

# Neurotoxic Consequences of High Dose Methamphetamine Abuse

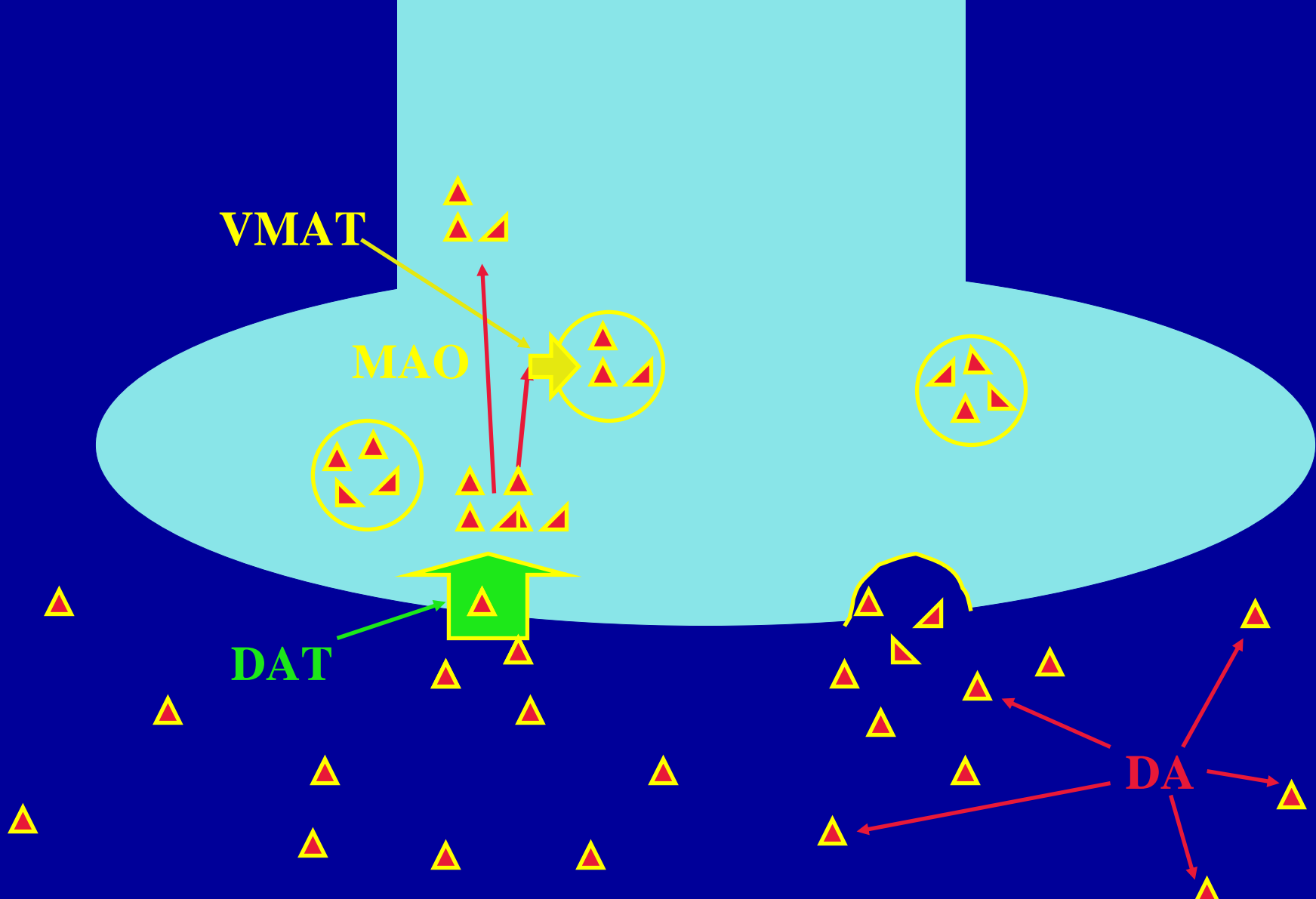
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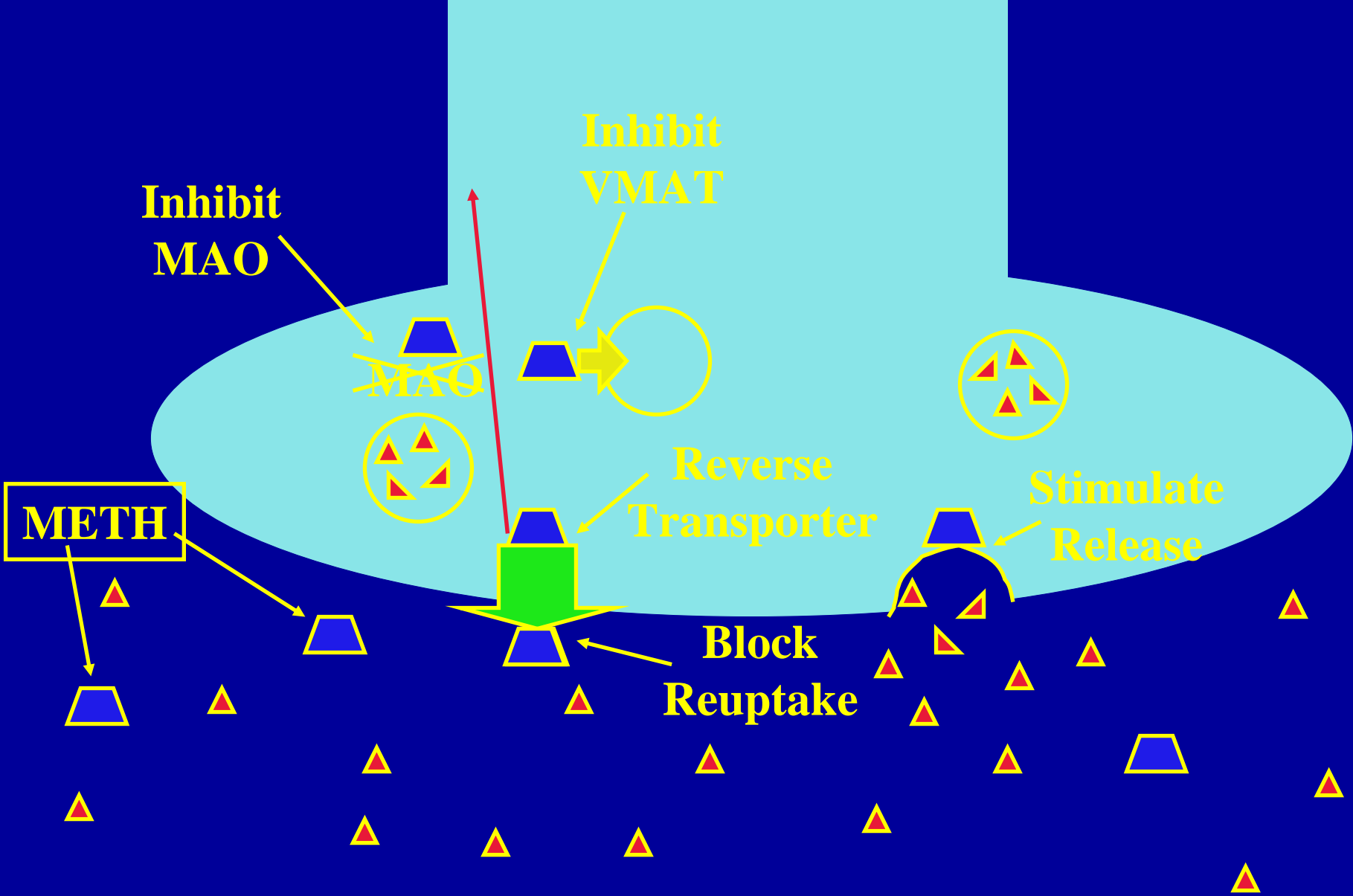
School of Medicine

