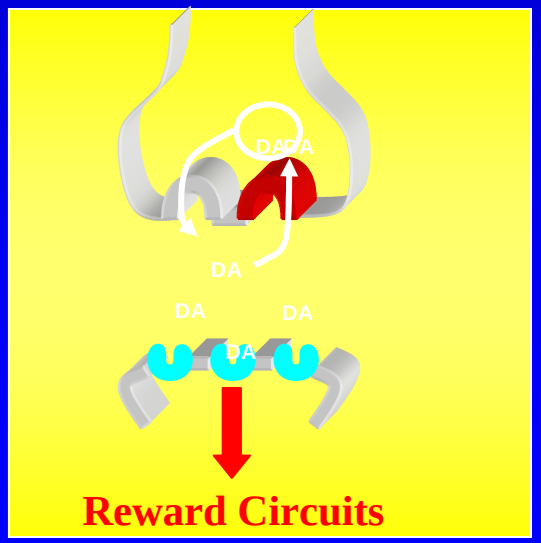
Chronic methamphetamine abuse has long lasting effects on the brain….

Dopamine D2 Receptors are Lower in Addiction

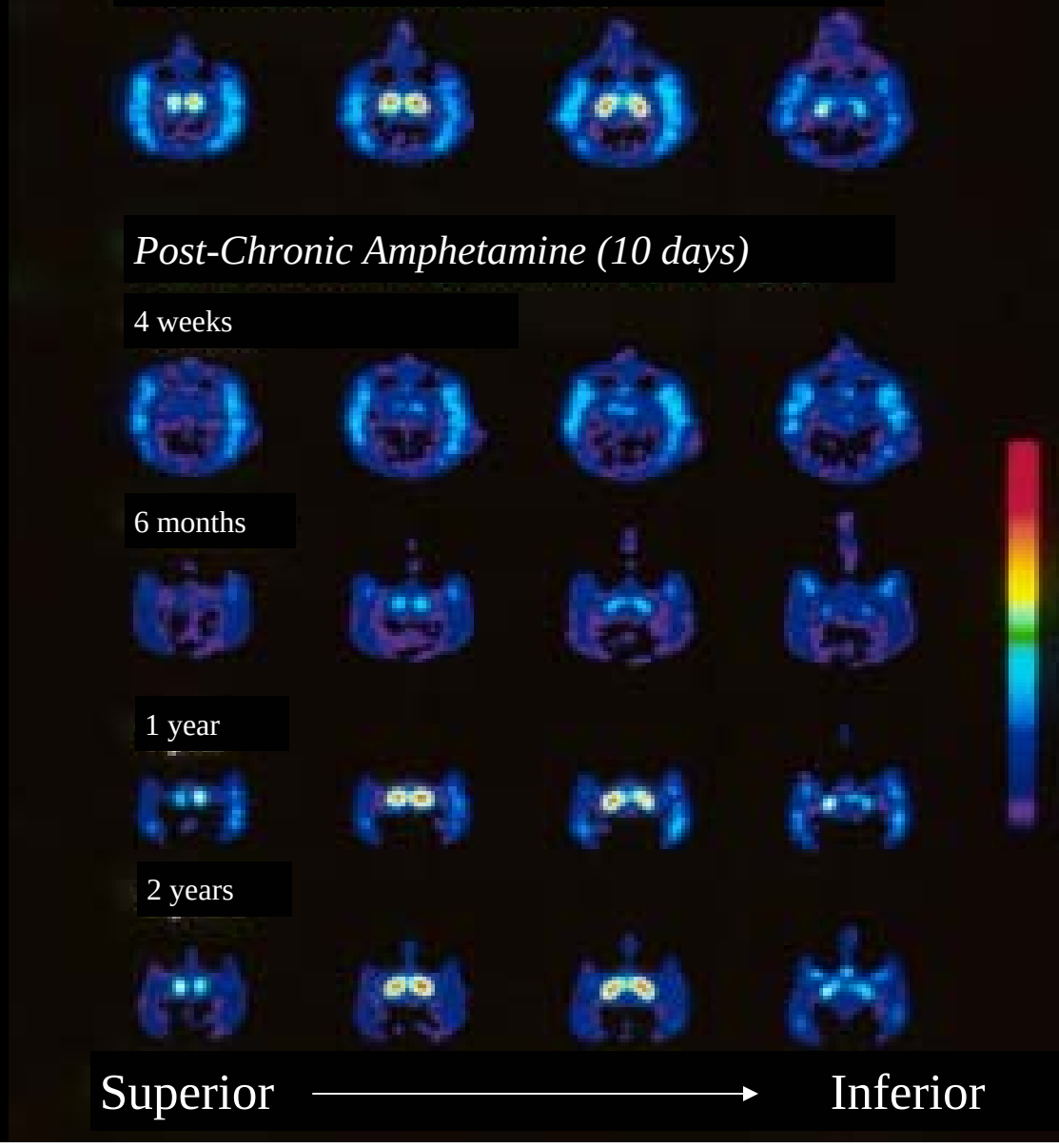


DA D2 Receptor Availability

Non-Drug Abuser



Striatal FDOPA Activity

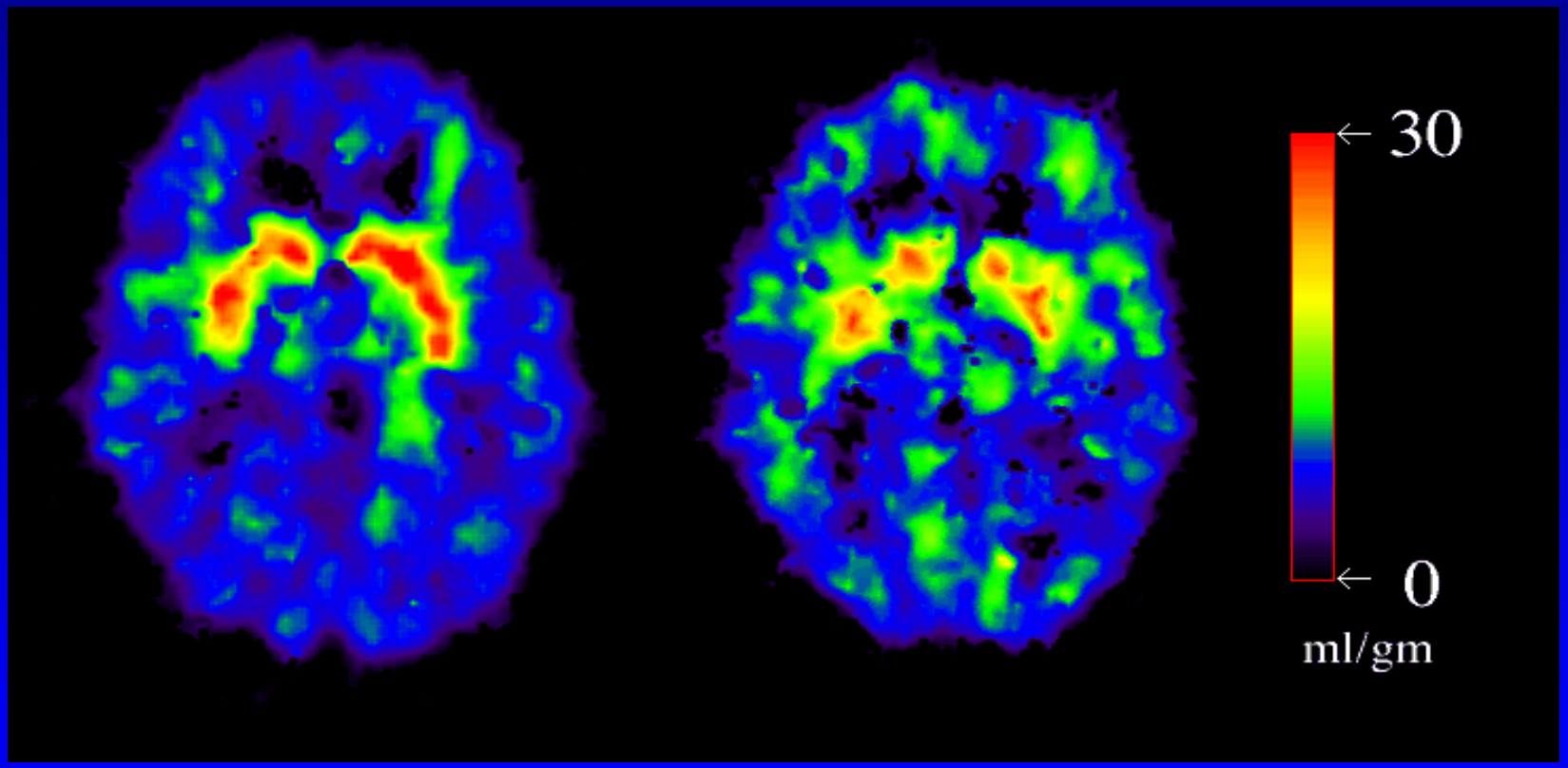


METH can be toxic to brain DA cells in laboratory animals.

It is therefore important to determine if METH induces similar changes in DA cells in humans and to assess their functional significance and degree of recovery

METHAMPHETAMINE

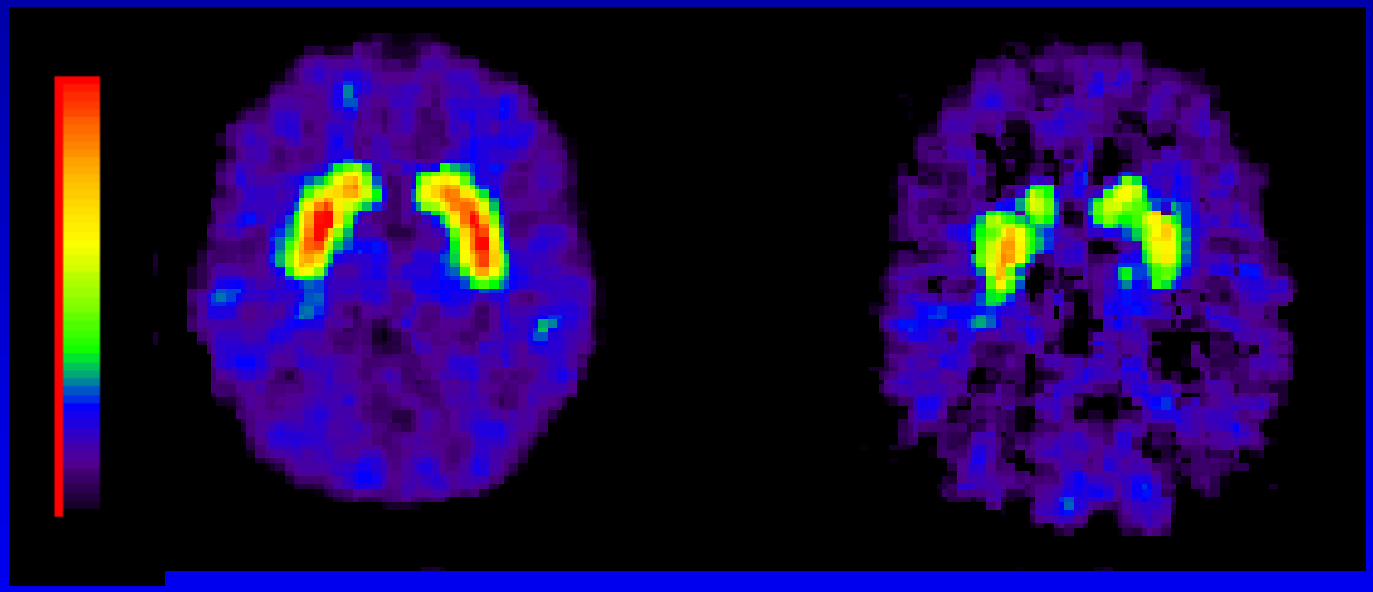
Dopamine Transporter Loss After Heavy Methamphetamine Use

