

# Methamphetamine, Behavior and Brain Imaging

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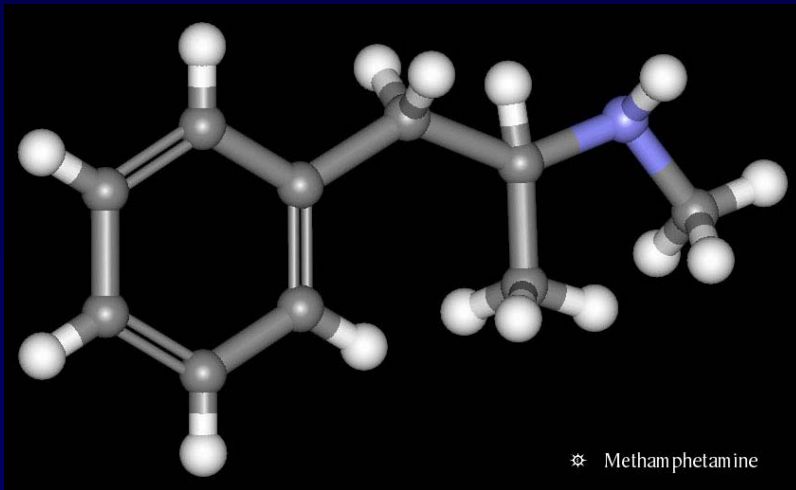
# AMPHETAMINES

## *Including Methamphetamine*

- MOST COMMONLY USED ILLICIT DRUG AFTER CANNABIS
  - >35 million regular users (WHO, 1997)
- 9.4 million Americans have used (DEA, 1999)
  - No longer restricted to the Southwest
  - Use steeply increased and expanded geographically

# What do we know about methamphetamine?

- *Meth, crystal, speed*
- *CNS stimulant*
- *Injected, smoked, snorted, ingested orally*



- Amphetamine derivative (prescribed 1950s, 1960s for obesity, depression)
- Prolonged , high level use produces *dependence*.

# What are the effects of methamphetamine?

- *Cardiac arrhythmias*
- *Stomach cramps*

## *Effects on the brain:*

- *stroke*
- *shaking*
- *anxiety*
- *insomnia*
- *paranoia*
- *hallucinations*

# What are the goals of brain imaging?

Figure out how drugs act.

Characterize addiction.

What's wrong in the brain? What circuits?

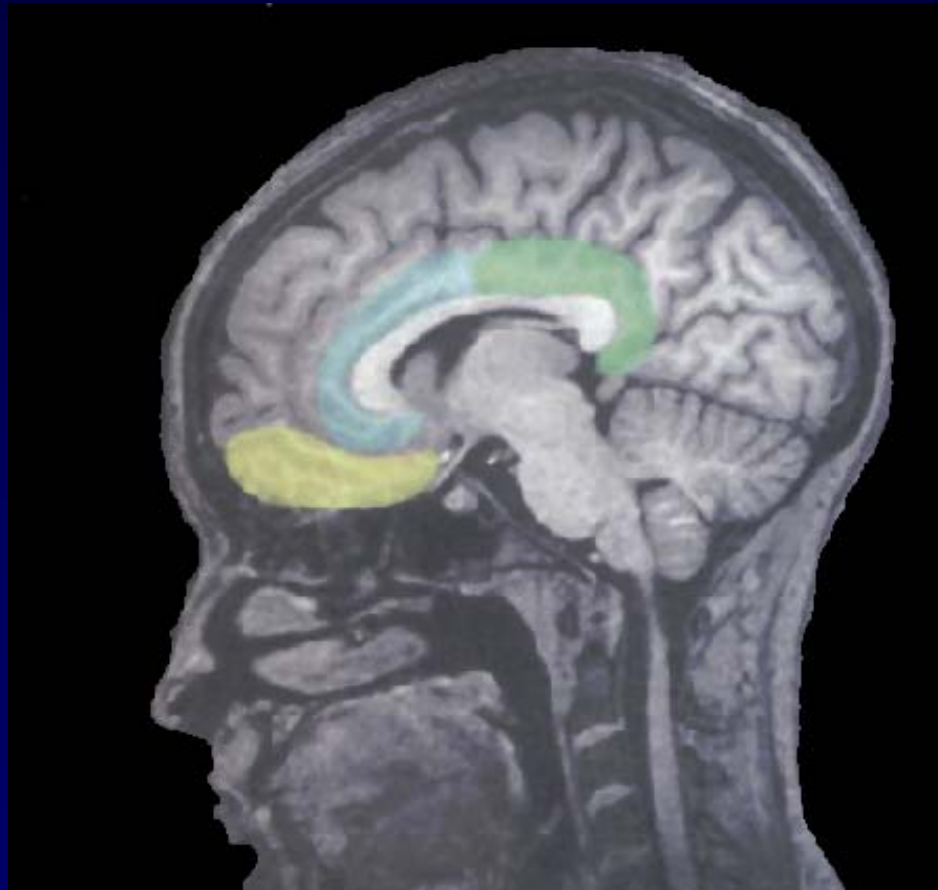
Advance treatment.

Provide a rational basis to design medicines or cognitive-behavioral therapies.

Methamphetamine users have emotional and cognitive deficits.

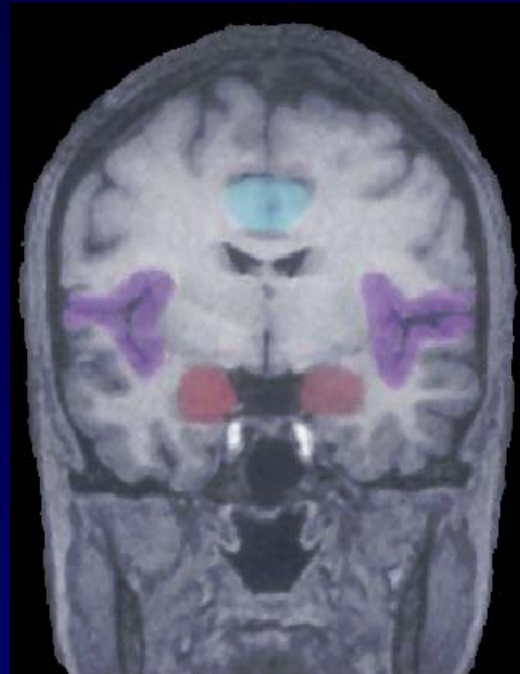
Where is the problem in the brain?  
*Focus on cortical-limbic circuits.*

The *orbitofrontal* and *cingulate* cortices participate in emotional experiences and cognitive processing.