# Research Strategies for Assessing the Long Term Neurotoxic Consequences of MA Abuse

- Laboratory Studies Using Animal Models\*
- Case Reports of Treatment Seekers
- Epidemiological Studies
- Post-Mortem Studies\*
- Laboratory Studies of Drug Exposed Humans\*



# Presynaptic Dopamine (DA) Neuron



# METHAMPHETAMINE

# Laboratory Studies Using Animal Models

- Control over genetic and environmental factors that may influence drug toxicity
- Rigorous control over drug exposure
- But
  - Relevance to human drug usage-dose, frequency
  - Difficult to study complex cognitive functions and mood alterations in non-humans

# Seiden, Fischman and Schuster, 1975

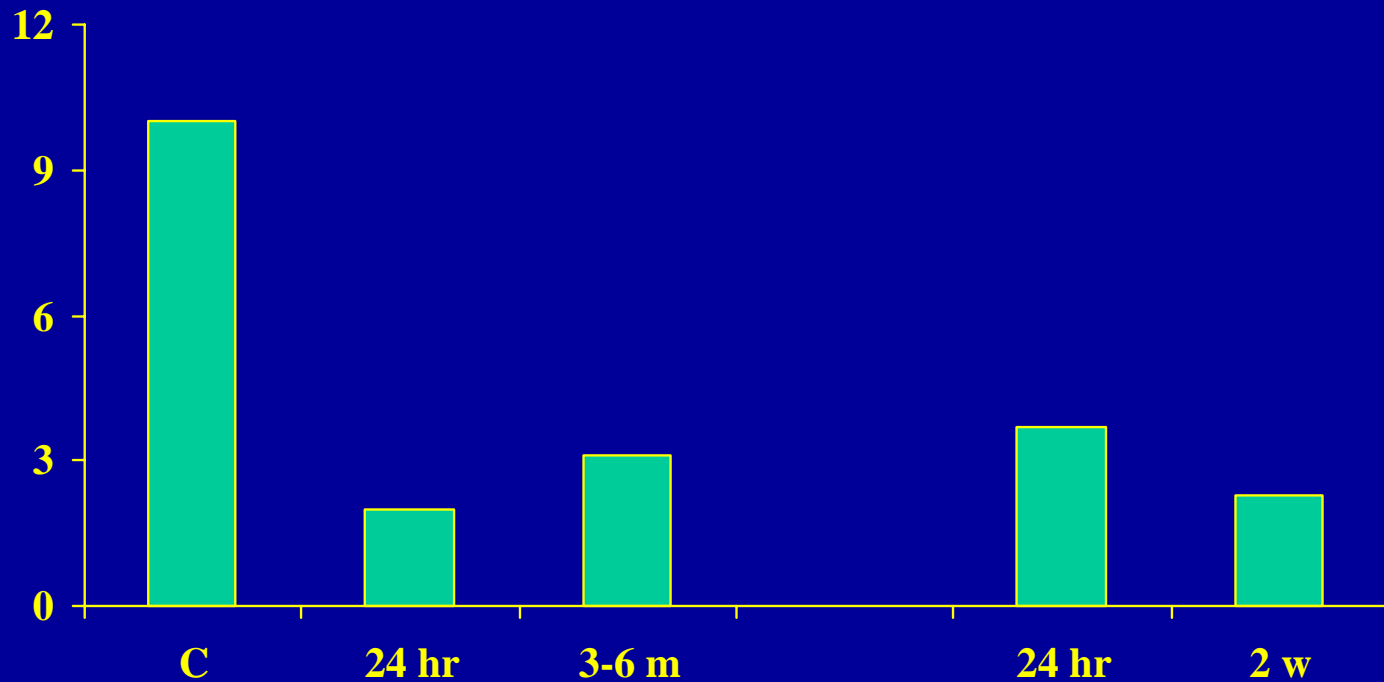
- Rhesus monkeys (12 controls - 11 MA)
- Methamphetamine IV every 3 hours
- Dosage gradually escalated over a 3-6 month period as monkeys became tolerant
- Final dose was between 24-52 mg/kg/day
- Animals sacrificed: 24 hrs after last dose or 3-6 months later