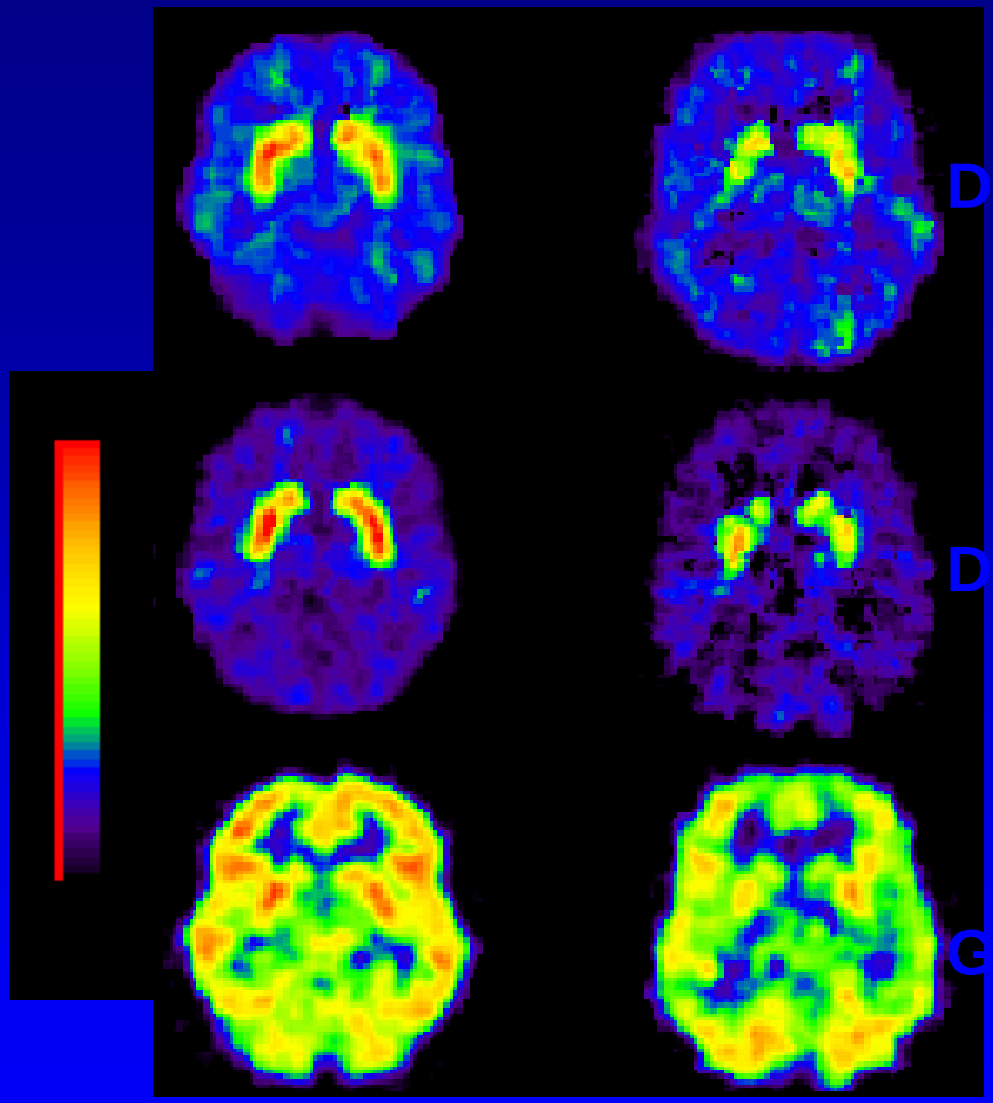


Comparison Subject **METH Abuser**

Source: Volkow, N.D. et al., Am J. Psychiatry, 158(3), pp. 377-382, 2001.

Methamphetamine Decreases Dopamine Receptors In the Human Brain



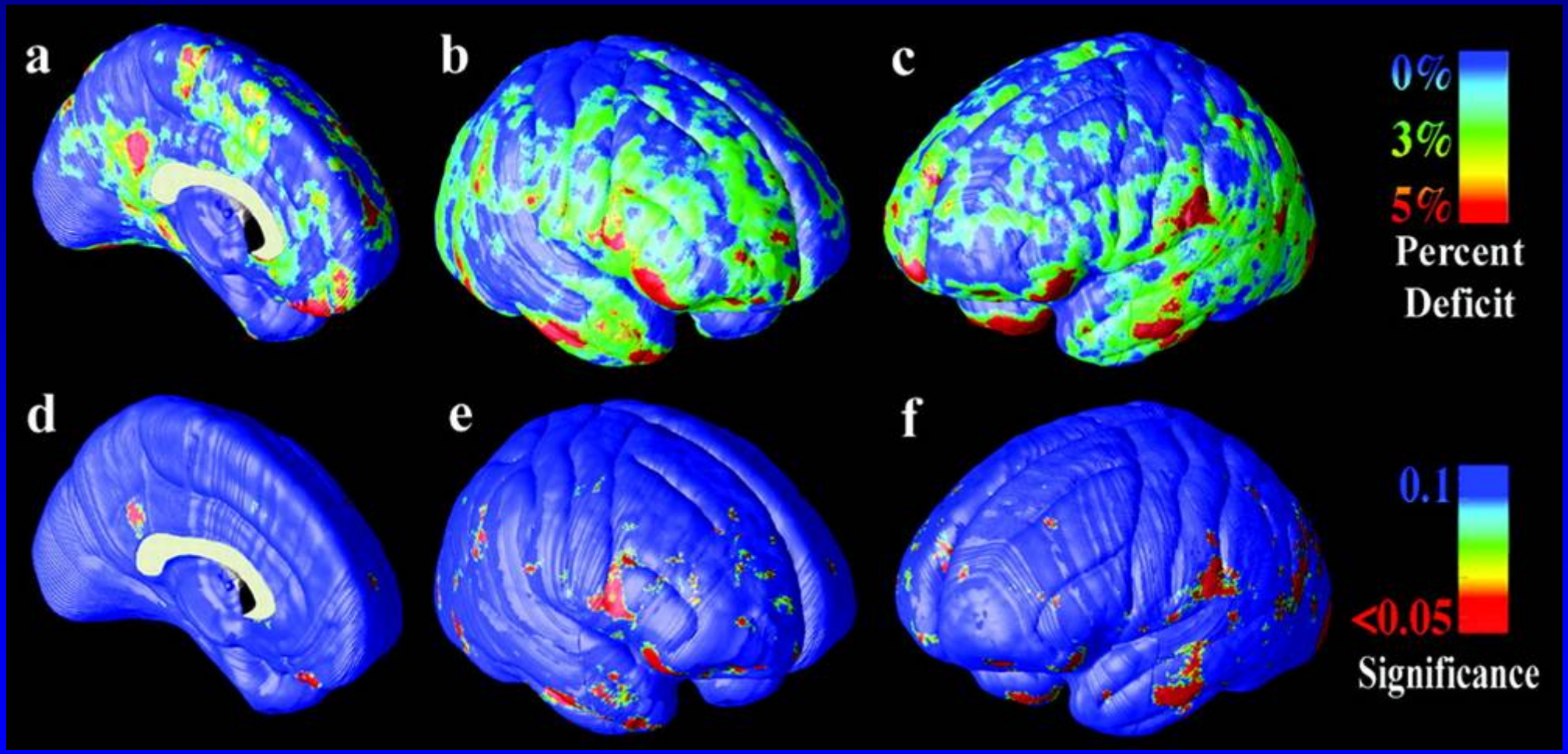


Dopamine Transporters
([^{11}C]d-*threo*-MP)

Dopamine Receptors
([^{11}C]raclopride)

Glucose Metabolism
([^{18}F]FDG)

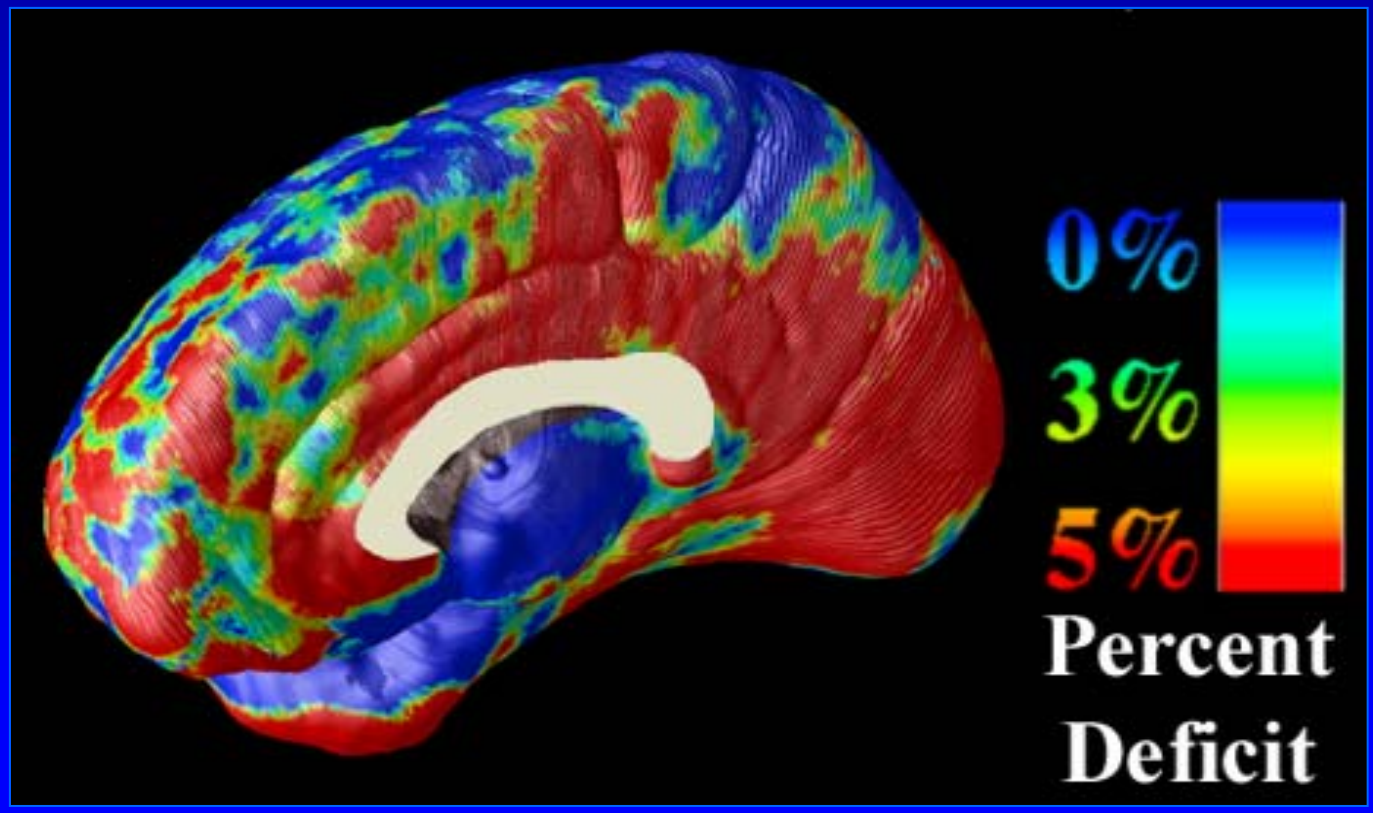
Gray Matter Reductions in Methamphetamine Users



Source: Thompson PM et al., Journal of Neuroscience, 24(26), pp. 6028-6036, June 30, 2004.

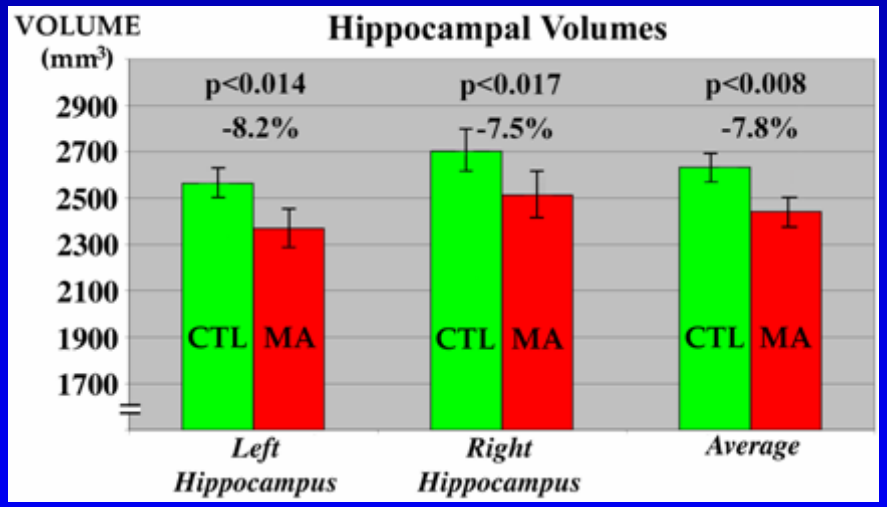
Infralimbic Cortex Even Has Structural Deficits

Methamphetamine users show Gray Matter Loss



Thompson PM et al. (2004): *J. Neurosci.* 24:6028.