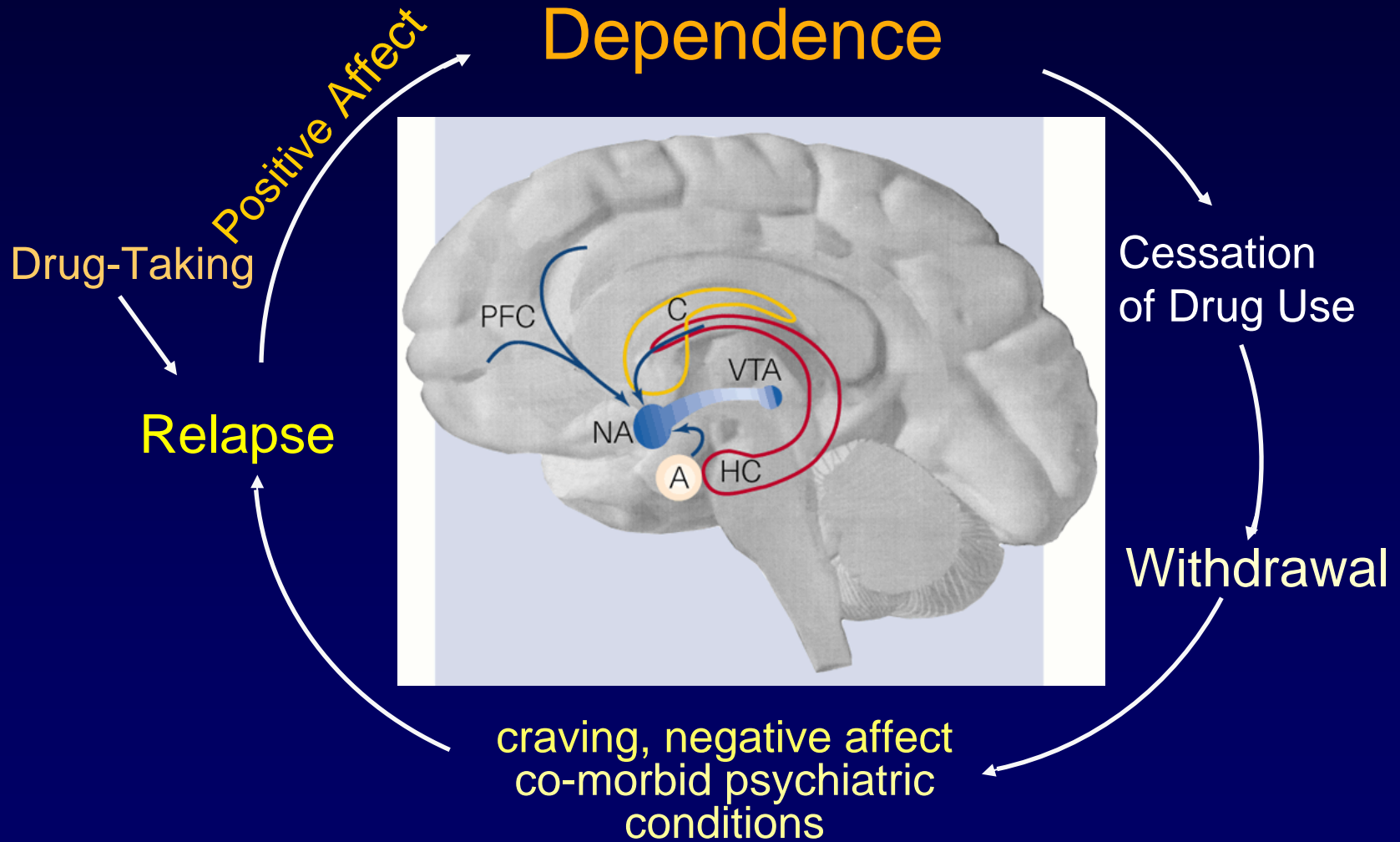
*R.J. Dolan, 2002*

The anterior cingulate and insular cortices participate in emotional experiences.



The amygdala links perception with emotion and memory.

# Affective State Varies Over Time



# Methamphetamine users have cognitive deficits in early abstinence.

- working memory
- learning
- abstract thinking
- logic

# Cognitive Deficits

	Controls (n = 23)	MA (n = 21)
<b>Working Memory</b>		
Digit symbol (# correct)	63.1 (2.2)	54 (2.3) **
<b>Learning</b>		
Selective Reminding		
Words Remembered	124 (3.4)	113 (3.4) **
Reminders (#)	20.5 (3.0)	35.3 (3.8) **
Discrimination Learning (# correct)	24.0 (1.3)	19.5 (1.8) *