# Seiden, Fischman and Schuster, 1975

- 6 rhesus monkeys
- Methamphetamine IV every 3 hours x 14 days
- Dosage 2-3 mg/kg x 8/24hrs
- Final dose was between 16-24 mg/kg/day
- Animals sacrificed: 24 hours or 2 weeks after last dose

# Caudate Dopamine (ng/mg protein)

(Seiden, Fischman and Schuster, 1975)



# Behavioral Consequences of High Dose Methamphetamine (MA)

(Laboratory Animals)

Chronic MA at doses depleting dopamine and serotonin has no permanent effect upon:

- Eating and drinking
- Timing behavior-DRL
- Hand-steadiness and motor strength
- Eye tracking
- Long term and working memory

# Replication of These Effects of High Dose Methamphetamine

Studies in rats, guinea pigs, cats, vervet and rhesus monkeys, and baboons have shown long term decreased levels of:

- Dopamine (DA) and serotonin (5-HT)
- Enzymes controlling dopamine and serotonin synthesis
- Dopamine and serotonin reuptake transporters
- Metabolites of dopamine and serotonin
- Nerve terminal fragmentation

But no cell body death and therefore nerve terminal regeneration can occur

# Other Drugs

- All amphetamines and congeners that cause the release of DA, 5-HT produce the same long term effects at **high doses** (10-20 x ED-50 for behavioral effects)
- Drugs such as methylphenidate and cocaine which block the reuptake of DA and 5-HT do not produce this spectrum of long-term neurochemical changes

OK- What About Humans Who  
Abuse Methamphetamine-Do  
They Show Indications of  
Neurotoxicity???

Human Studies Are Tough!!!!

# Case Reports of Neurocognitive Impairment in Treatment Seekers

- Biased sample-who comes for TX?
- Biased recall-attribution
- Poly-drug abuse
- Failure to confirm exposure-e.g. hair testing
- Cause or effect??
- But can be useful to guide more controlled research

# Epidemiological Studies

- Potential for studying a representative sample of drug exposed population
- But
  - Defining population is easy- getting a representative sample to participate is hard
  - Confirming drug exposure-hair testing
  - Poly-drug abuse
  - Co-existing psychiatric conditions
  - Cause or effect?

# Post-Mortem Studies

- Uncertain drug history- hair testing??
- Small sample size
- Co-morbidity
- Quality of sample
  - Cause of death
  - Terminal anoxia
  - etc