Methamphetamine Abusers have Hippocampal Volume Deficits



Thompson PM *et al*. (2004): *J. Neurosci.* 24:6028.

Implication:

Brain changes resulting from prolonged use of psychostimulants, such as methamphetamine may be reflected in compromised emotional, cognitive, and motor functioning

Subjects

Detoxification in METH abusers – Control

	Early (n = 12)	Late* (n = 13)	Sı Controls @ (n = 21)
Age range (years)	21 - 47	26 - 38	21 - 43
Age mean (years)	32 ± 8	33 ± 5	32 ± 8
Gender	7 F, 5 M	9 F, 4 M	6 F, 15 M
Years of METH use (range)	2 - 20	2 - 20	0
Years of METH use (mean)	11 ± 7	12 ± 6	0
Amount of METH use (g/day)	3 ± 5	3 ± 4	0
Last day of METH use (range in months)	0.5 - 6	6 - 36	0
Last day of METH use (mean in months)	2.1 ± 1.4	14 ± 7	0

Subjects

METH Abusers:

Inclusion Criteria:

DSM IV criteria for METH-dependence

METH use of at least: 0.5 g/day, 5 days a week and 2 years

2 weeks or more of abstinence

Exclusion criteria:

seropositive for HIV,

co-morbid psychiatric illness and/or neurological disease,

drug-dependence other than METH and nicotine.

Controls:

Methods

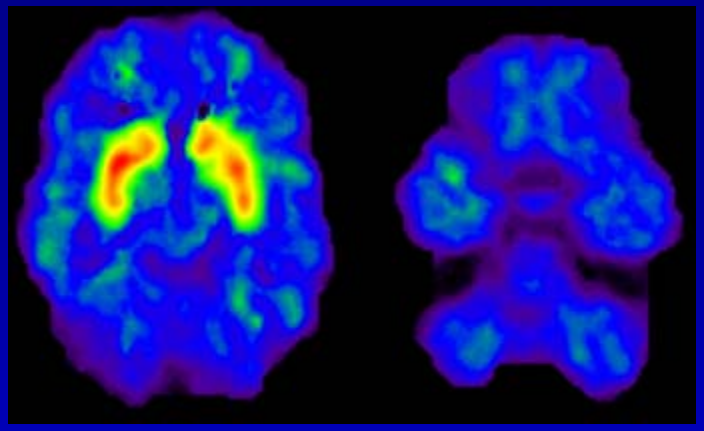
Scanner : CTI 931 (15 slices, 6x6x6.5 mm FWHM).

Tracers: **DAT**: 4-8 mCi of [^{11}C]*d-threo*-methylphenidate
Dynamic scans obtained for a total of 84 min.
Metabolism: 4-8 mCi of FDG.
Twenty min emission scan started 35 after injection

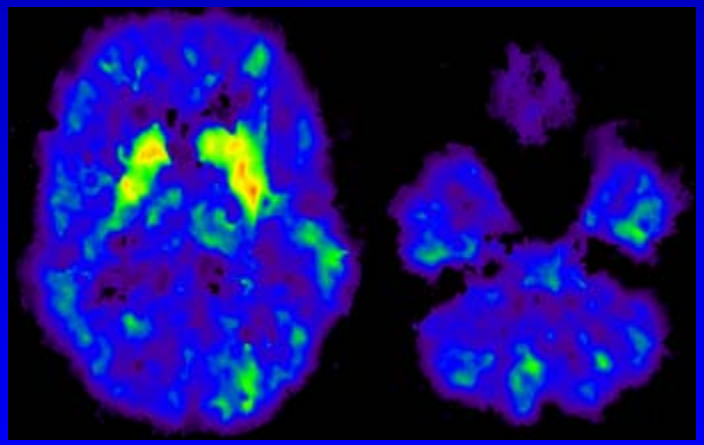
Model: **DAT:** The ratio of DV in striatum to that of DV in CB corresponds to (Bmax/Kd) +1 and was used as model parameter of DAT availability.

Metabolism: Patlak graphical

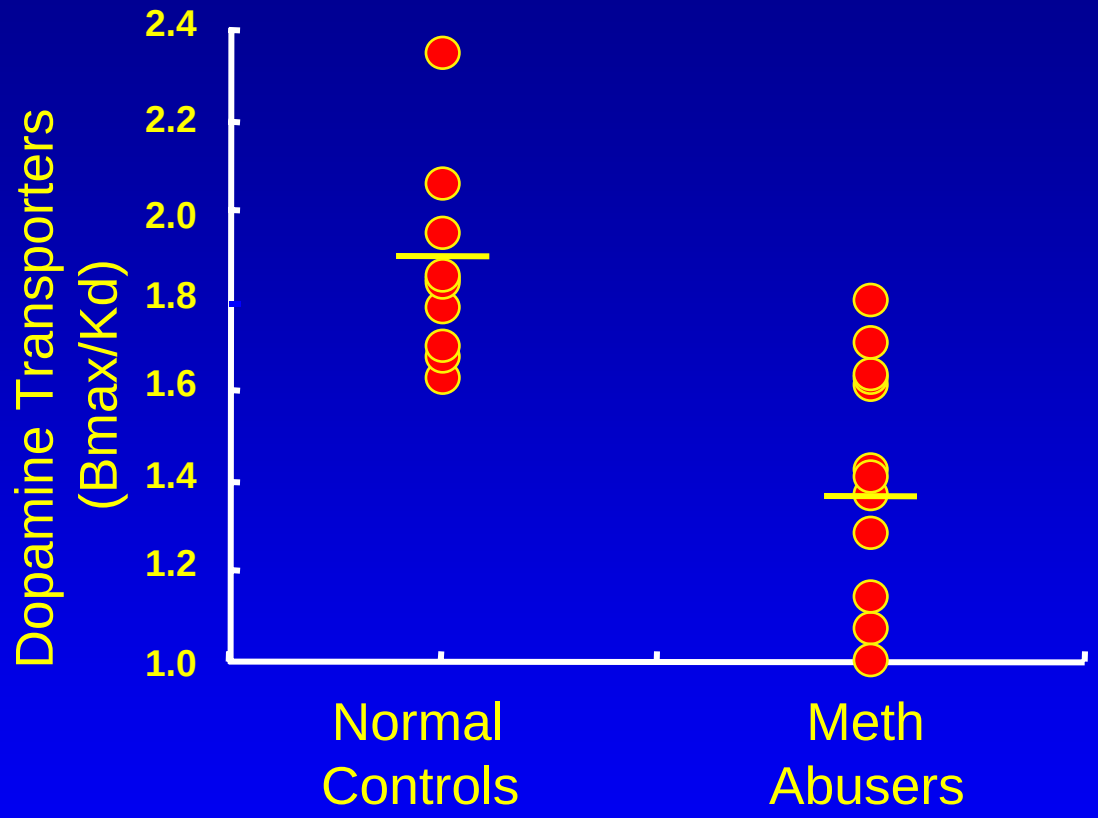
Dopamine Transporters in Methamphetamine Abusers



Normal Control



Methamphetamine Abuser

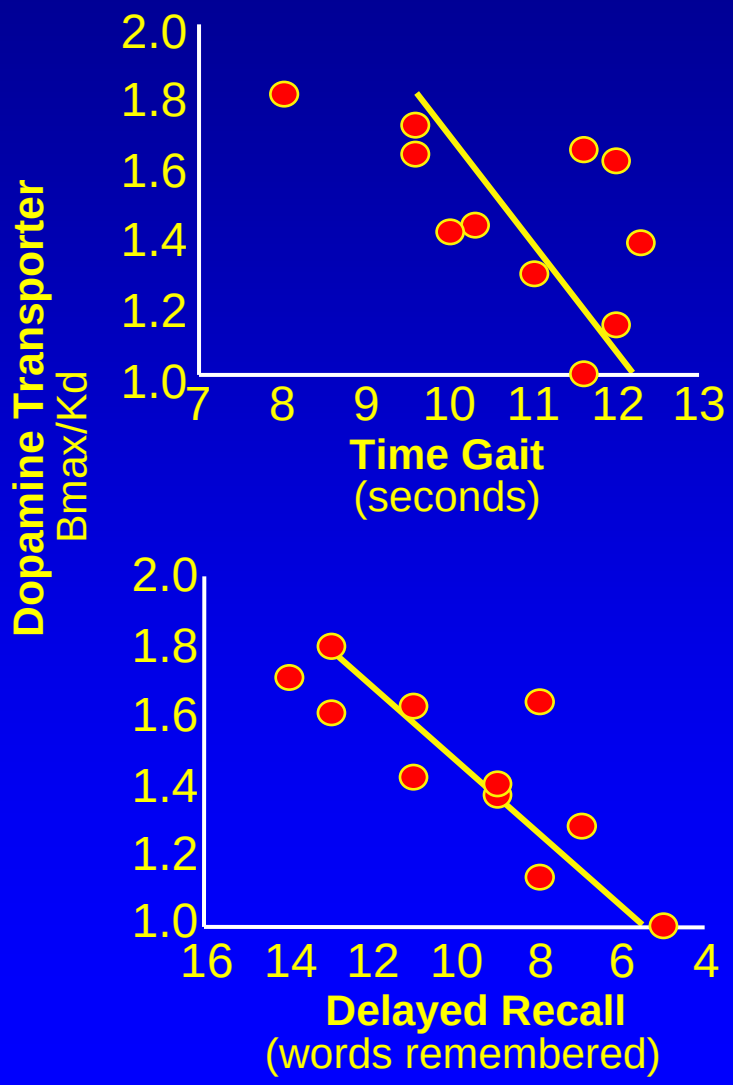


$p < 0.0002$

Methamphetamine abusers have significant reductions in dopamine transporters.