significant from control, \*p<.05; \*\*p <.01

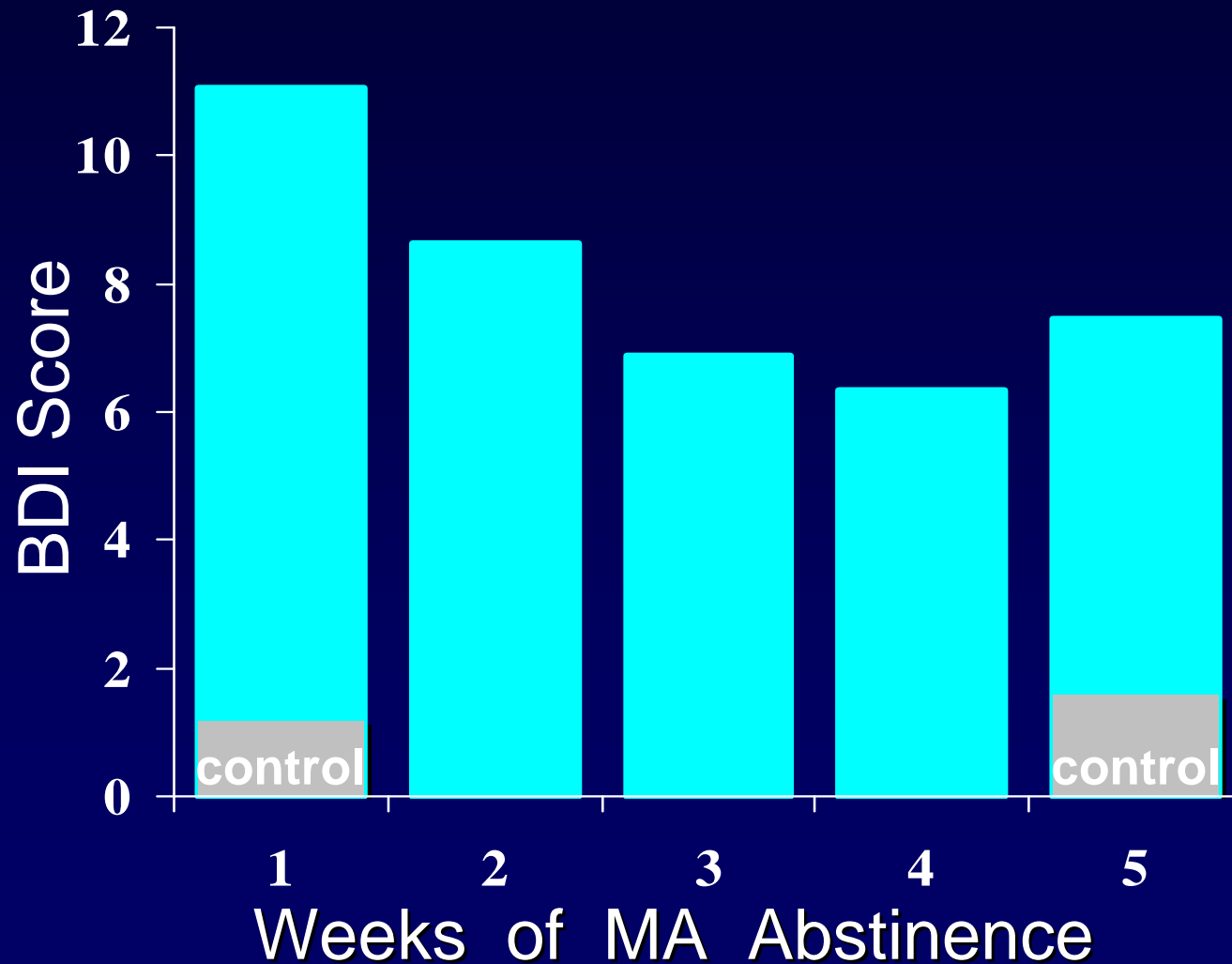


# Hypotheses

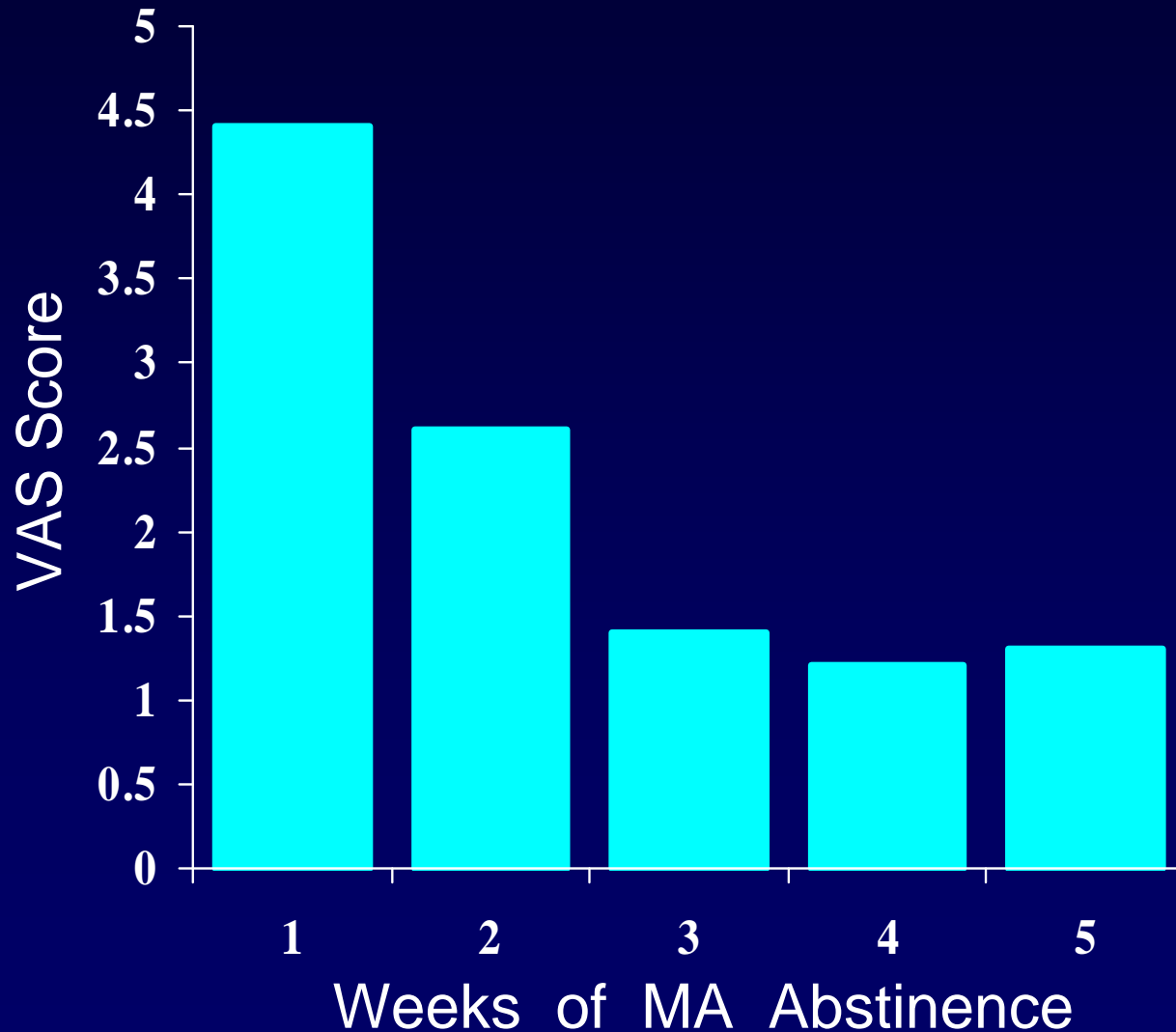
Methamphetamine abusers in early abstinence  
have affective deficits as well.

These deficits reflect dysfunction in  
specific brain regions.

# Depression Scores in Abstinent Methamphetamine Users



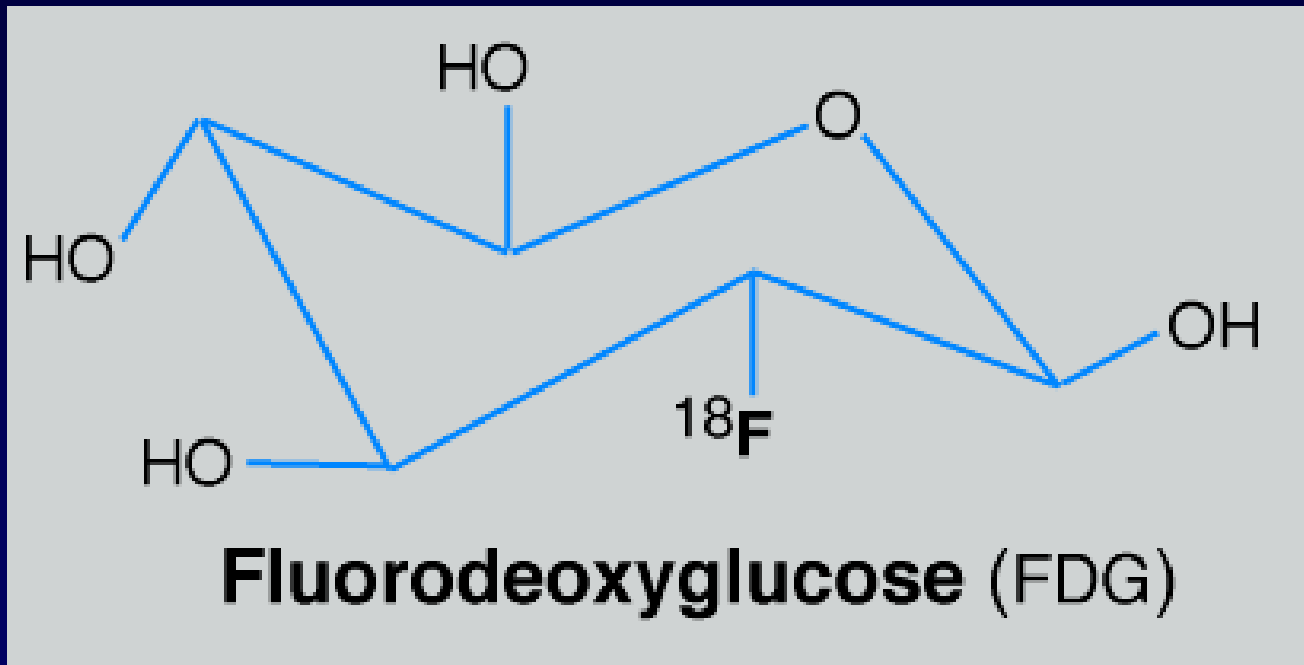
# Methamphetamine craving drops dramatically over 3 weeks.



# Methods

- MA and control groups
- Urine drug screens to show MA use
- Abstinence maintained on a research ward
  - PET scan and cognitive tests
  - PET scan -- FDG/auditory CPT

Fluorodeoxyglucose (FDG) is injected as a tracer for brain function.

