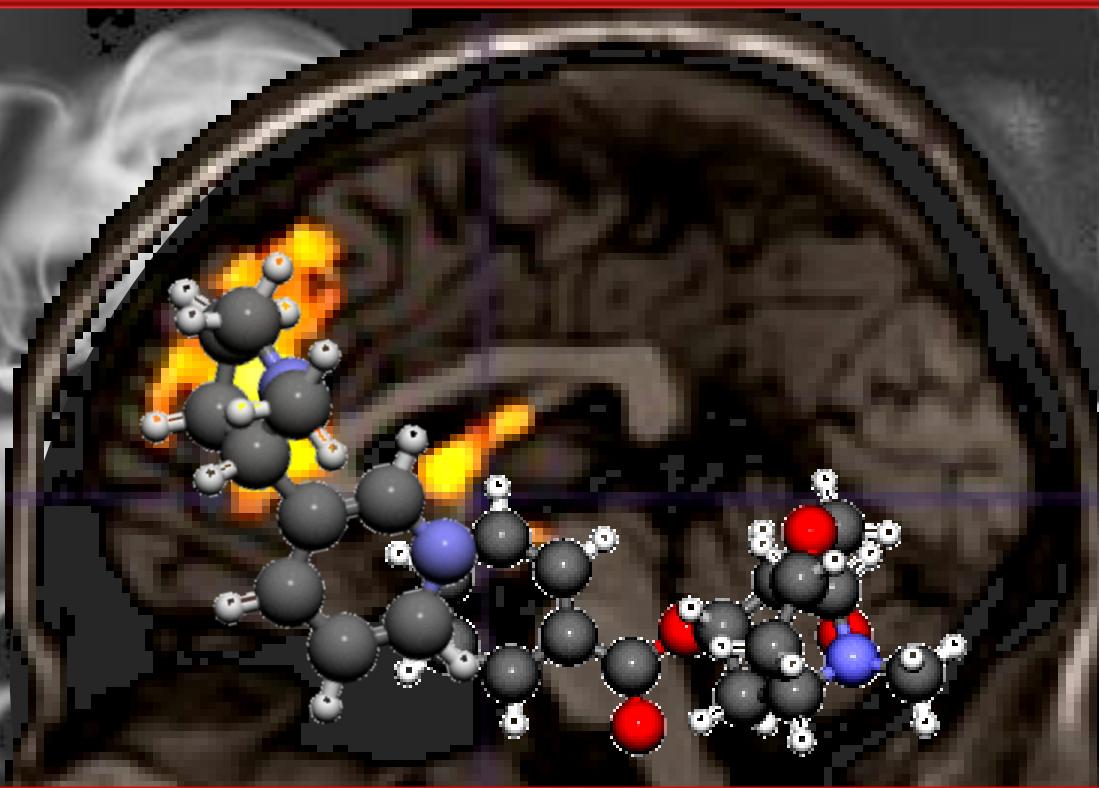


# How Do Drugs Enslave Our Brains?



Nora D. Volkow, M.D.  
Director

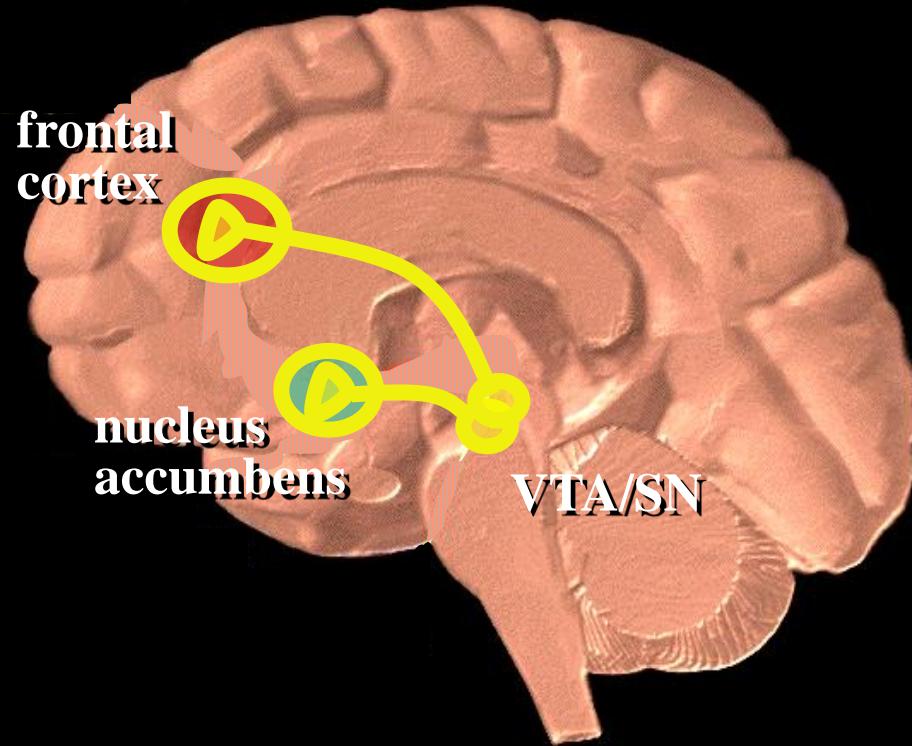