BNL - UCLA - SUNY
NIDA - ONDCP - DOE

Dopamine Transporters in Methamphetamine Abusers



Motor Task

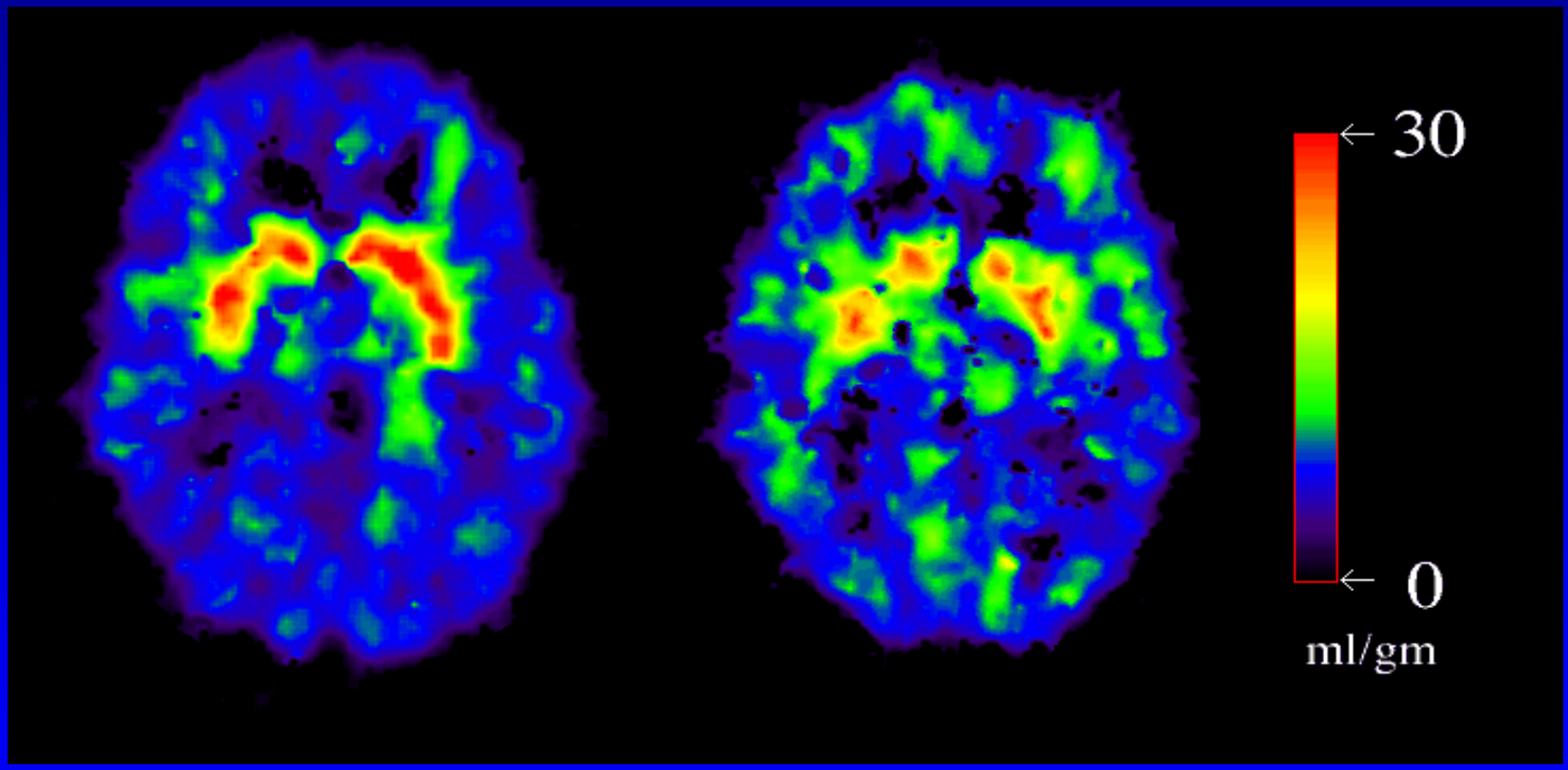
Loss of dopamine transporters in the meth abusers may result in slowing of motor reactions.

Memory Task

Loss of dopamine transporters in the meth abusers may result in memory impairment.

BNL/UCLA/SUNY
NIDA, ONDCP, DOE

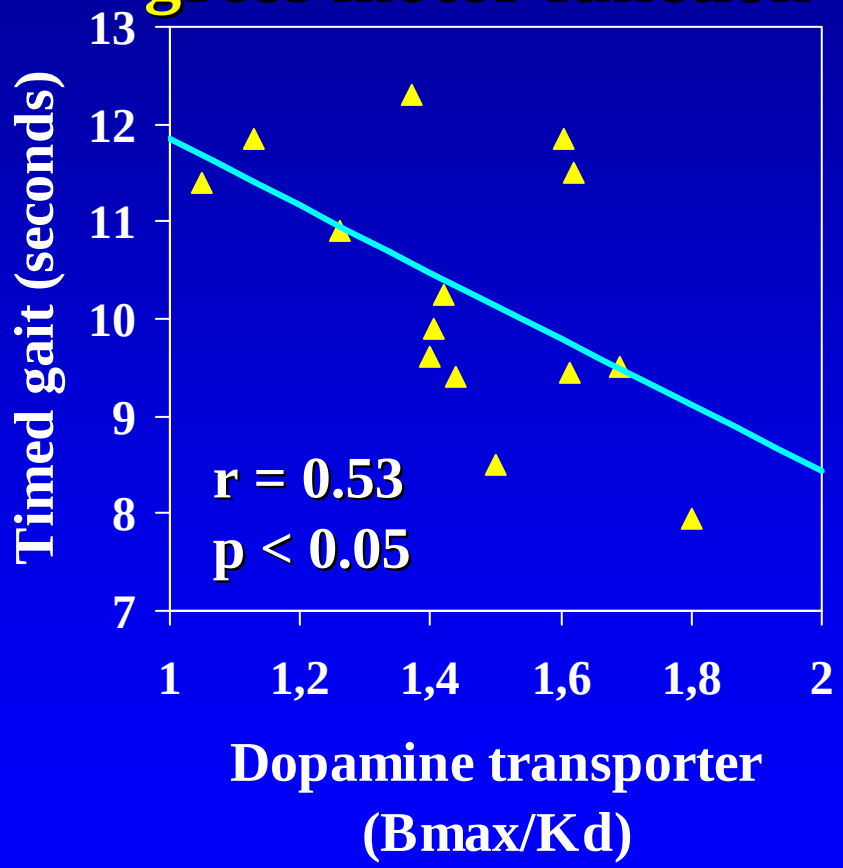
Dopamine Transporter Loss After Heavy Methamphetamine Use



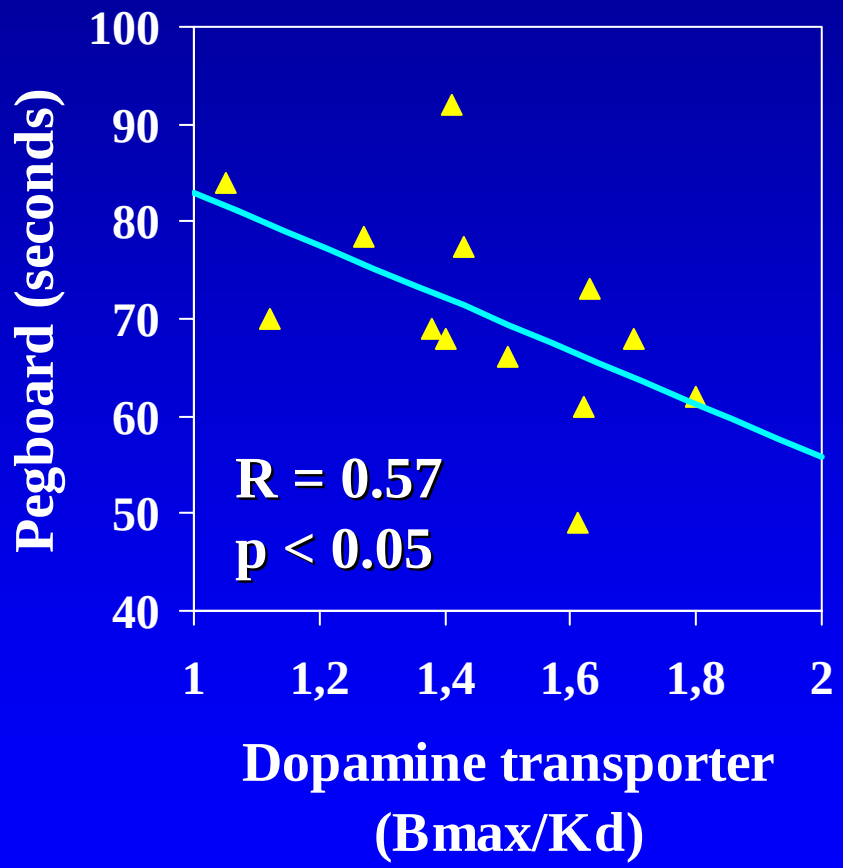
Source: Volkow, N.D. et al., Am J. Psychiatry, 158(3), pp. 377-382, 2001.

Dependence of Motor Speed on Striatal DAT

gross motor function



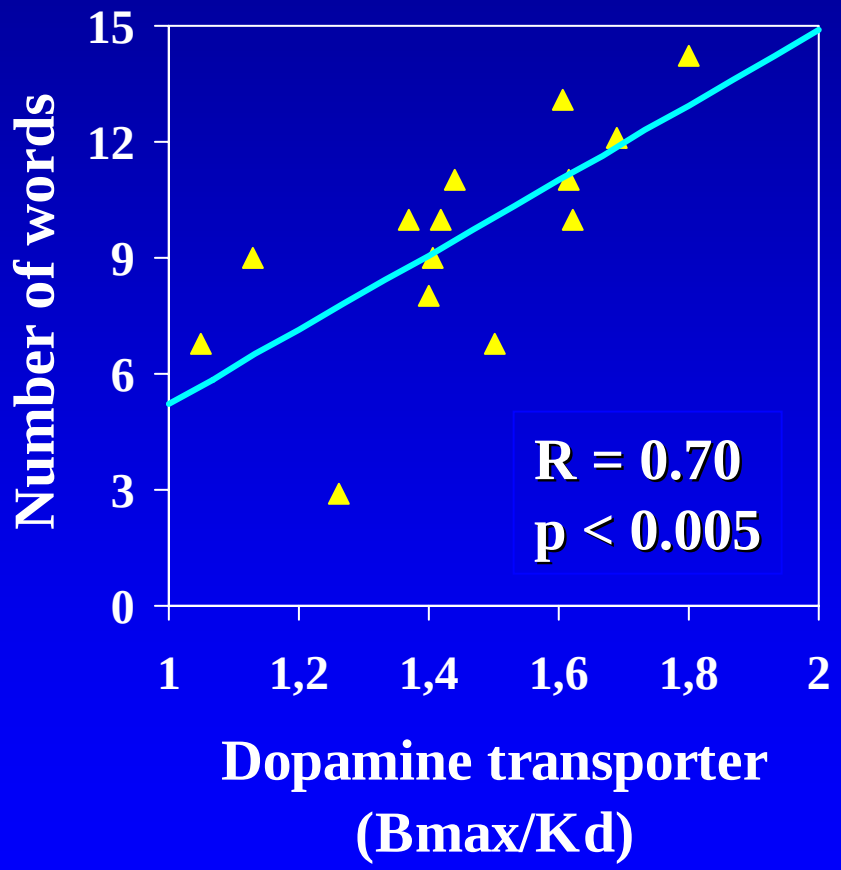
fine motor function



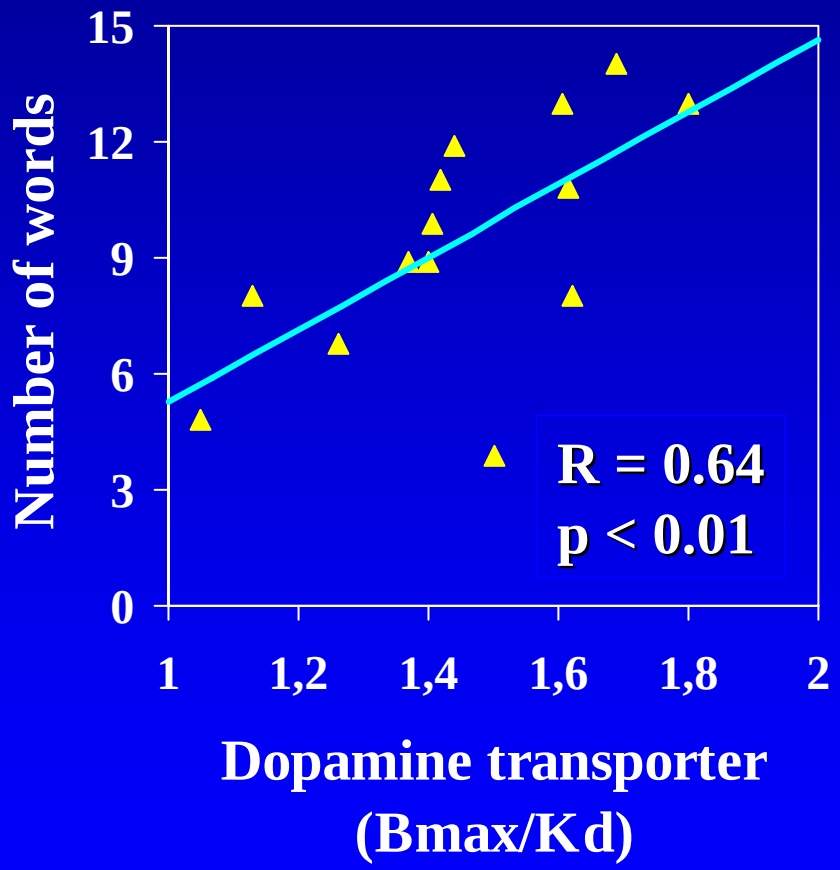
Volkow et al, AJP (in press)

Dependence of Verbal Memory on Striatal DAT

Interference recall



Delayed recall



Volkow et al, AJP (in press)