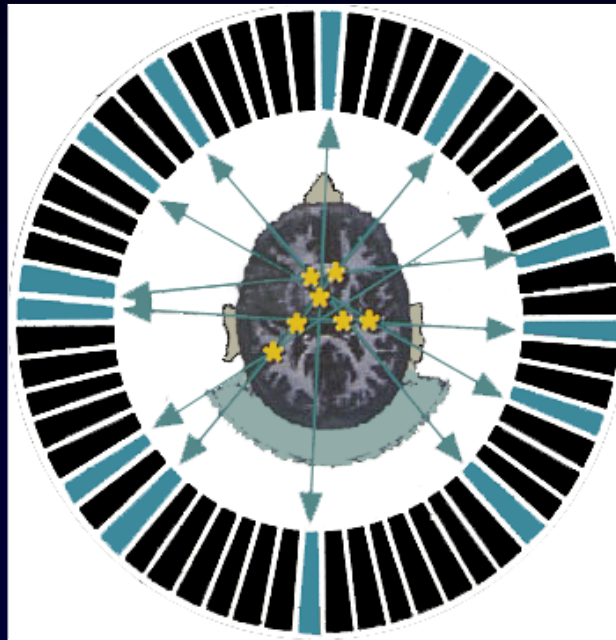


*FDG is taken up by brain regions in proportion to their activity. It is visualized in the brain by PET scans.*

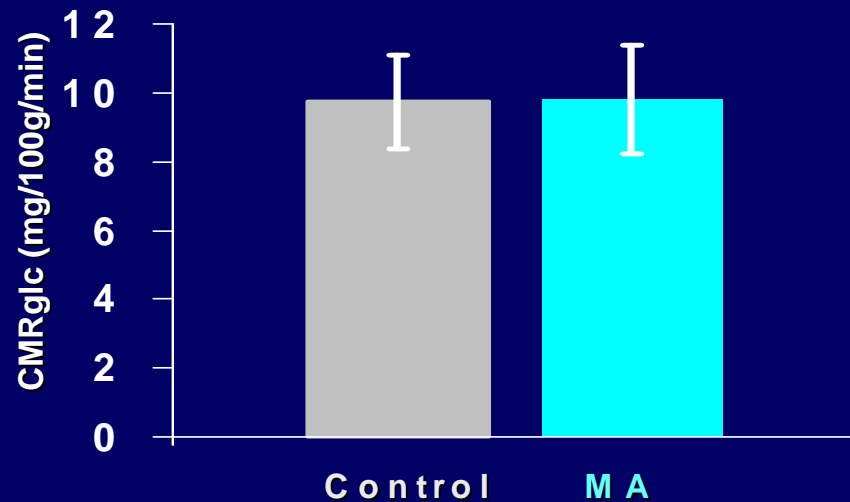
# PET Scanning

*A Nuclear Medicine procedure*

Detectors linked to a computer system reconstruct an image.

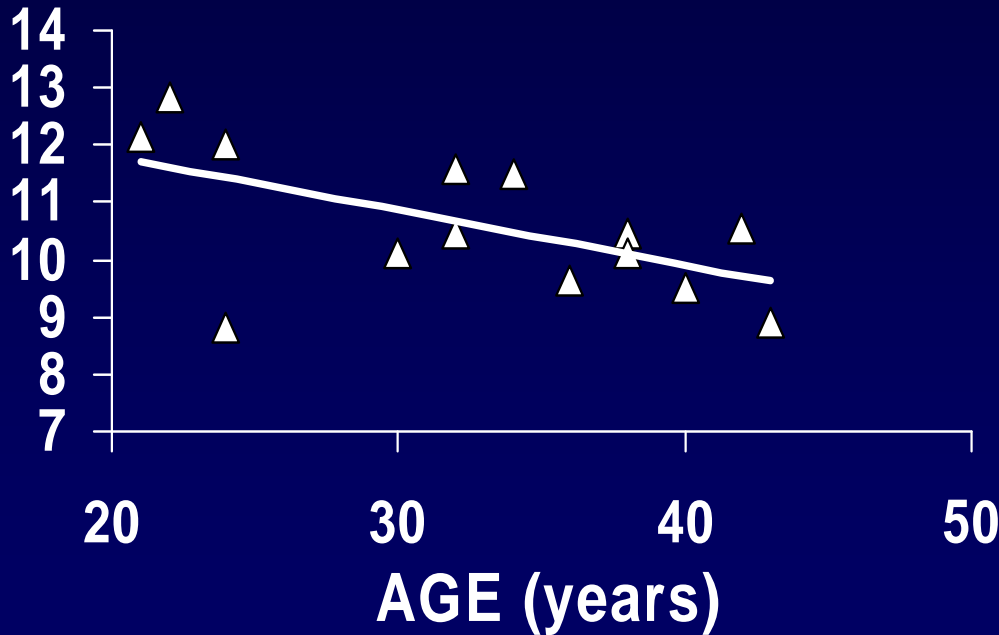


PET scans with FDG show normal whole brain metabolism in early abstinence from methamphetamine.



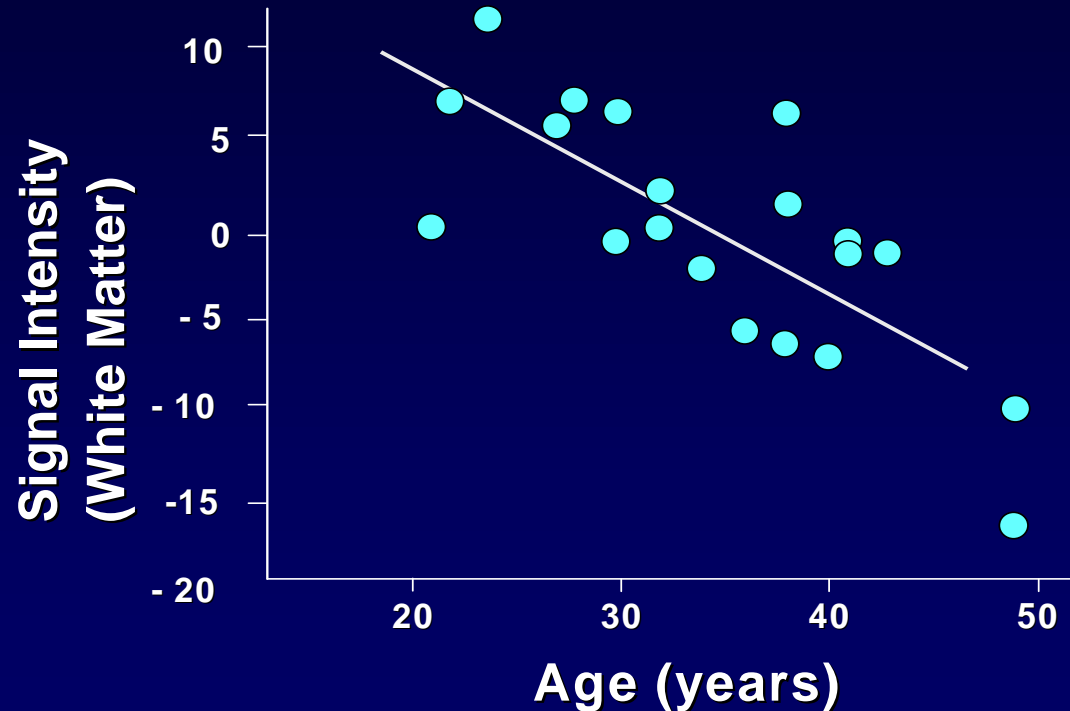
# Brain activity varies with age in methamphetamine users – not in control subjects.