National Institute  
on Drug Abuse

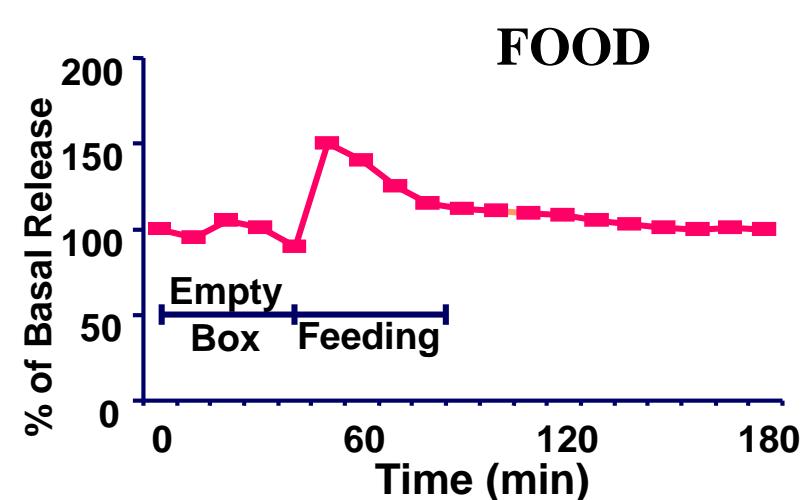
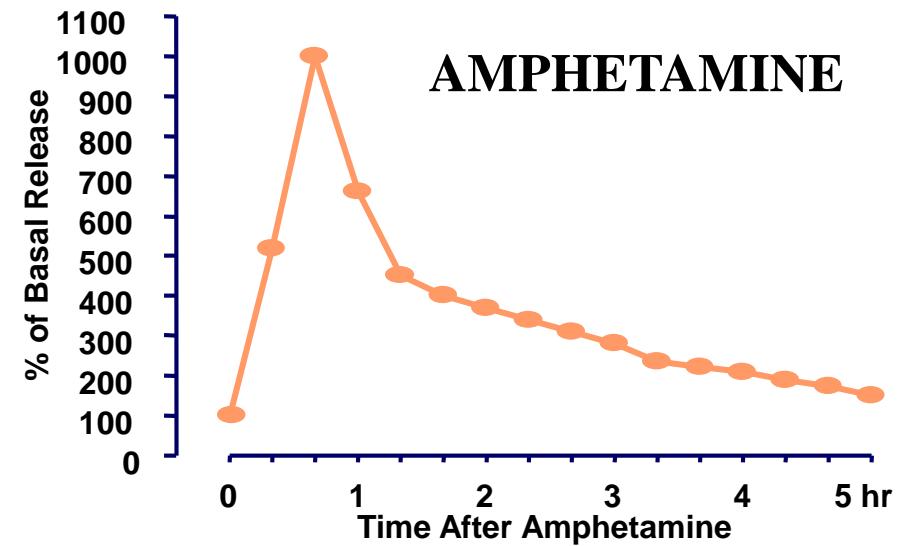