Summary

- Significant DAT loss in METH abusers tested at early detoxification that is larger in caudate than putamen.
- Decreases in DAT are associated with motor slowing and impaired memory
- [illegible]

Conclusion

- **DAT recovery with detoxification could reflect**
  - **Recovery of damaged terminals**
  - **Compensation by viable terminals**

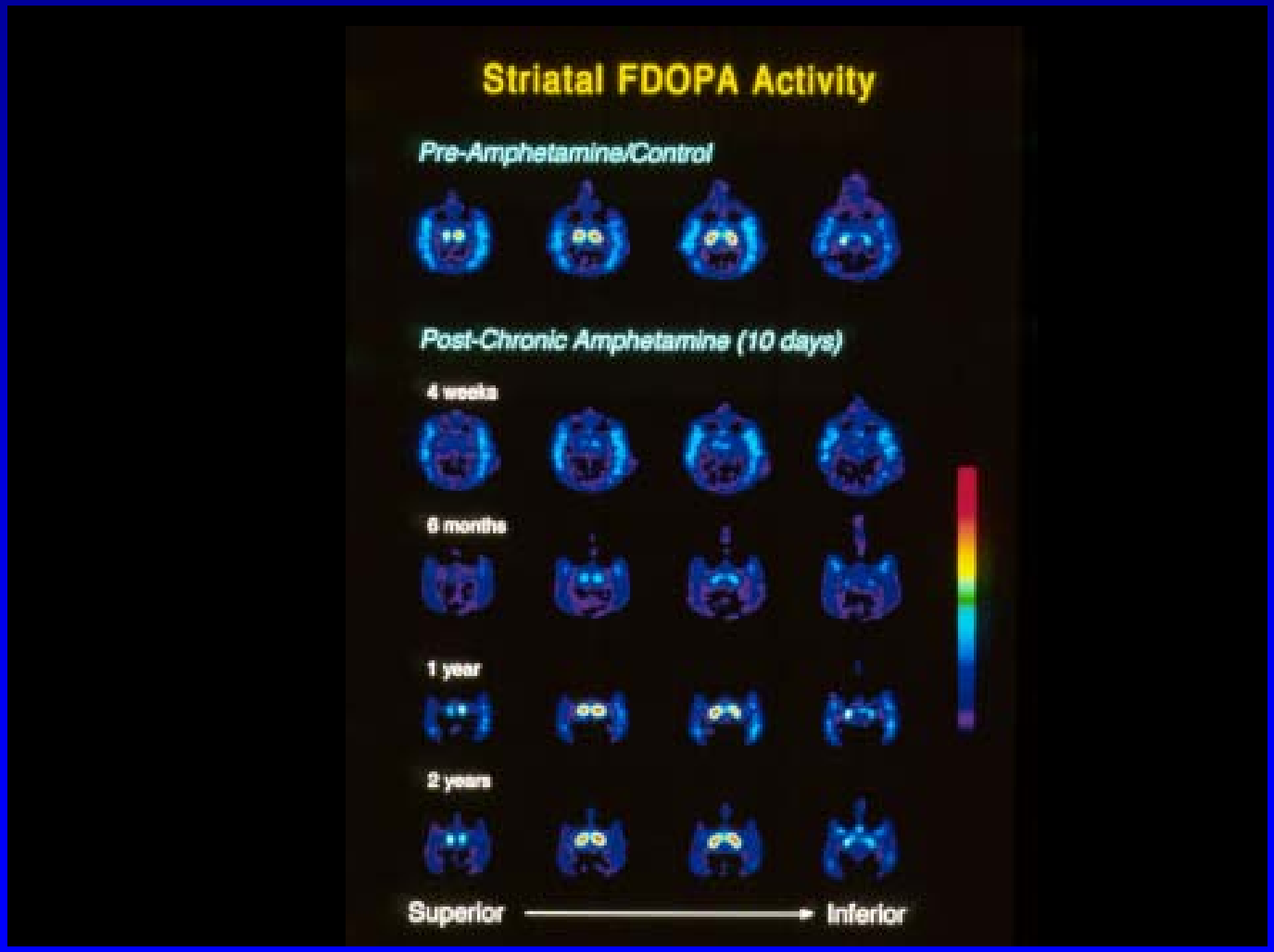
  or

  - **Decreases in expression of the DAT**
  - **Decreases DAT trafficking and internalization**

- ***DAT recovery while beneficial was insufficient for complete***

Recovery?
What do we know?

Chronic Amphetamine Causes Lasting Changes

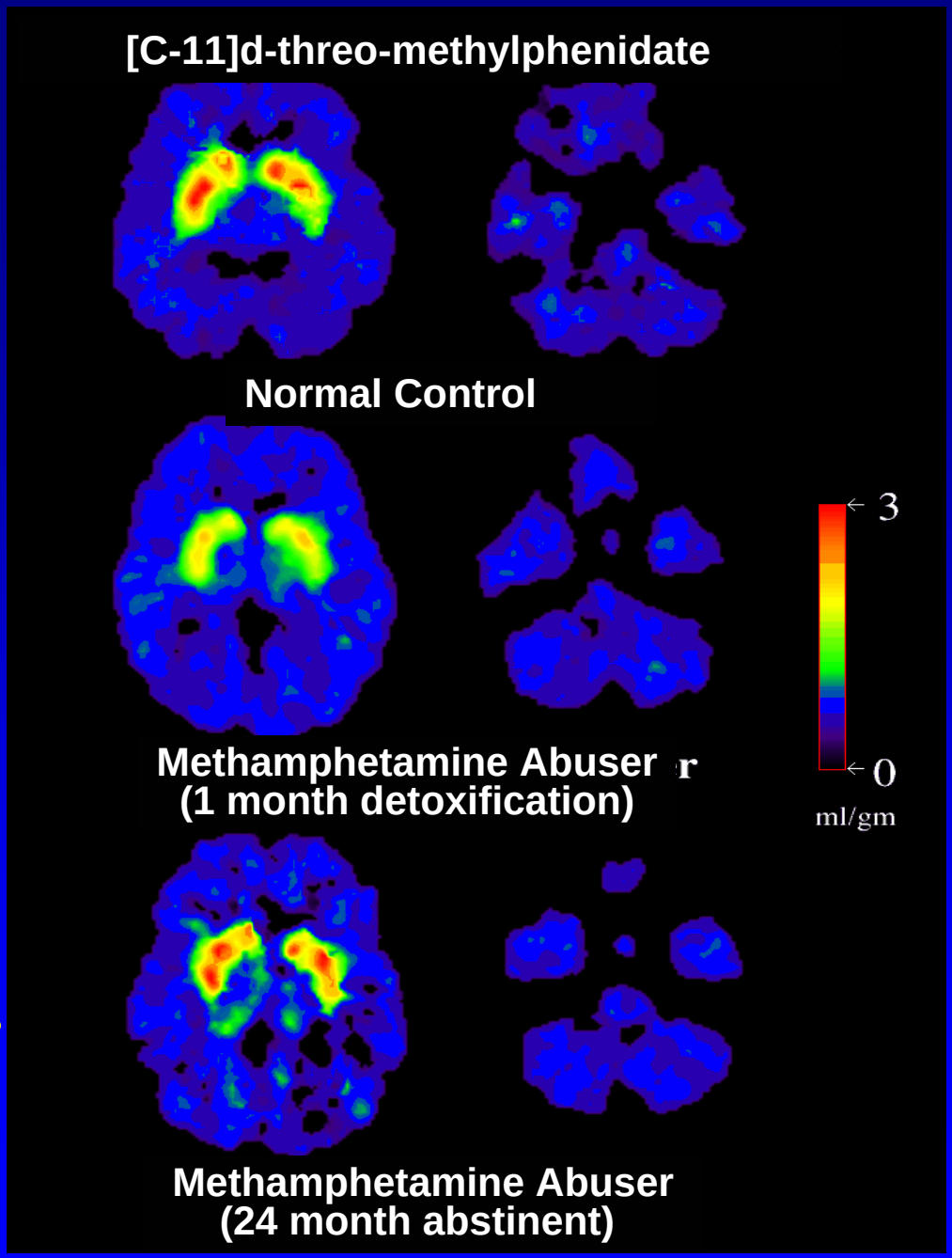


We Have Generated A Lot of Evidence Showing That…

Prolonged Use of Methamphetamine Can Change the Brain In Fundamental and Long-Lasting Ways

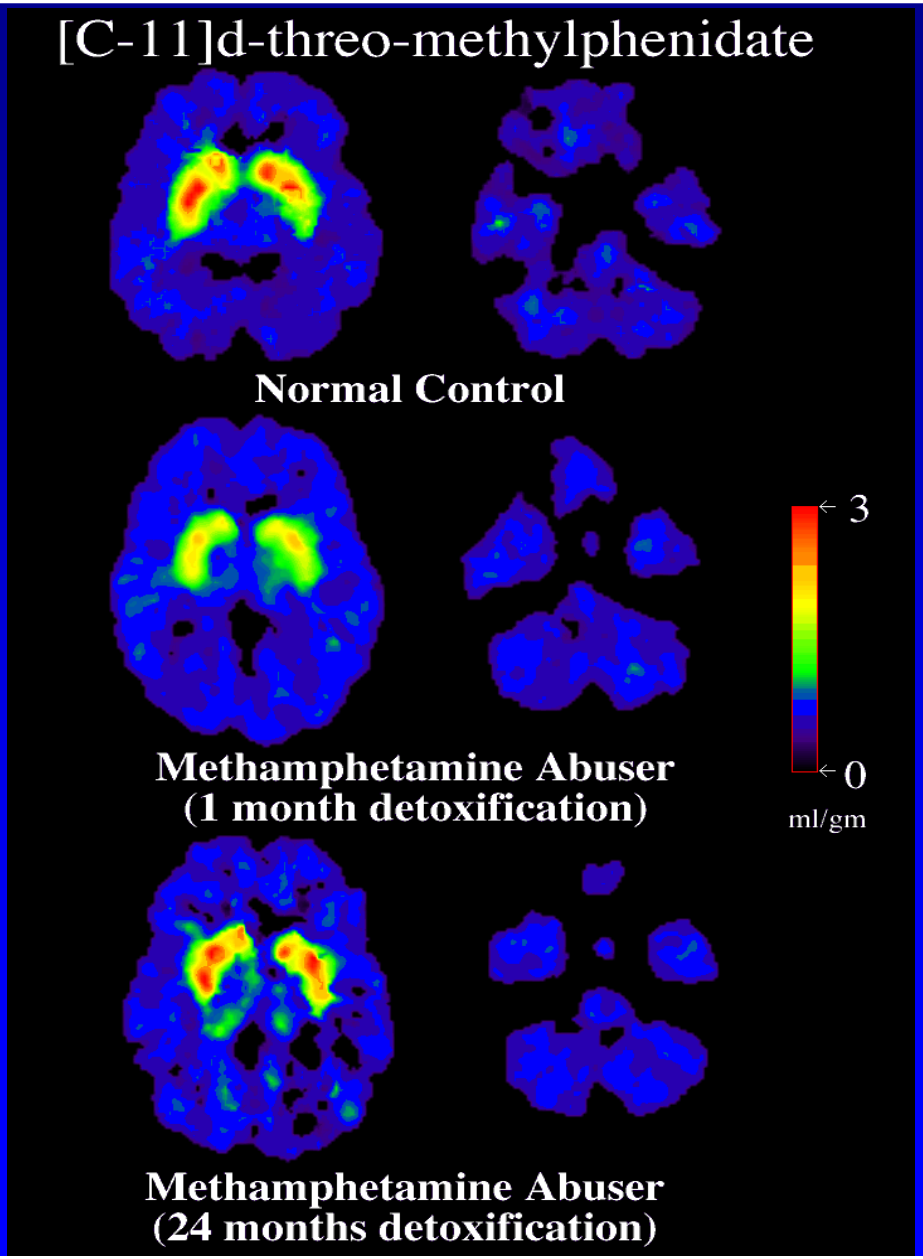
Is there recovery?