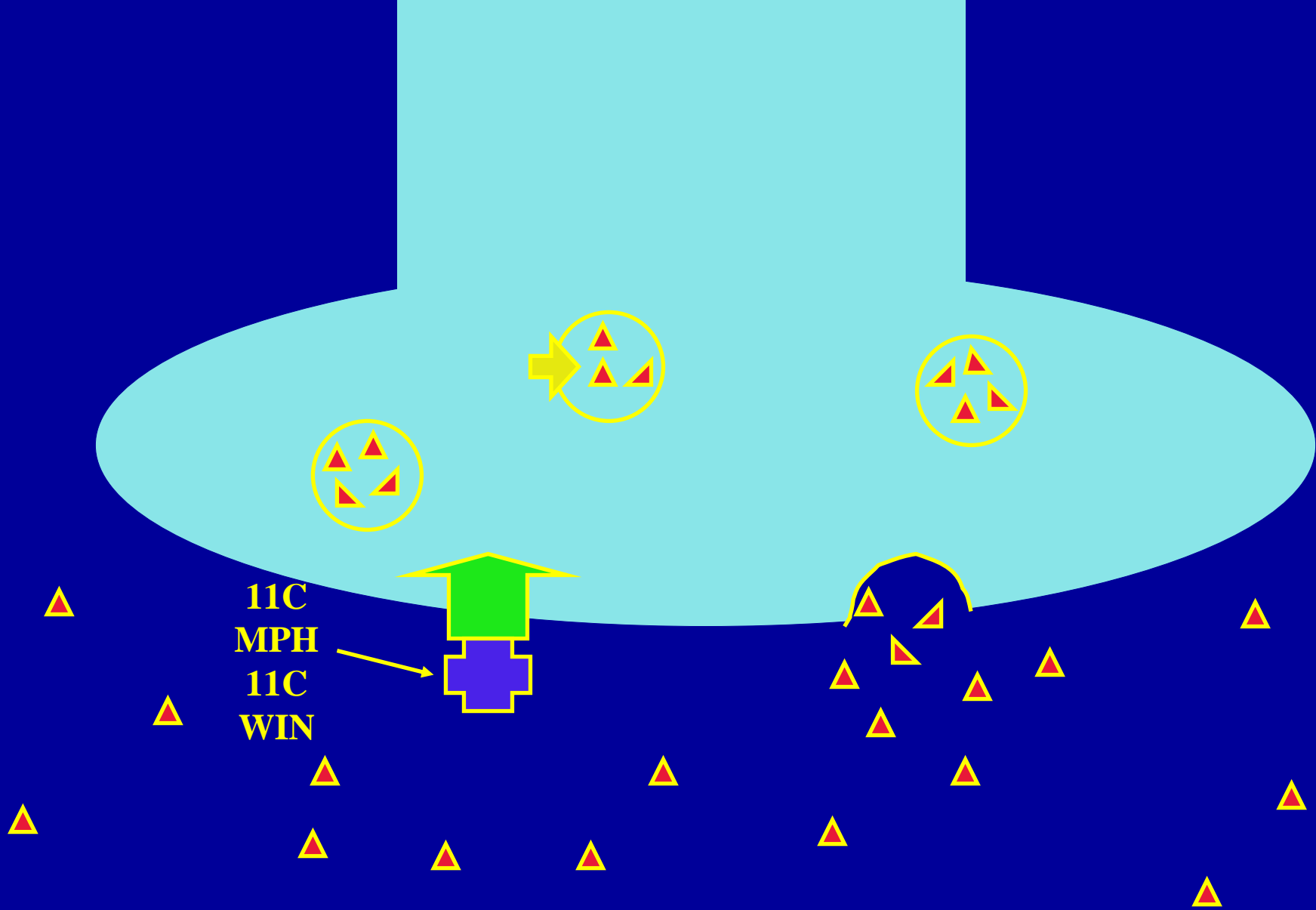
# Post Mortem Study of DA Nerve Terminals in Chronic MA Abusers

Wilson et al. 1996

- Levels of DA, tyrosine hydroxylase and DAT significantly lower in caudate, putamen and nucleus accumbens-  
importantly, no differences in 5-HT markers
- However, VMAT levels and dopa decarboxylase levels were not lower than controls

# Laboratory Studies of Drug Exposed Humans

- Confirm drug history- e.g. hair analysis
- Rigorously assess:
  - Mood states
  - Cognitive and motor abilities
  - Responsiveness to drug challenges
  - DA and 5-HT integrity using SPECT, PET and analysis of DA and 5-HT metabolites in the CSF



11C  
MPH  
11C  
WIN

# PET Radioligands

# Lower DAT Levels in Abstinent MA and Methcathinone Abusers

(McCann, et al 1998)

- Six ex-MA and 4 ex-MC abusers compared to 10 controls and 3 PD patients using the DAT-PET ligand (11C) WIN-35,428
- MA and MC abusers showed significantly lower DAT binding potential in the caudate (-25 and -24%) and putamen (-25 and 16%)
- PD patients showed a significantly larger (46-68%) decrement in DAT binding in the caudate and putamen

# DAT Reduction-Psychomotor Impairment in MA Abusers

Volkow, et al 2001

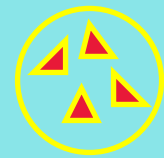
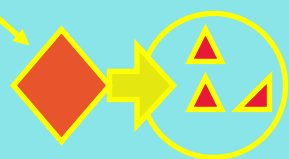
- 15 ex-MA abusers compared to 18 controls using the DAT PET ligand (11C) d-threo-methylphenidate
- MA abusers showed significantly lower DAT binding potential in the caudate (-28 %) and putamen (-21%)
- DAT reduction showed a significant correlation with motor impairment and motor slowing

# DAT, VMAT2 and Neurocognitive Function in Former High Dose MA Abusers

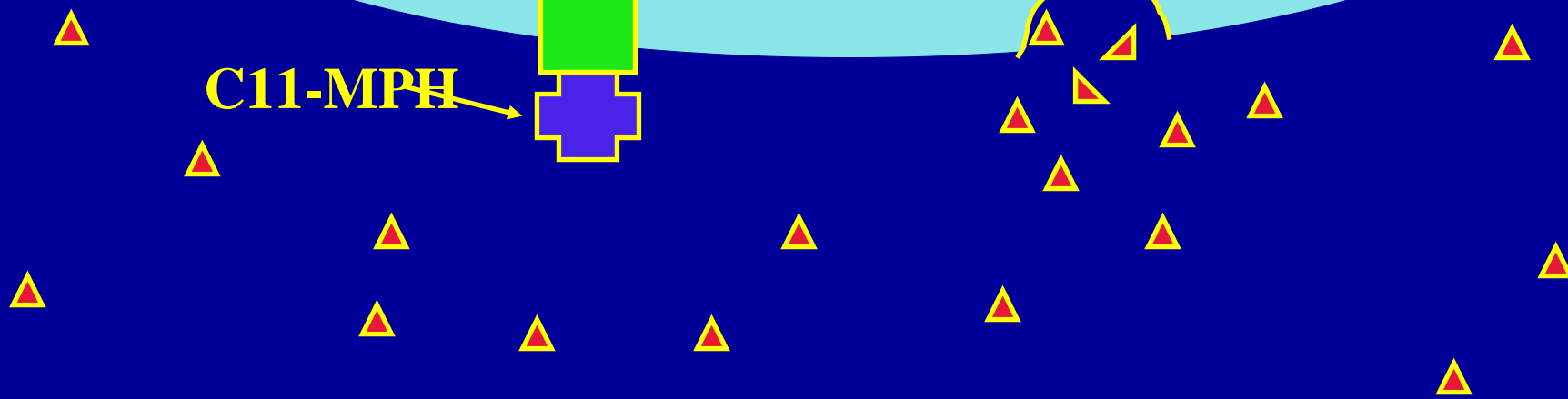
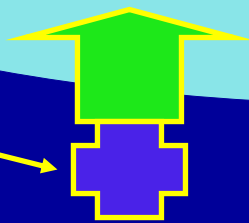
Johanson, \*Frey, \*Kilbourne,  
Lundahl, Keenan and Schuster