Metabolic rate  
(mg/100 g/min)



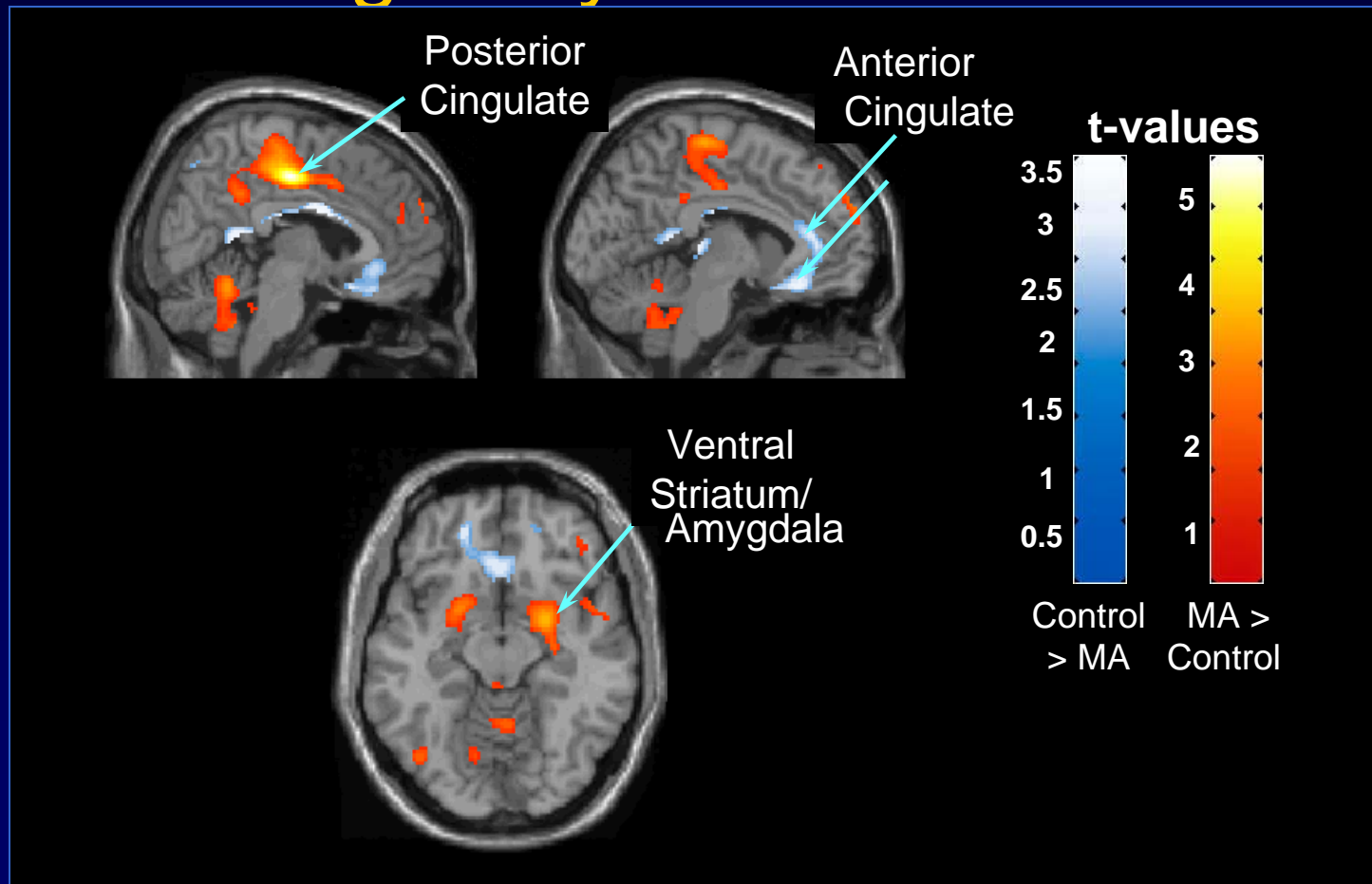
*MA reduces reserve –  
less compensation for aging.*

# White matter (MRI scans) varies with age in methamphetamine users.

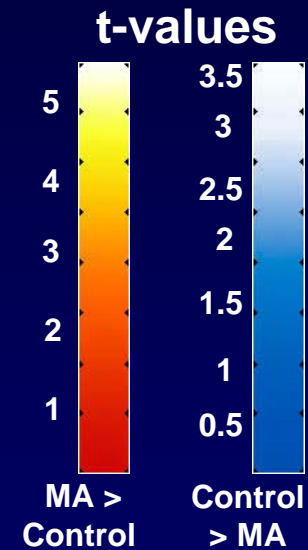
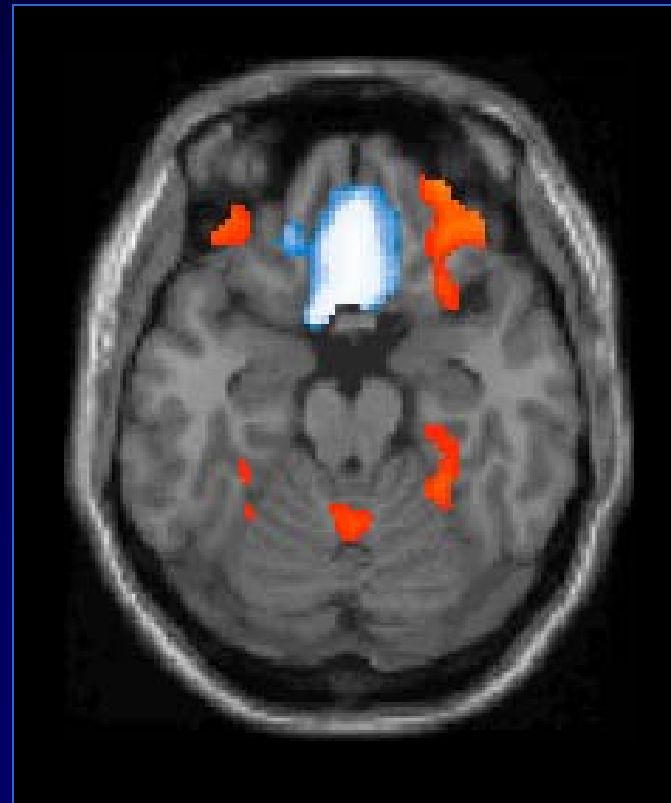


*Cortical white matter increases until the mid-30s in healthy people – not in methamphetamine users.*