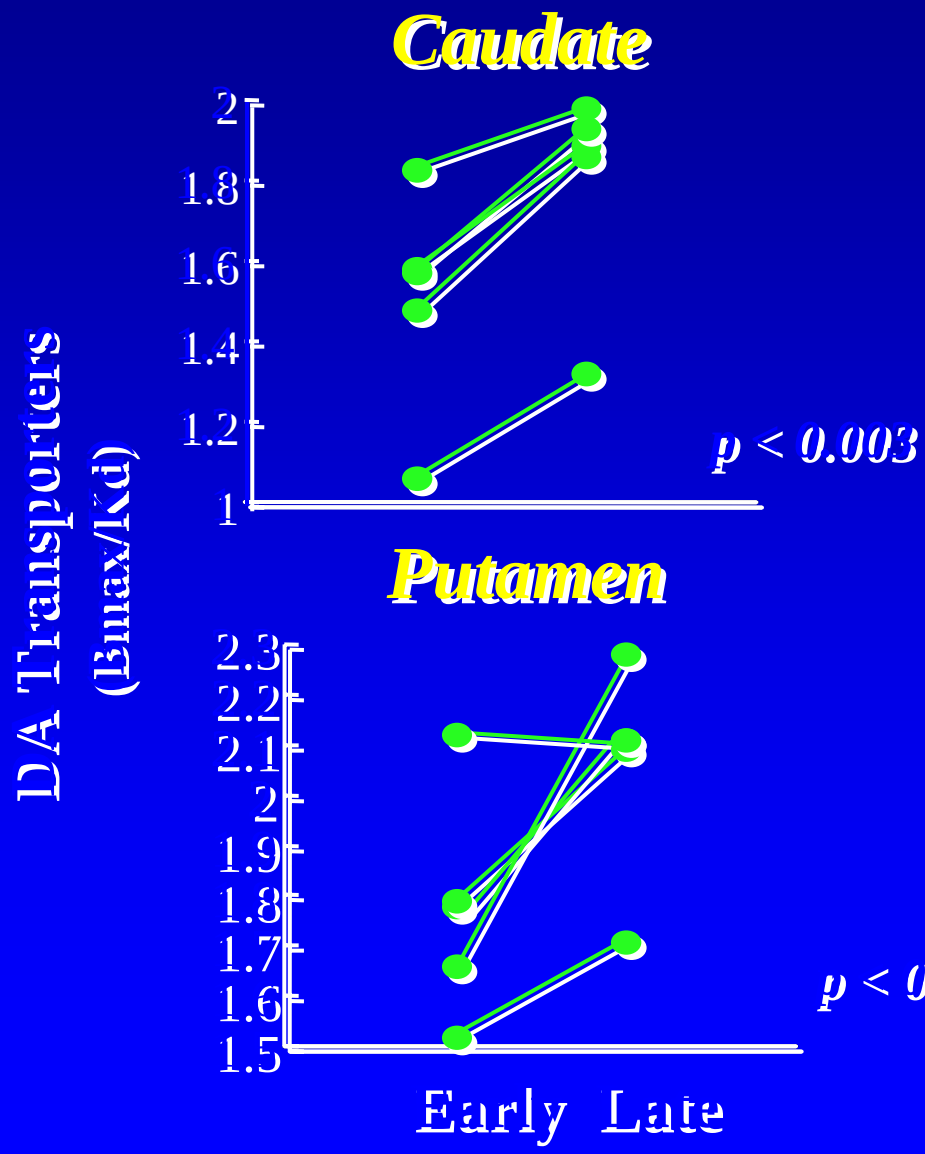
DAT Recovery with prolonged abstinence from methamphetamine



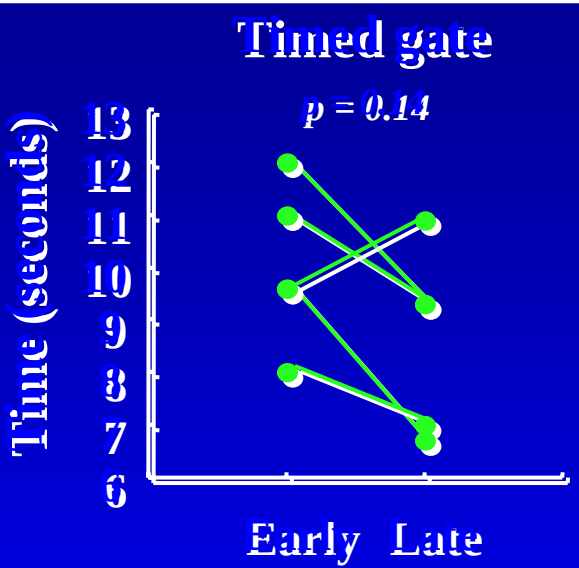
Source: Volkow, N.D. et al., Journal of Neuroscience, 21(23), pp. 9414-9418, December 1, 2001.

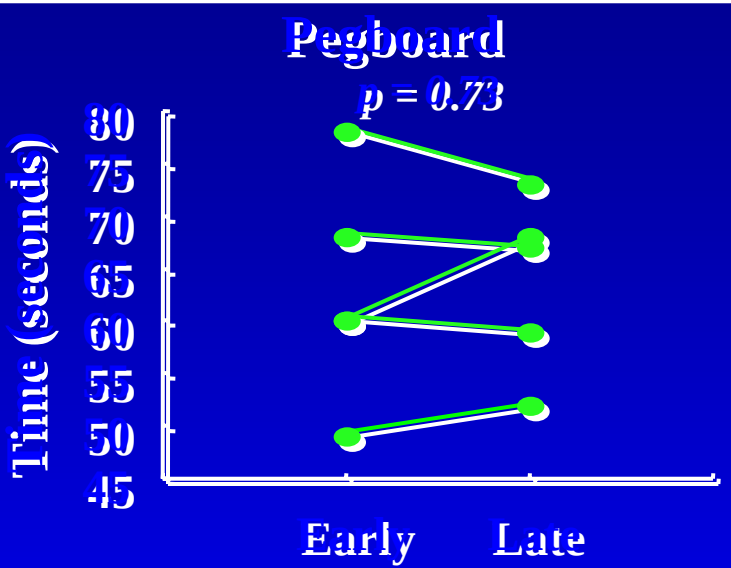
Effects of Detoxification on DAT



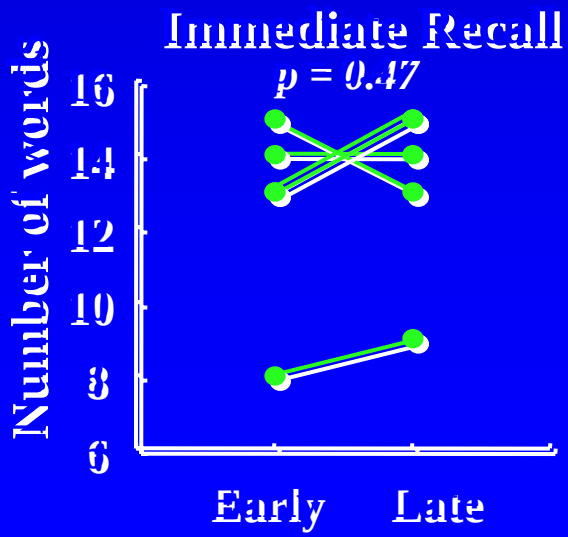


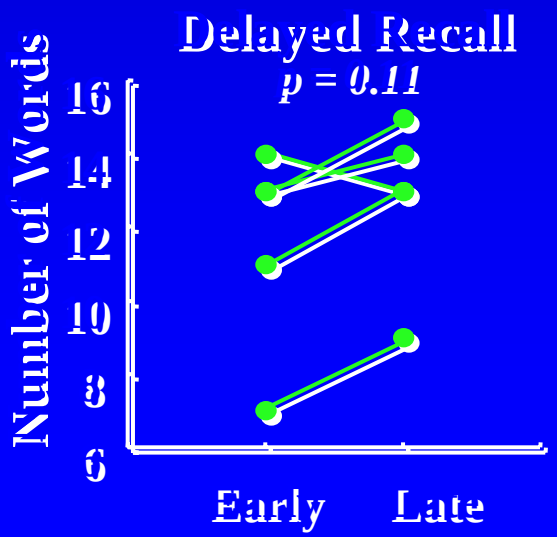
Neuropsychological Function in METH Abusers During Early and Late Detoxification