\*U. of Michigan SOM

**C11-DTBZ**



**C11-MPH**



# **PET Radioligands**

# Methods

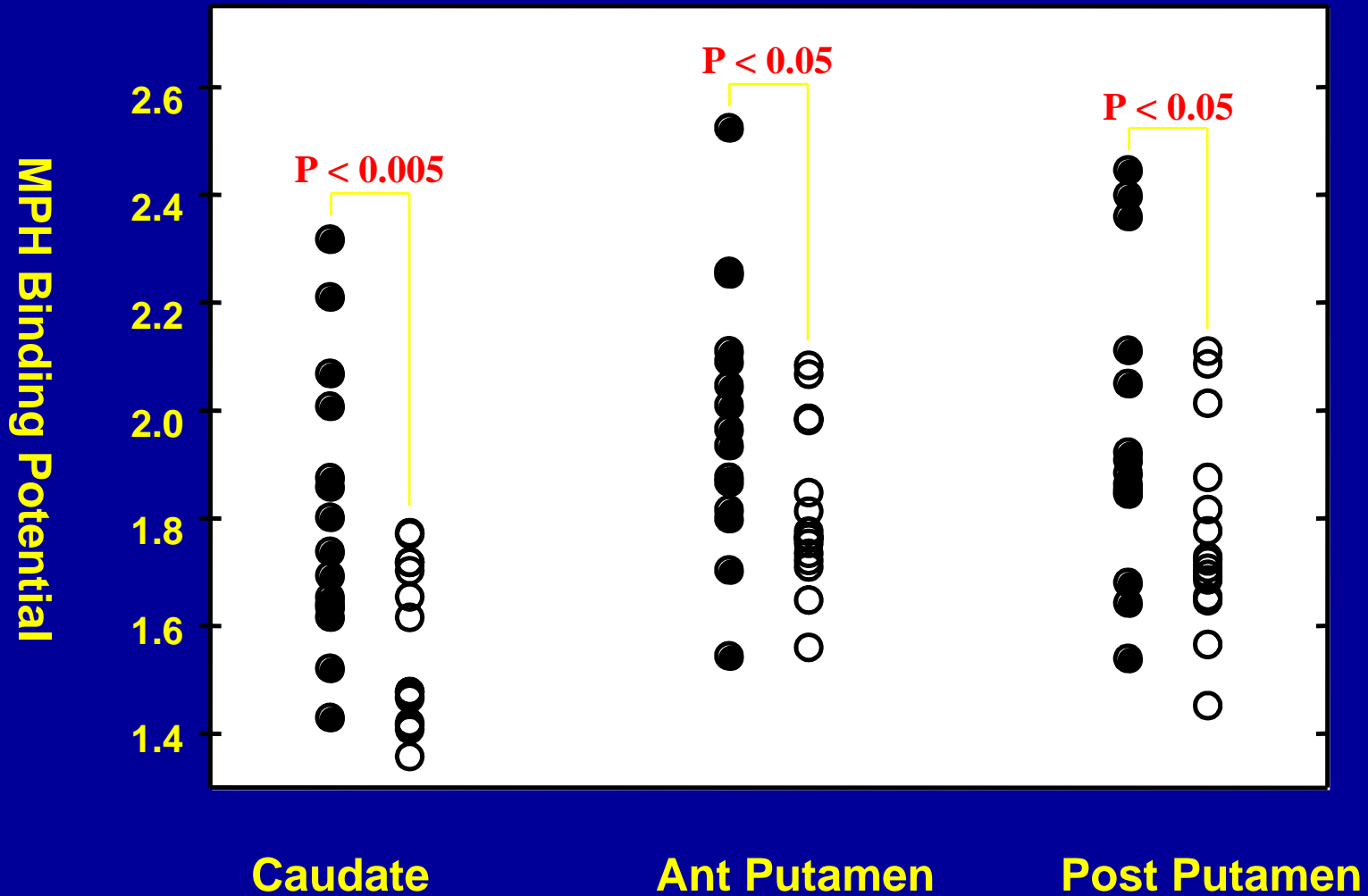
- **Subjects**: 16 former methamphetamine abusers; 10 yr of use; last regular use 3 yr prior to PET; last use 1 yr prior; 18 matched (age, gender, ethnicity and IQ) controls with no psychostimulant exposure
- **VMAT2 PET**: Seimens HR<sup>+</sup> scanner; infusion/equilibrium administrations of [<sup>11</sup>C]DTBZ and [<sup>11</sup>C]de threo MPH
- **ROI**: 3 striatal locations: Caudate Nucleus; Anterior Putamen; Posterior Putamen compared to Brodman areas 16, 17, 18
- Neurocognitive testing: Motor Function, Cognition, Explicit Memory, Working Memory, Executive Function, Decision Making Task.