# Regional brain activity is abnormal in methamphetamine abusers during early abstinence.

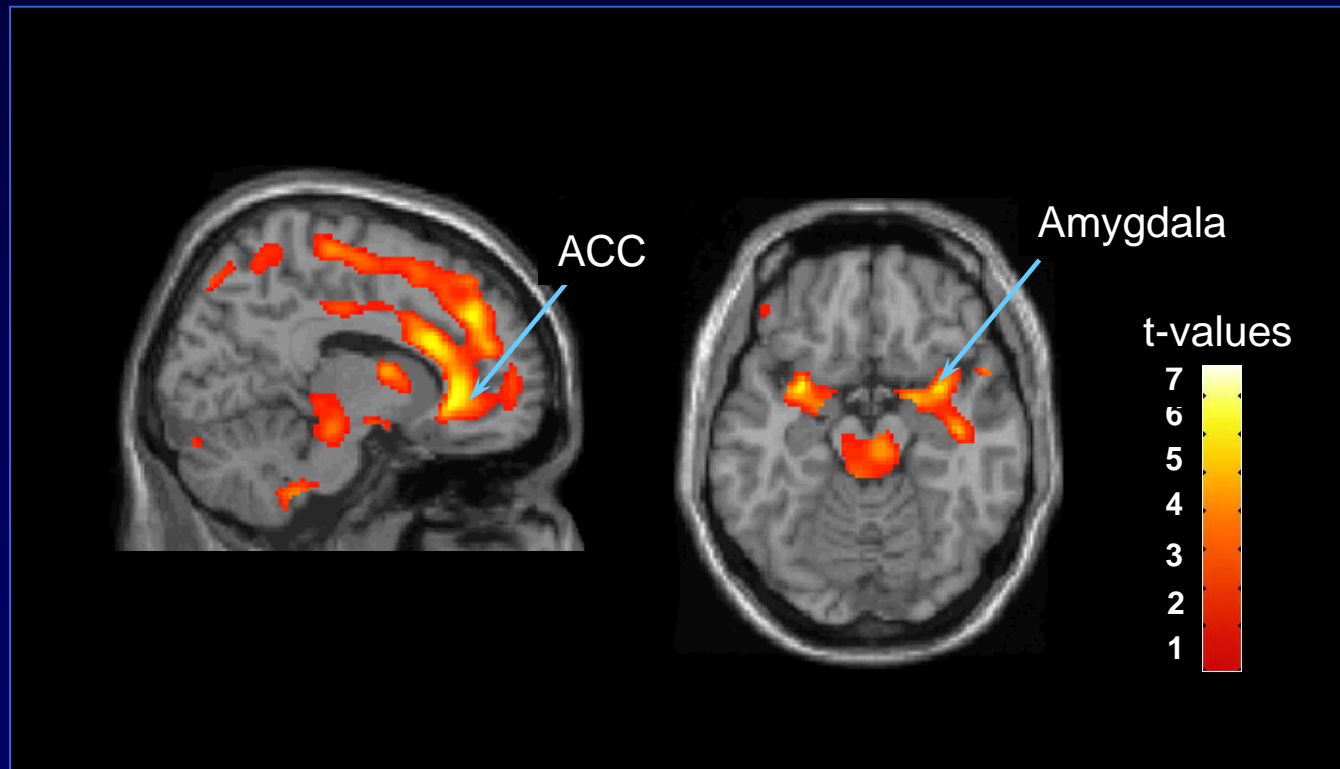


# Orbitofrontal Dysfunction in Methamphetamine Abusers



# Depressive Symptoms in MA Abusers

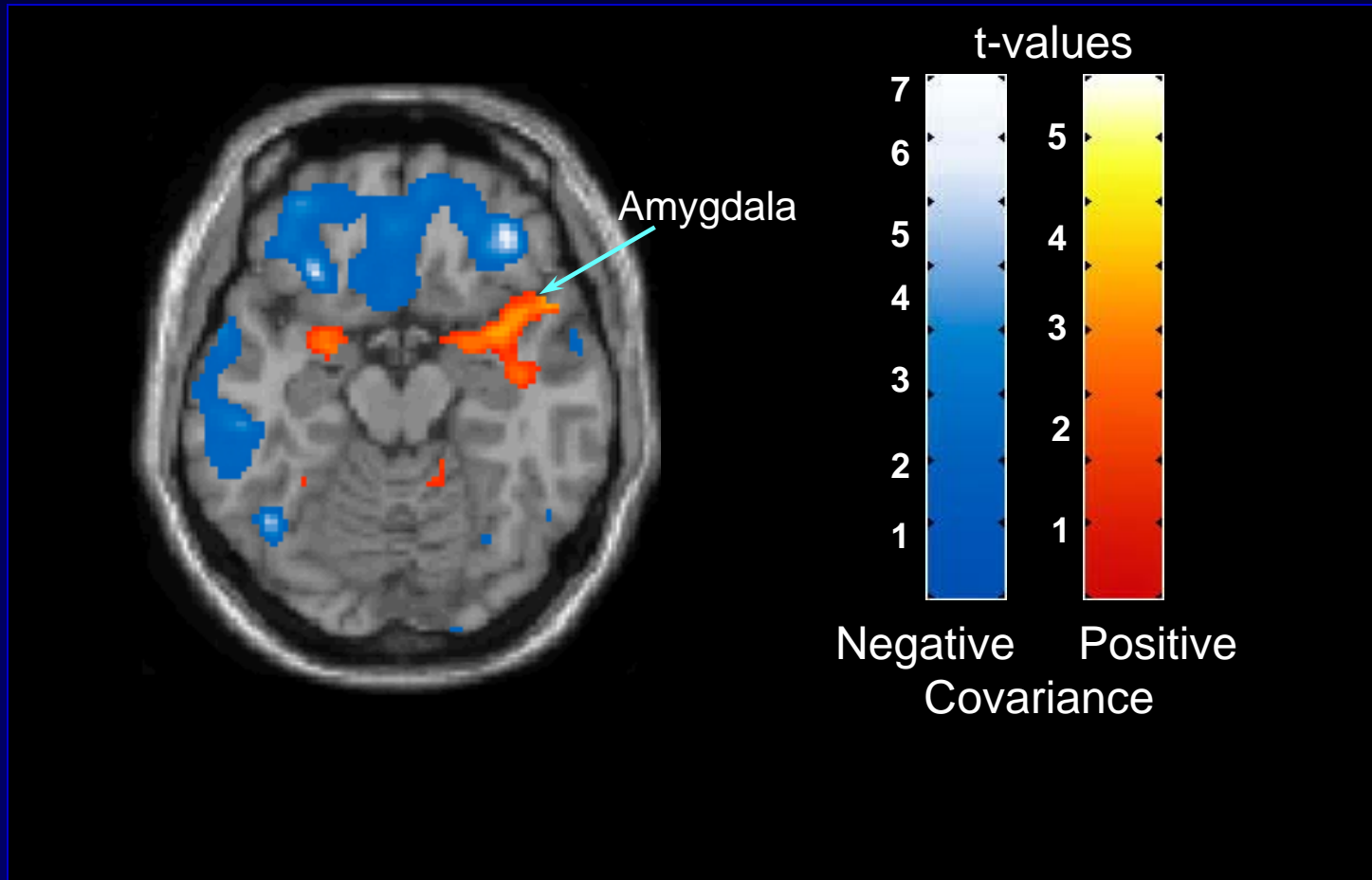
*Positive Covariance with Activity  
of Anterior Cingulate and Amygdala*