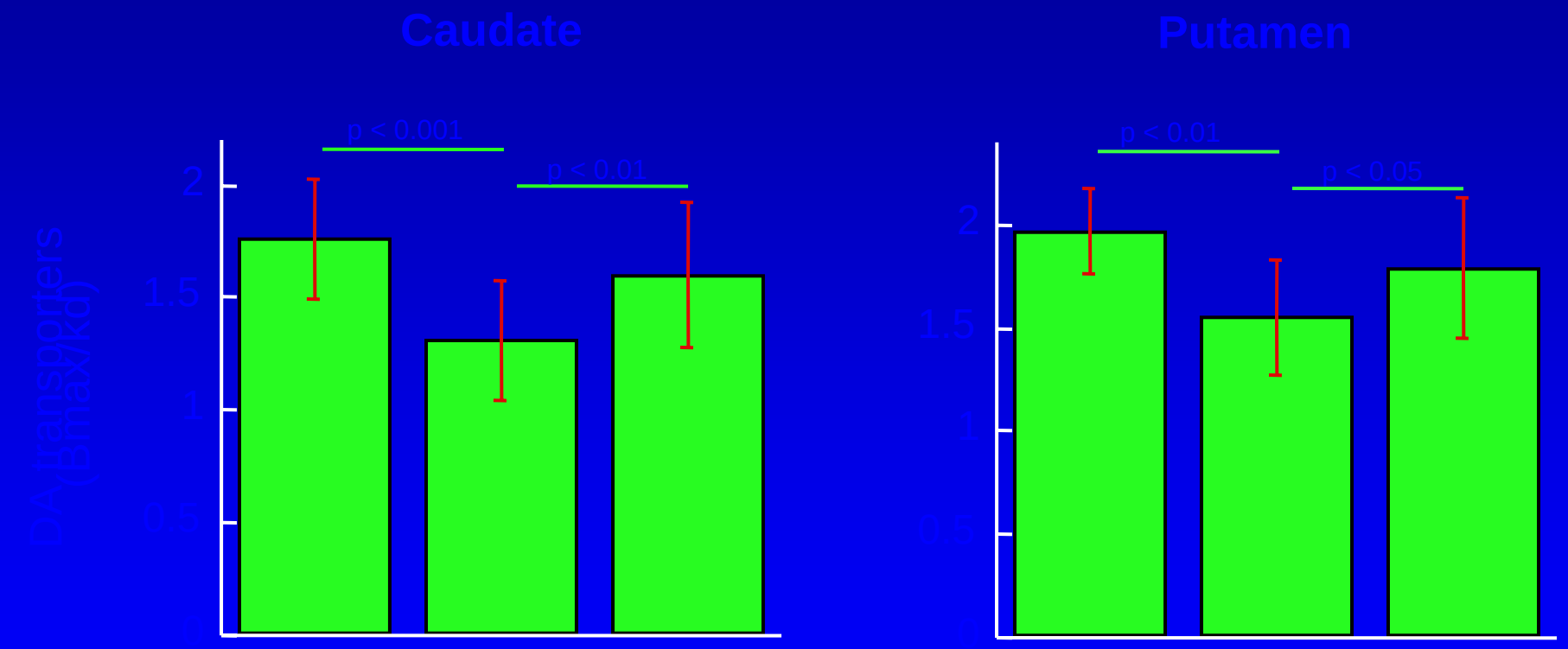
Motor



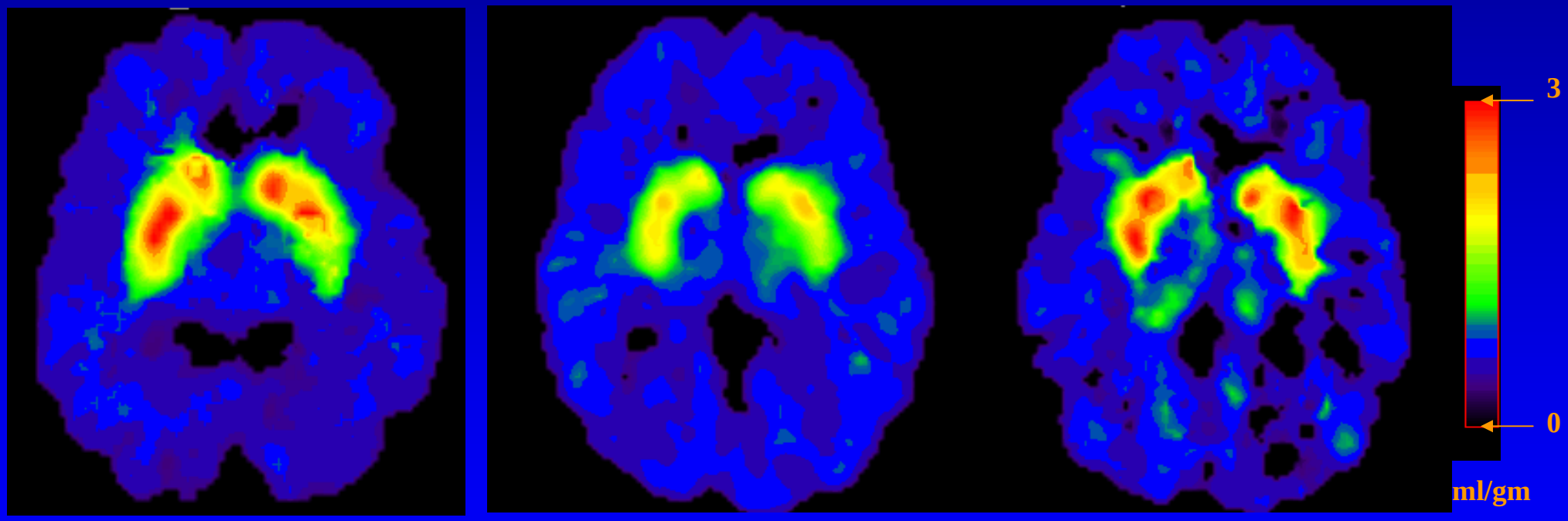


Memory

DAT in Methamphetamine Abusers Tested During Early or During Late Detoxification



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



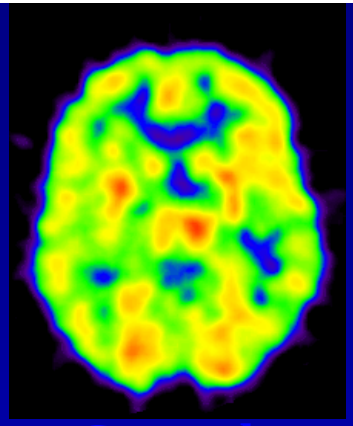
Normal Control

METH Abuser
(1 month detox)

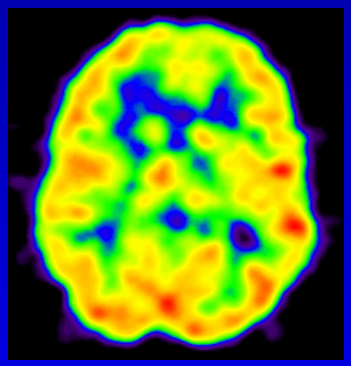
METH Abuser
(24 months detox)

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

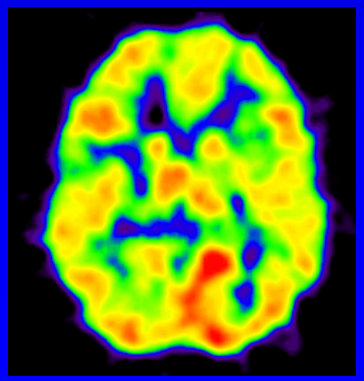
Brain Metabolism in METH Abusers with Abstinence



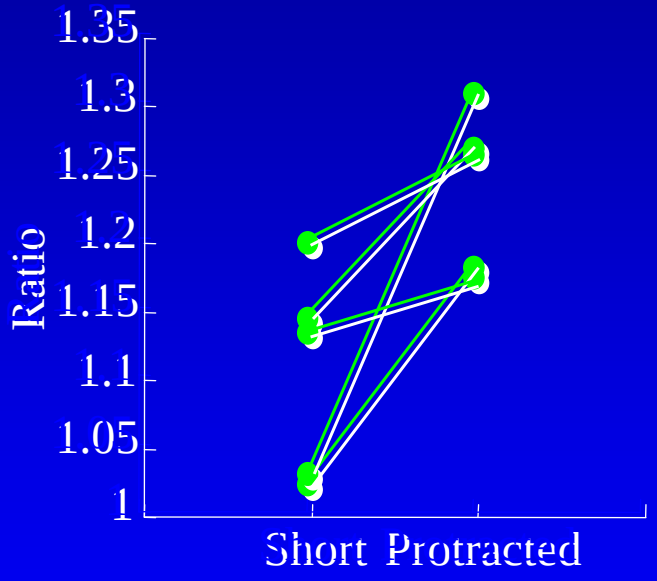
Control



METH Abuser (3 m Detox)

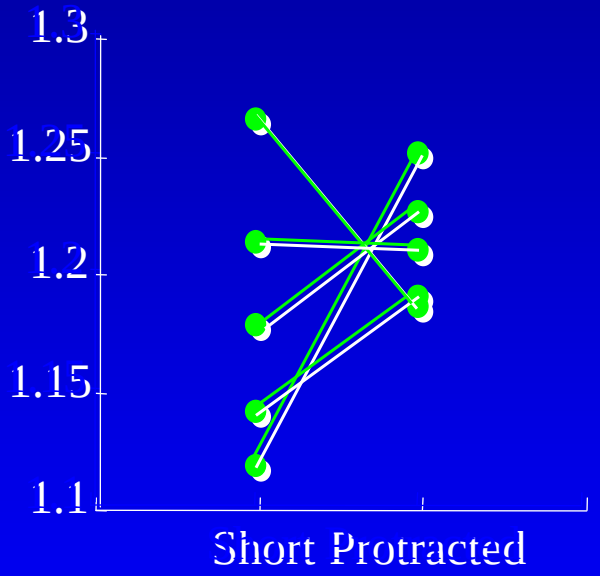


Thalamus



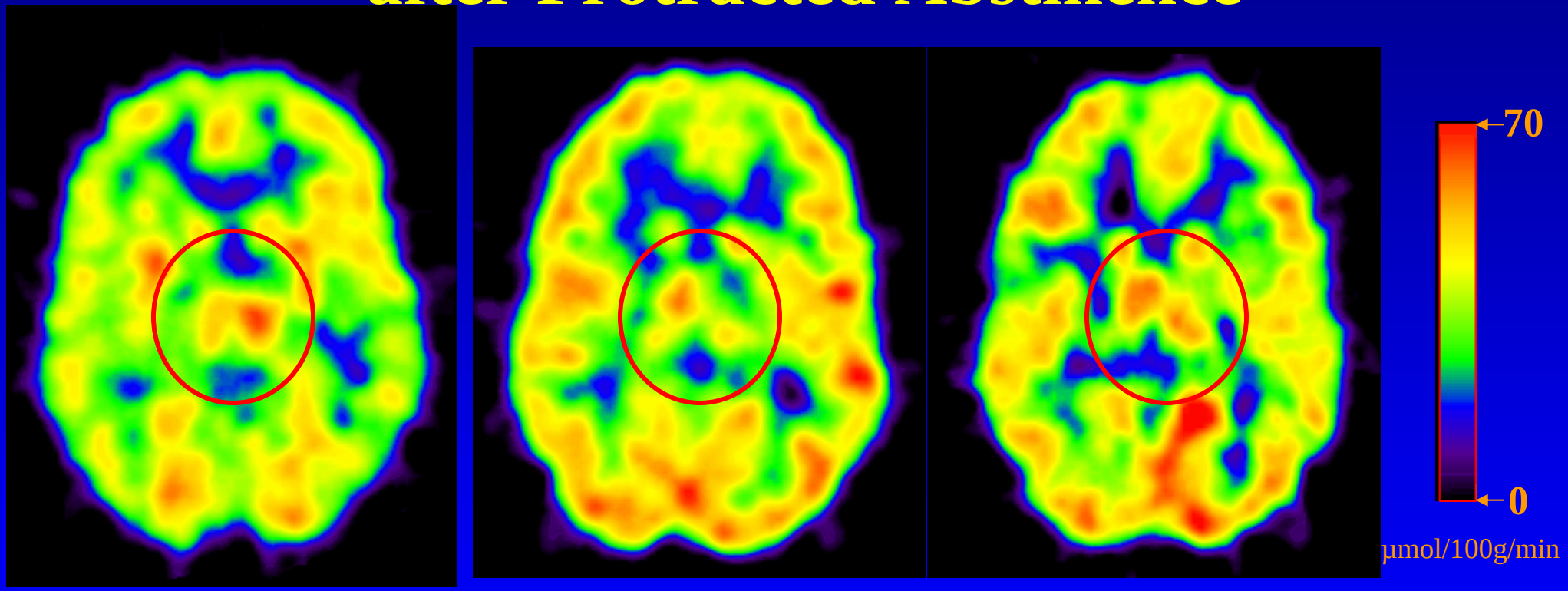
+12 ±9%, p ≤ 0.015

Striatum



+2.7 ±6.7%, p = 0.34

Partial Recovery of Brain Metabolism in Methamphetamine (METH) Abuser after Protracted Abstinence



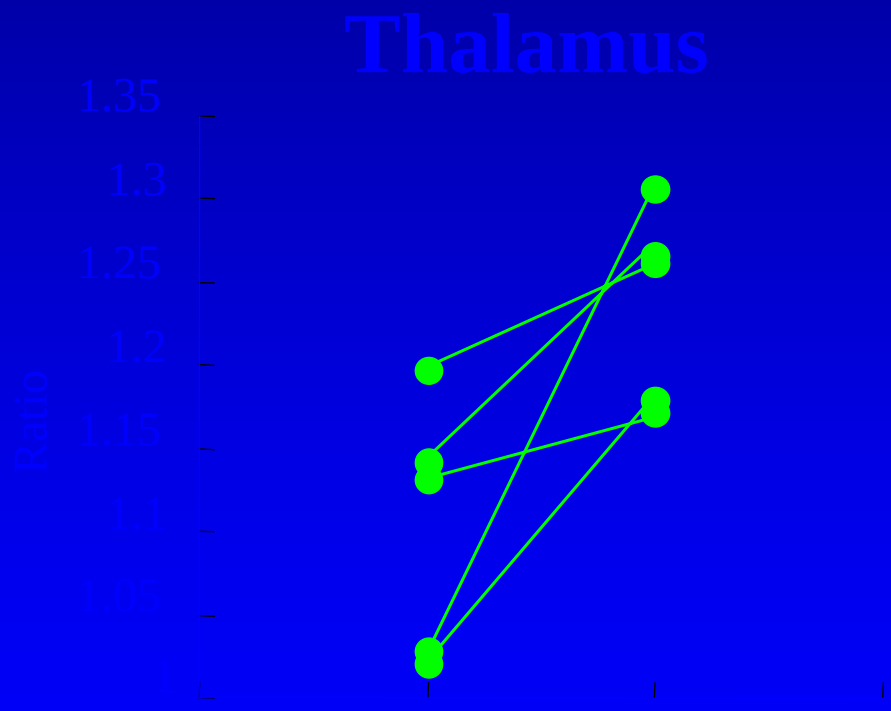
Control Subject
(30 y/o, Female)

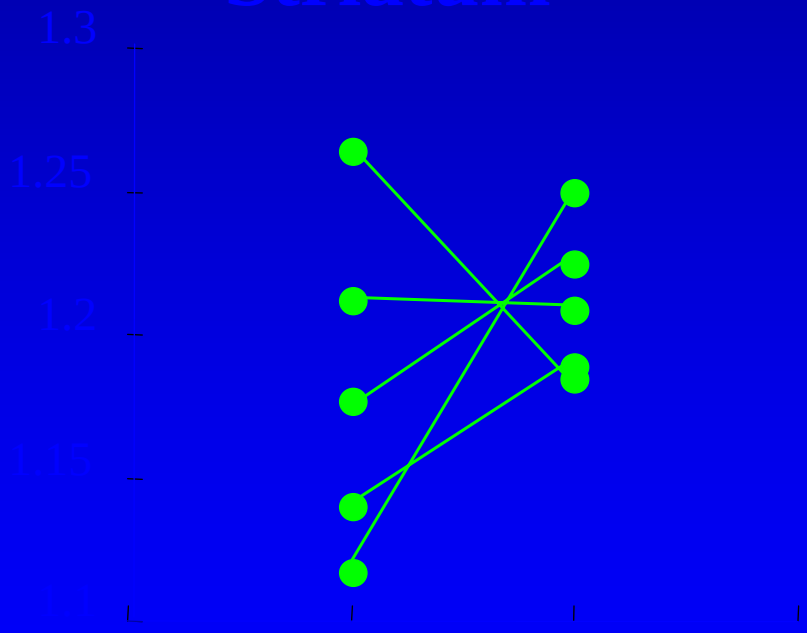
METH Abuser
(27 y/o, Female)
3 months detox