# VMAT and DAT Binding Potential

	<i>Caudate</i>	<i>Anterior Putamen</i>	<i>Posterior Putamen</i>	<i>Putamen</i>	<i>Striatum</i>
<b>C11- DTBZ</b>					
Users (n=15)	2.20 (0.25)*	2.60 (0.26)*	2.66 (0.28)	2.63 (0.26)	2.48 (0.25)*
Controls (n=18)	2.48 (0.40)	2.91 (0.42)	2.95 (0.51)	2.93 (0.46)	2.78 (0.42)
Users/Controls %	89	89	90	90	89
<b>C11-MPH</b>					
Users (n=15)	1.56 (0.15)**	1.81 (0.15)*	1.77 (0.19)*	1.79 (0.16)*	1.72 (0.15)**
Controls (n=18)	1.85 (0.30)	2.04 (0.32)	2.01 (0.35)	2.03 (0.33)	1.97 (0.32)
Users/Controls %	84	89	88	88	87

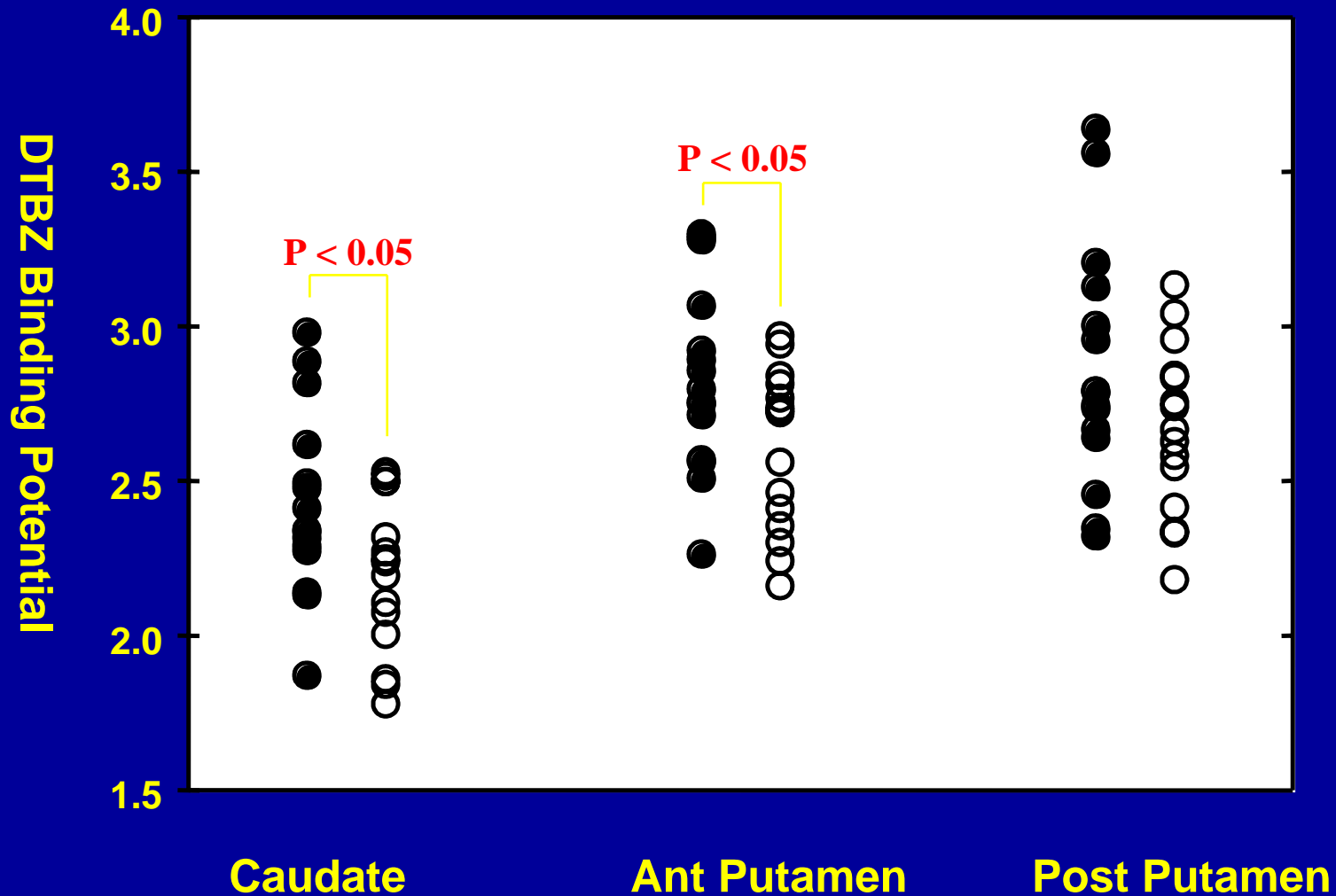
# BP DAT

## MA and Matched Controls



# BP VMAT

## MA and Matched Controls



# Neurocognitive Results

31 MA and 33 Controls

# Motor Function

- Finger tapping
- Grooved Peg Board
- Digit Symbol Substitution Task

**No differences**

# Explicit and Working Memory

- California Verbal Learning Task
- Paired Associates Learning
  
- Spatial Working Memory
- Delayed Matching to Sample
- Rapid Visual Processing

**No differences**

# Executive Function

- Trail Making Test
  - Word List Generation\*
  - Animal Fluency
  - ID/ED Shift
  - Stockings of Cambridge\*
- \* MA abusers significantly better than matched controls, otherwise no differences