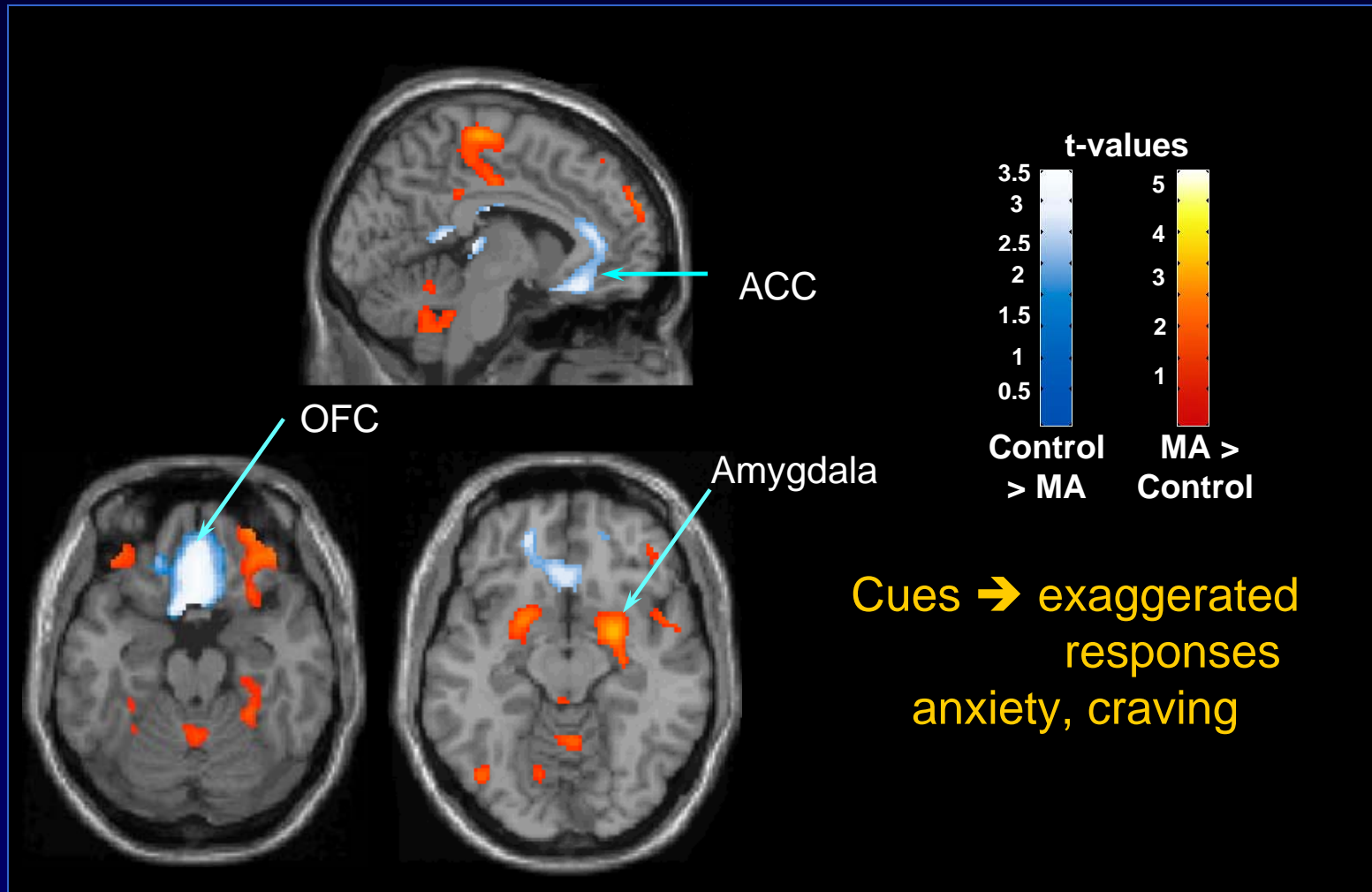
# Anxiety in MA Abusers

*Negative Covariance with Cortical Activity*

*Positive Covariance with Amygdala Activity*



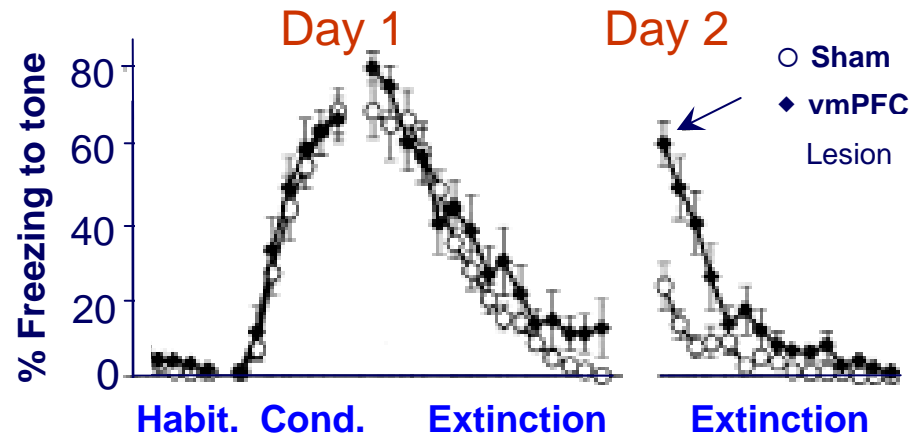
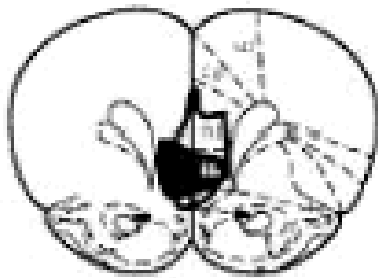
# Loss of Cortical Inhibition of the Amygdala



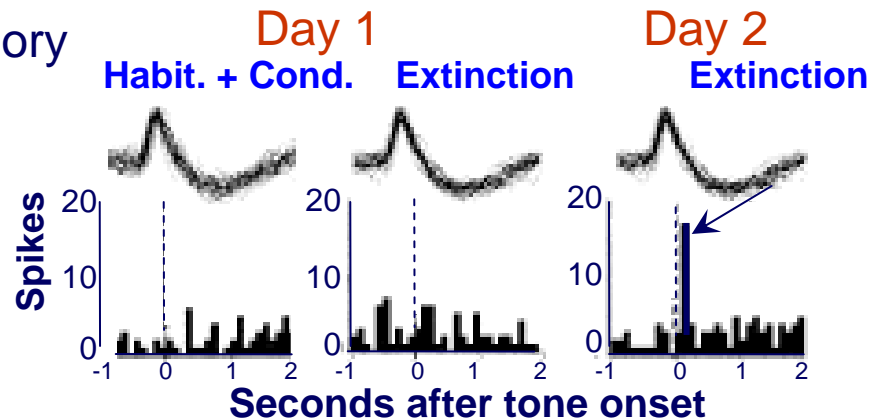
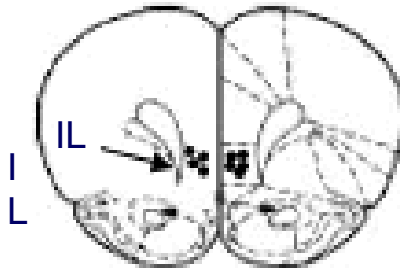
# Infralimbic Cortex

## *Role in Recall of Extinction*

vmPFC lesions block recall of extinction

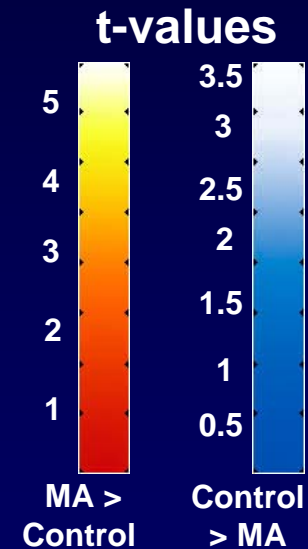
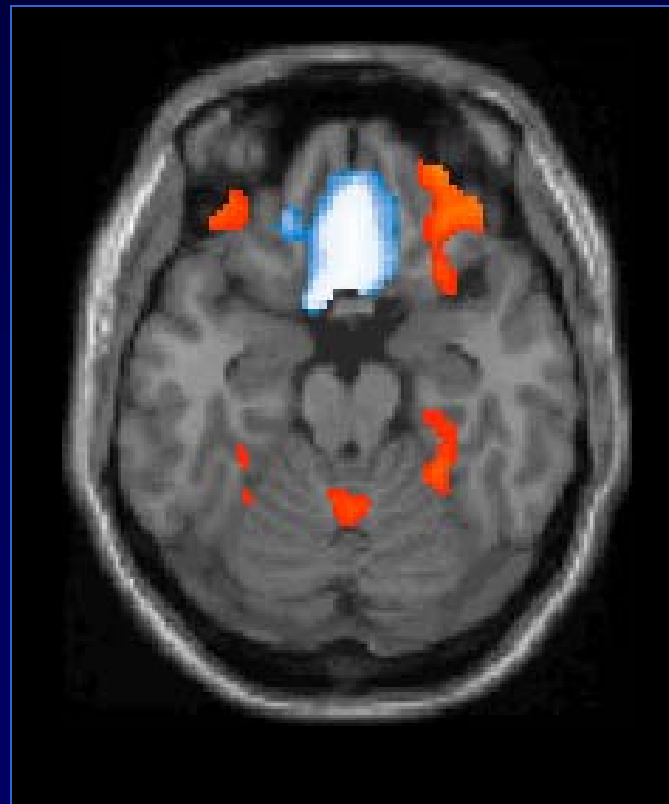