METH Abuser
(27 y/o, Female)
13 months detox

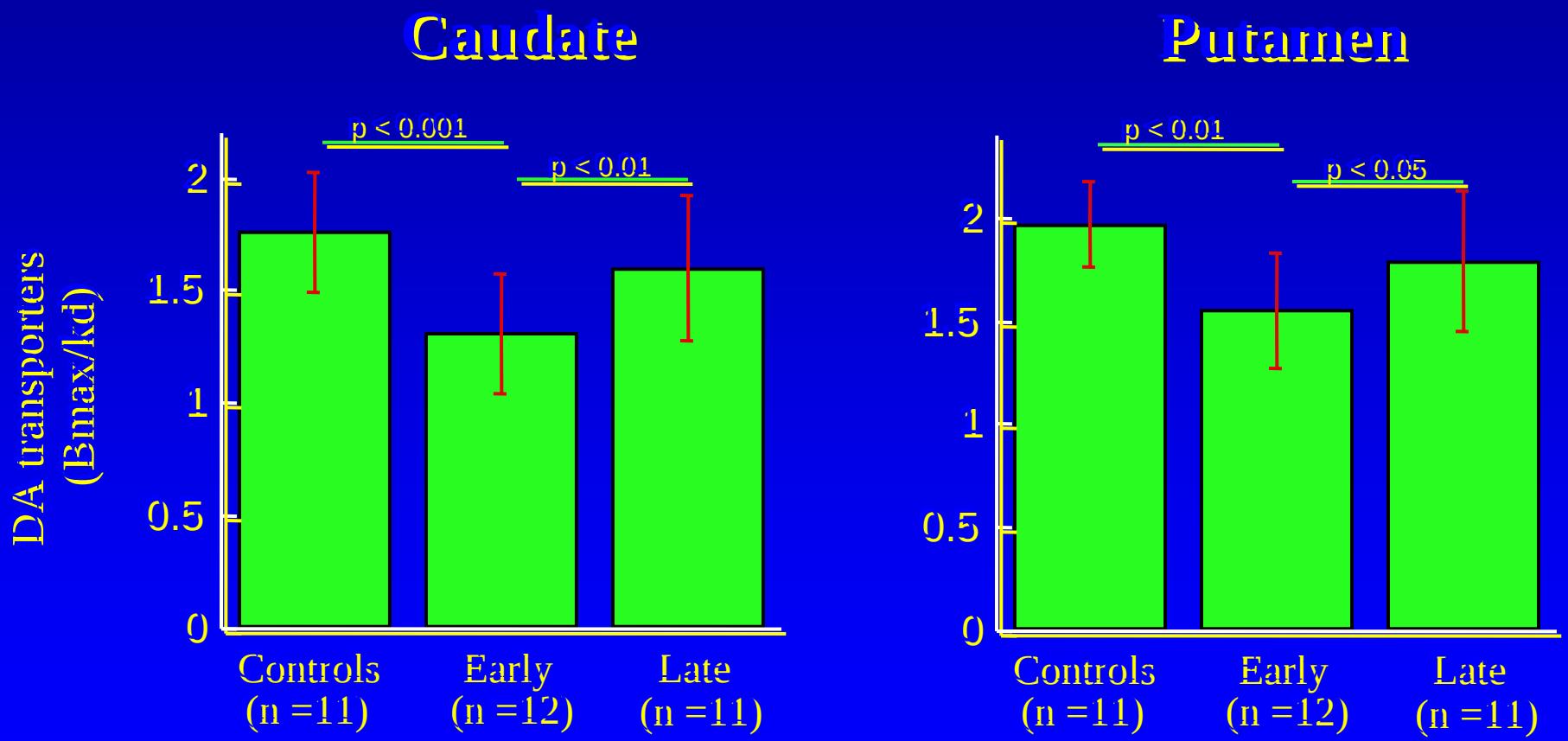
Source: Wang, G-J et al., Am J Psychiatry 161:2, February 2004.

Thalamic and Striatal Metabolism in METH Abusers During Early and Late Detoxification





DAT in Methamphetamine Abusers Tested During Early or During Late Detoxification



Summary

Increases in Metabolism

Early: posterior parietal cortex (precuneus)

Late: posterior parietal cortex (precuneus)

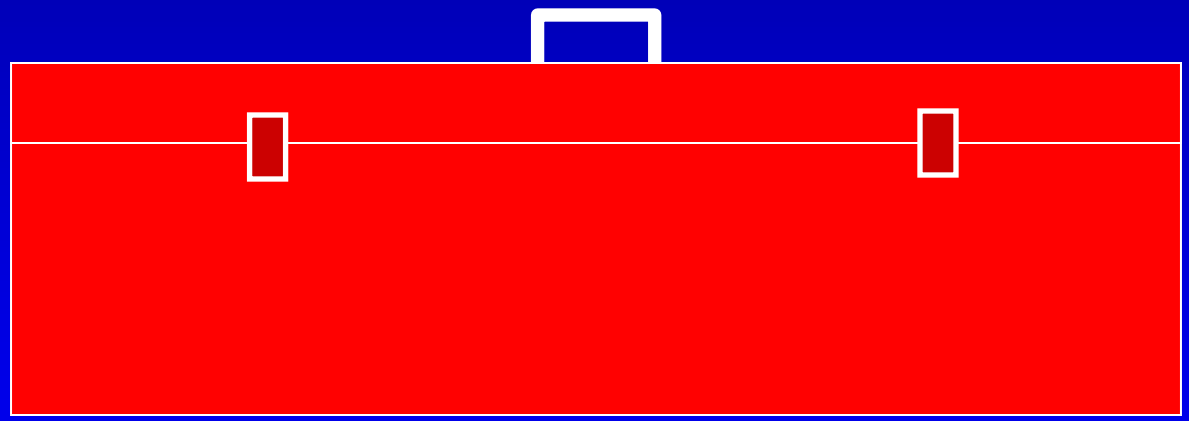
Decreases in Metabolism

Early: caudate, NAc, insula, thalamus, mesencephalum

Late: caudate, NAc, insula

Recovery in thalamic metabolism associated with

We Have A Variety Of Effective Treatment Options In The Clinical Toolbox



…And We Are Trying To Improve Existing And Develop New Options

In Order to Develop Effective Treatments
What Do We Need to Do To…

- Counteract neuroadaptations that underlie the addictive process?

- Reverse METH's Neurotoxic Effects?

Treatments for Methamphetamine

- Cognitive Behavioral Therapies
- Contingency Management
- MATRIX Model
- New Medications (treatment and overdose) are being developed

Methamphetamine Addiction Pharmacotherapies in Clinical Trials

Phase I

Aripiprazole
Atomoxetine
Bupropion
Carvedilol
Clonidine
Lobeline
Modafinil
Perindopril
Prazosin
Rivastigmine
Sertraline
Topiramate

Phase II

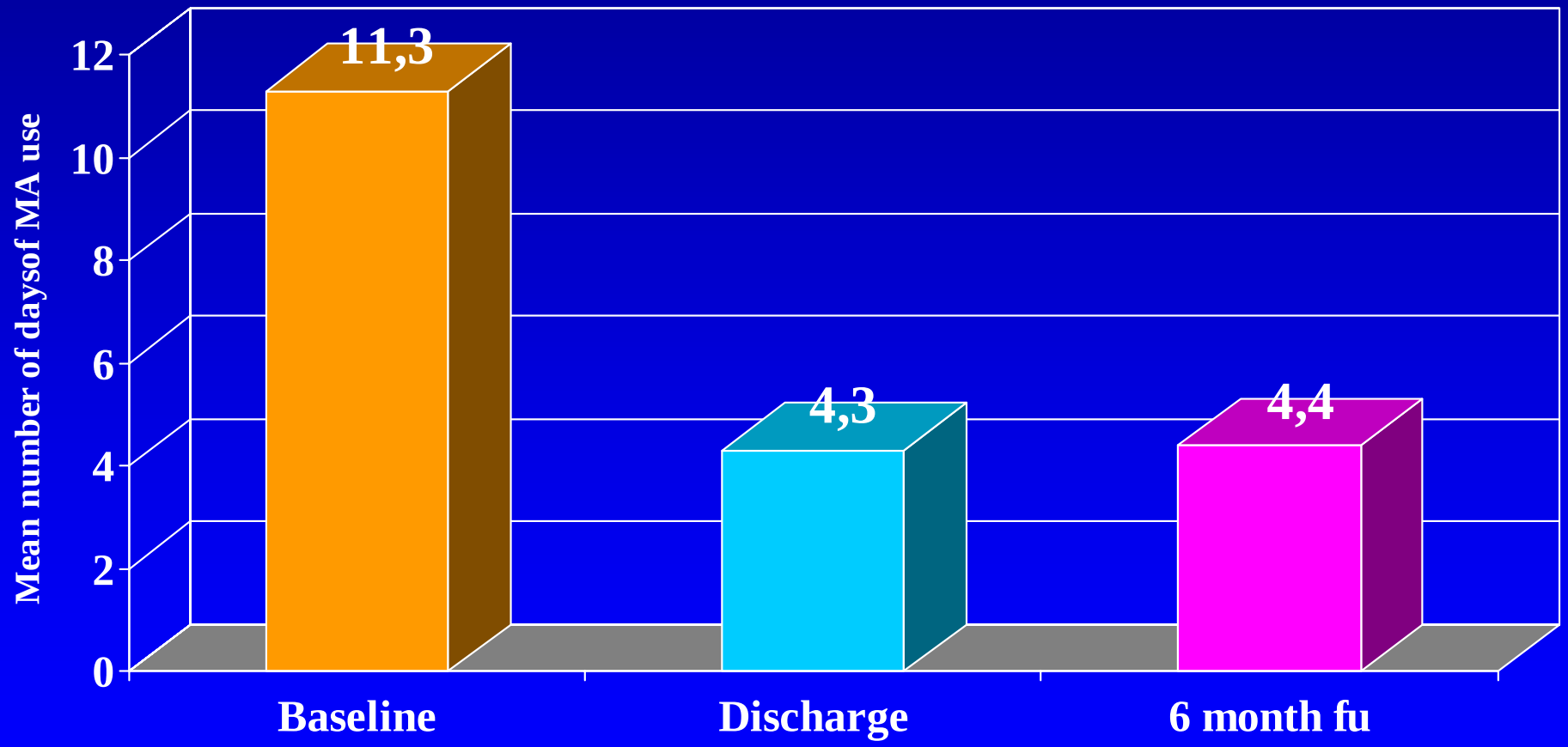
Baclofen
Bupropion
Gabapentin

Clinical Challenges for Treatment of Methamphetamine Addiction

- Poor treatment engagement rates
- High dropout rates
- Severe paranoia
- High relapse rates
- Ongoing episodes of psychosis
- Severe craving
- Protracted dysphoria

Many patients may require medical/psychiatric supervision and need ongoing treatment with antipsychotic medications

Self-report of MA use at enrollment, discharge, and 6 month follow-up following Matrix treatment



Rawson et al, Addiction, 99, p 708, 2004

The Goal of Treatment
is to help the brain and the person
recover normal function

What We Need To Know – Future Plans

- Demographics - who is using meth and why
- Brain mechanisms of meth action and addiction
- Improved Prevention
- Genetic/environmental factors in vulnerability to meth addiction
- Progression from meth use to addiction
- Better Treatments: Behavioral and Pharmacotherapies
- Prenatal effects

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