POINTS: 125

75

RED

BLUE

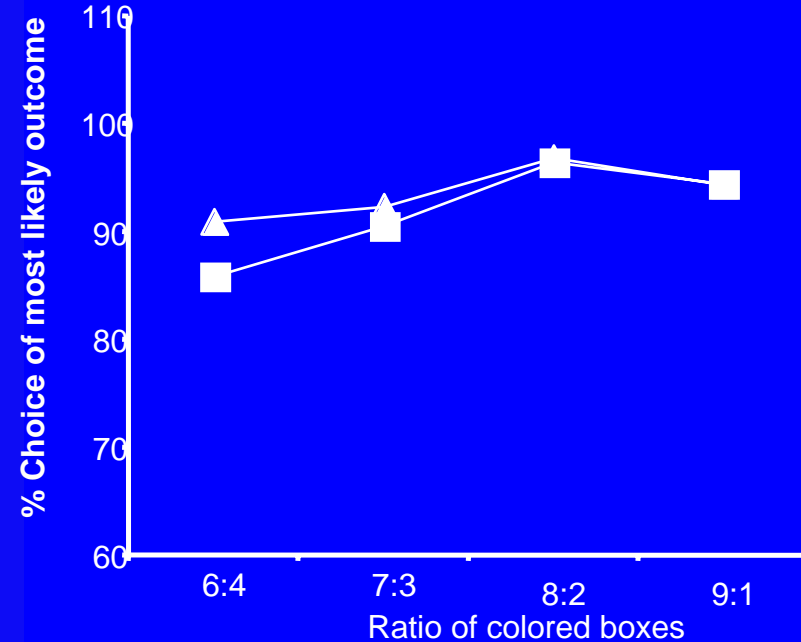
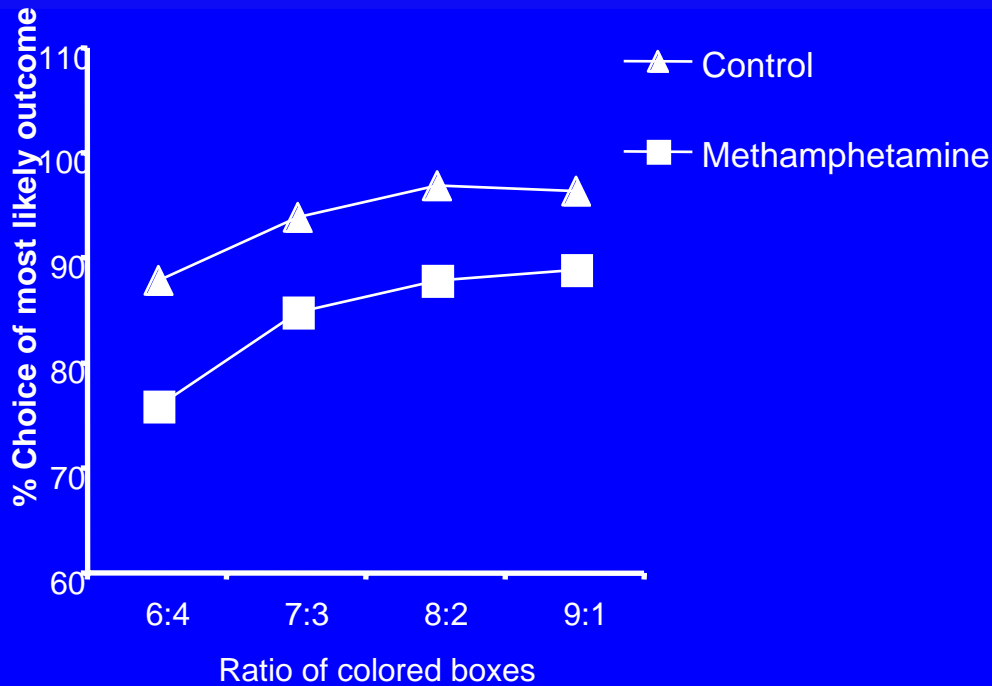
# Data Analyses

- Speed of decision making. How long it takes the subject to decide which color box is hiding the token
  - Measured by mean deliberation time
- Quality of decisions (percent choice most likely)
  - On what percentage of trials the subject chose the most likely outcome (i.e. the color with the most number of boxes)
- Risk-adjustment (percent bet)
  - Rate at which a subject increases the percentage of the available points put at risk in response to more favorable ratios of red:blue boxes
  - e.g. 9 red:1 blue vs. 4 red:6 blue