Infralimbic neurons signal extinction memory

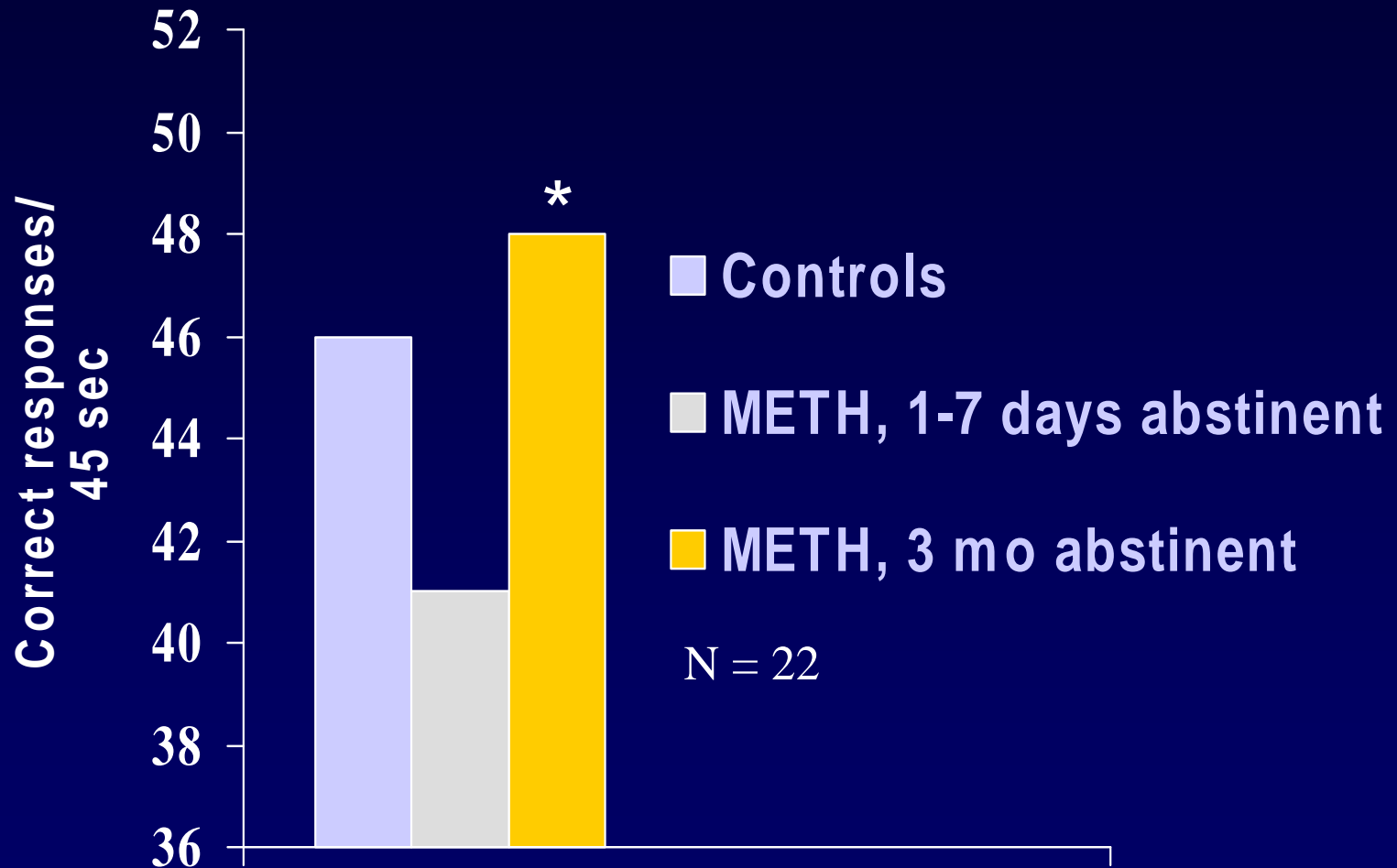


*Adapted from GJ Quirk and DR Gehlert, 2003*

# Orbitofrontal dysfunction shows recovery with continued abstinence.



# Some cognitive functions improve with continued abstinence.



# Conclusions

Cortical dysfunction in methamphetamine dependence

involves regions associated with negative affect:

*Orbitofrontal, Cingulate, Insular*

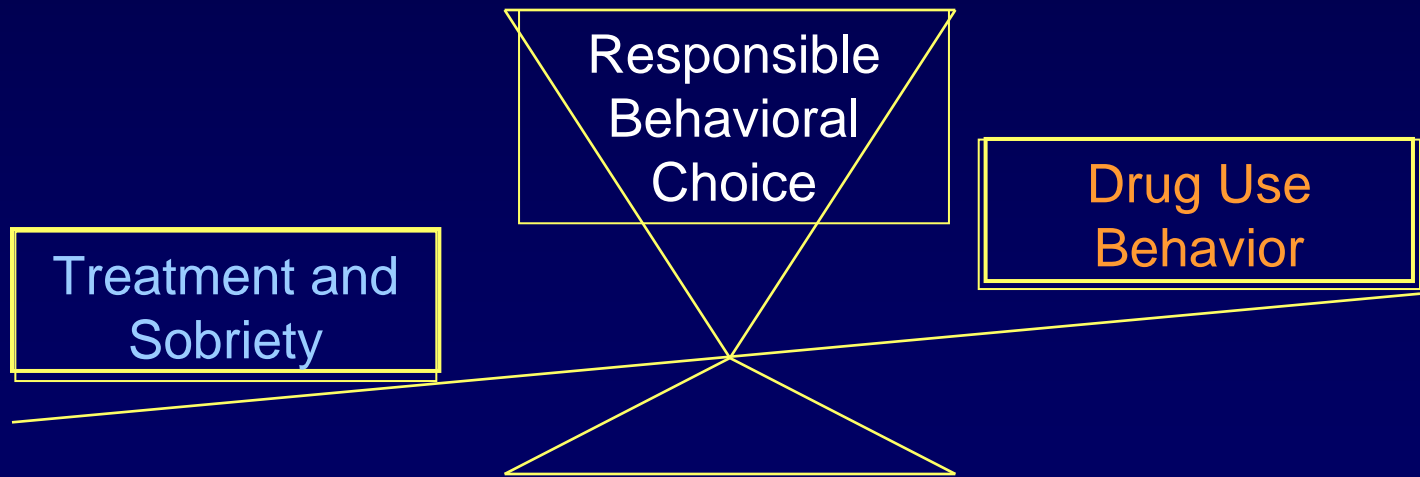
**Negative affect (depression, anxiety)**

- Has *direct* effects on drug taking
- Has *indirect* effects through influencing executive cognitive functions.

# Can imaging help to develop effective treatments?

*Knowledge of affected circuitry can*

- *Identify targets for medications.*
- *Identify brain systems amenable to behavioral therapy*  
*- a moving target.*



# Collaborating Investigators

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