# Previous Findings

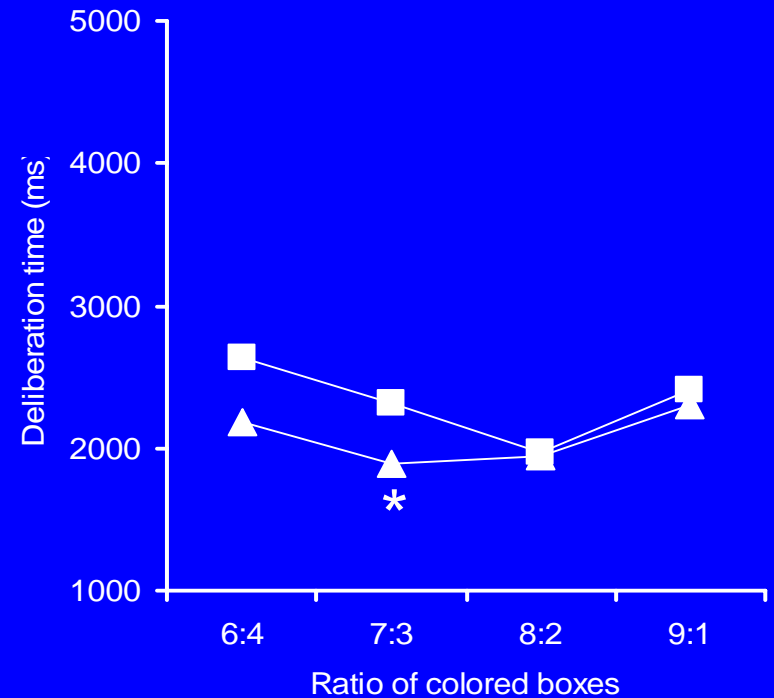
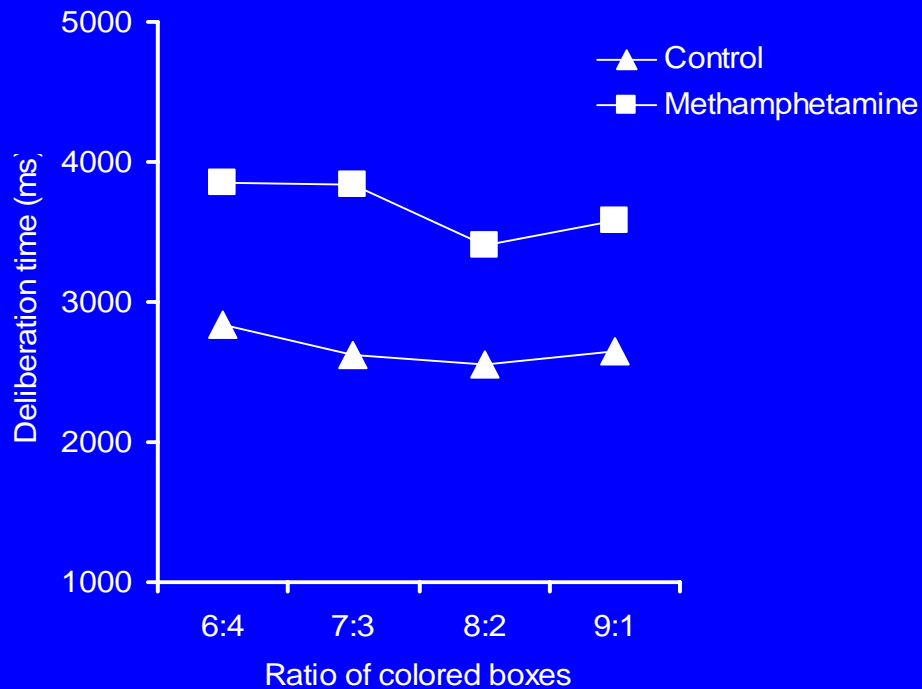
- Rogers et al. (1999)
  - METH abusers
    - Suboptimal decisions-choose less likely more often (correlated with years of abuse)
    - Increased deliberation time before choice
  - Orbitalfrontal PFC lesions
    - Same deficits as METH abusers

# Quality of Decision Making



Taken from Rogers et al. (1999)

# Speed of Decision Making



Taken from Rogers et al. (1999)

# Conclusions I

- Animal research has clearly shown that amphetamines produce long-term, probably irreversible neurochemical changes in DA and/or 5-HT neurons. Levels of transmitters, synthesizing enzymes and membrane uptake transporters (DAT and SERT) are significantly depleted.
- There is also evidence for nerve terminal degeneration, but no cell body death and hence terminal regeneration can occur.

## Conclusions II

It has been difficult to show any impairment in cognition, motor function or other behaviors of animals associated with the long lasting neurochemical changes produced by high dose amphetamine regimens. Recently, however, there have been reports by some investigators of subtle impairments in learning and memory.

# Conclusions III

- Post mortem brain studies of MA abusers have shown decreases in the concentration of DA, DAT and tyrosine hydroxylase but not VMAT.
- Human PET and SPECT studies have shown lower DAT binding in the caudate and putamen of former MA abusers
- In our study, the BP for the DAT ligand (C11) MPH and the VMAT ligand (C11+) DTBZ showed a small but statistically significant lower level in the caudate and putamen.
- The lower BP for both DAT and VMAT suggests structural changes in a small number of DA neurons in the striatum. But these long term changes in humans are much smaller than those reported in animal studies and other human studies. But are they clinically significant?

# Conclusions IV

- In our study, no neurocognitive deficits were found
- No deficits were found in decision-making
- Further in several measures former MA abusers showed superior performance.
- **HOWEVER!!!!!!!**

# Conclusions V

- MA abusers in our study had abstained from regular MA use for over 3 years
- Thus, it seems likely that there may have been regeneration of DA nerve terminals and functional recovery
- Such recovery in DAT levels has been previously been reported by Volkow (2001) but functional deficits in motor function and memory persisted
- We do not know what explains the differences in our findings but believe it is recovery of function

# The Future

- Need better controlled larger scale prospective studies using both VMAT, DAT and SERT PET ligands in a prospective study of MA abusers.
- Must control for age, gender, IQ, educational level, psychiatric co-morbidities and other drug use.
- Drug abstinence must be confirmed with clinic records and hair testing