@NIDAnews

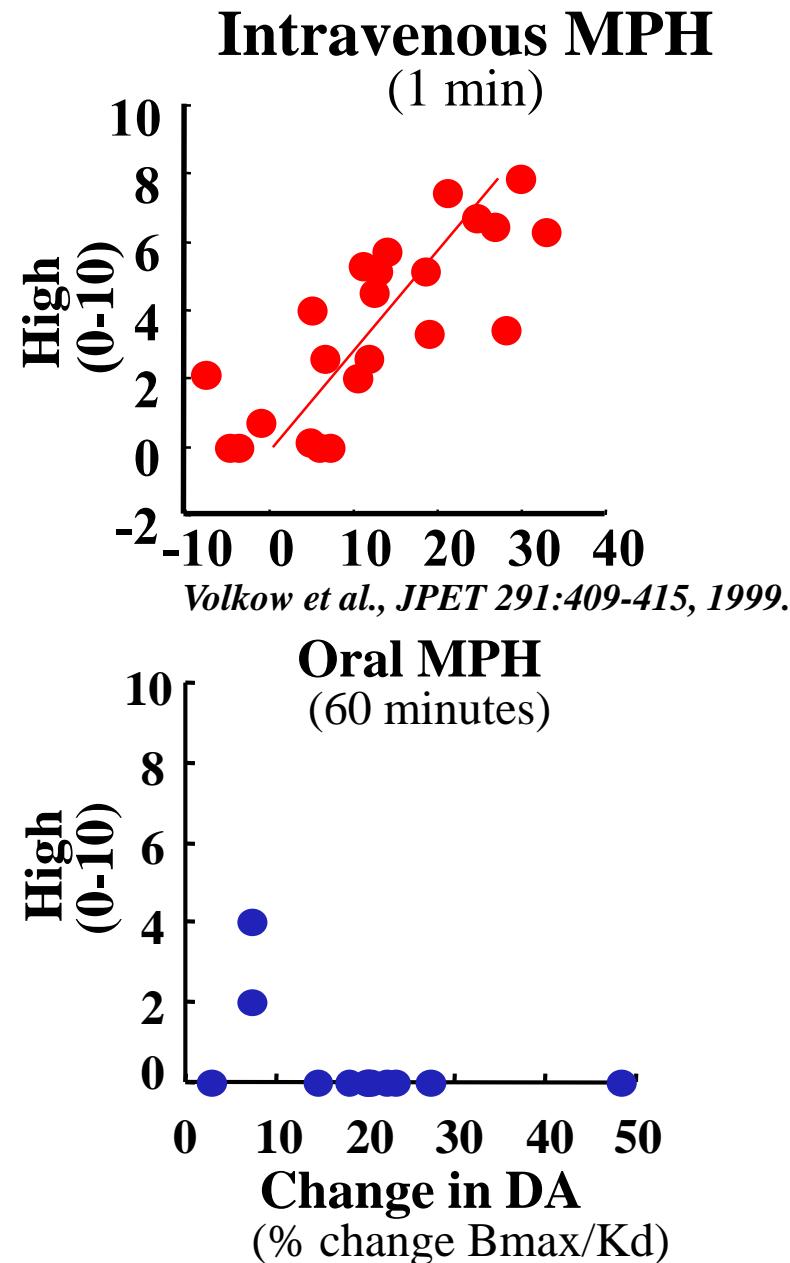
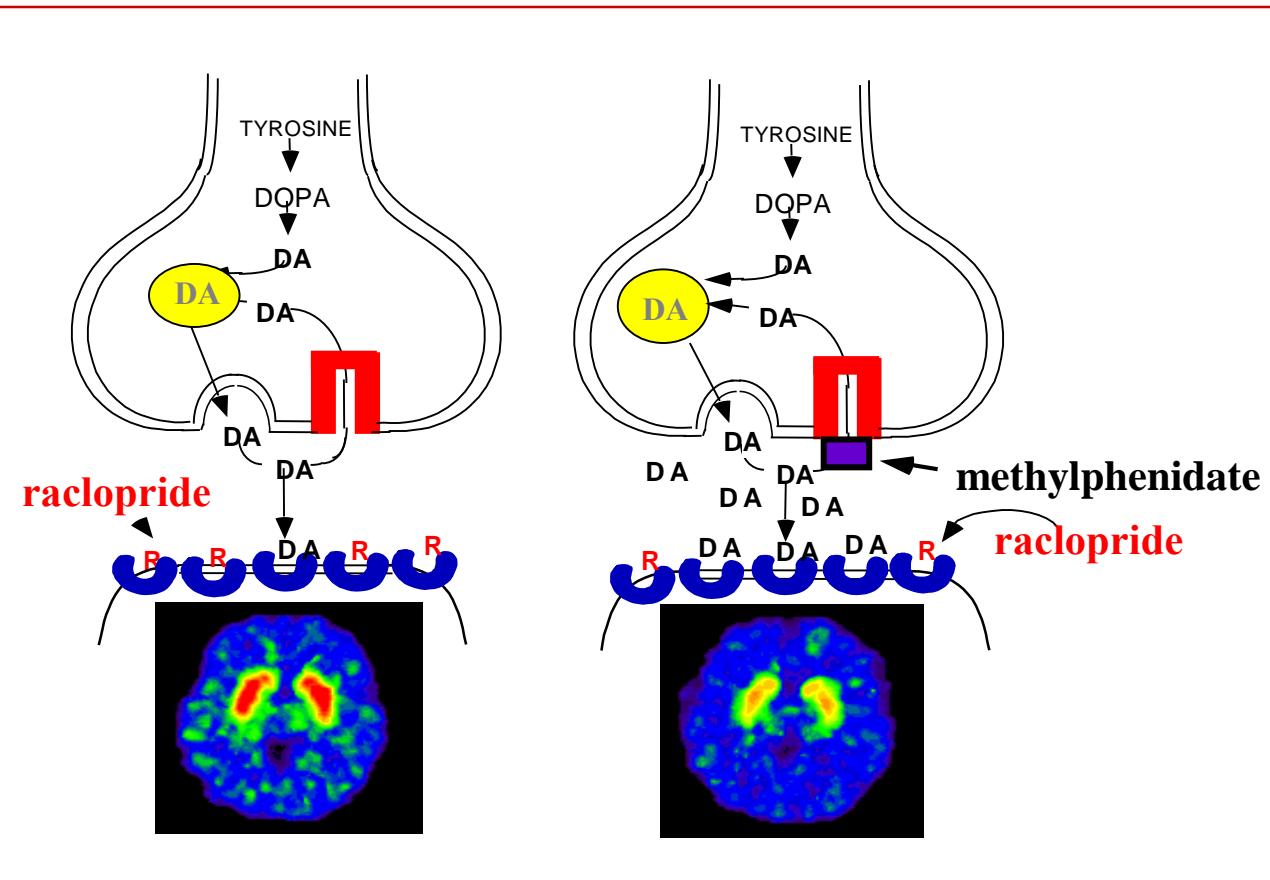
# Natural & Drug Reinforcers Increase Dopamine in NAc



Drugs of abuse increase DA in the Nucleus Accumbens, which is believed to trigger the neuroadaptations that result in addiction

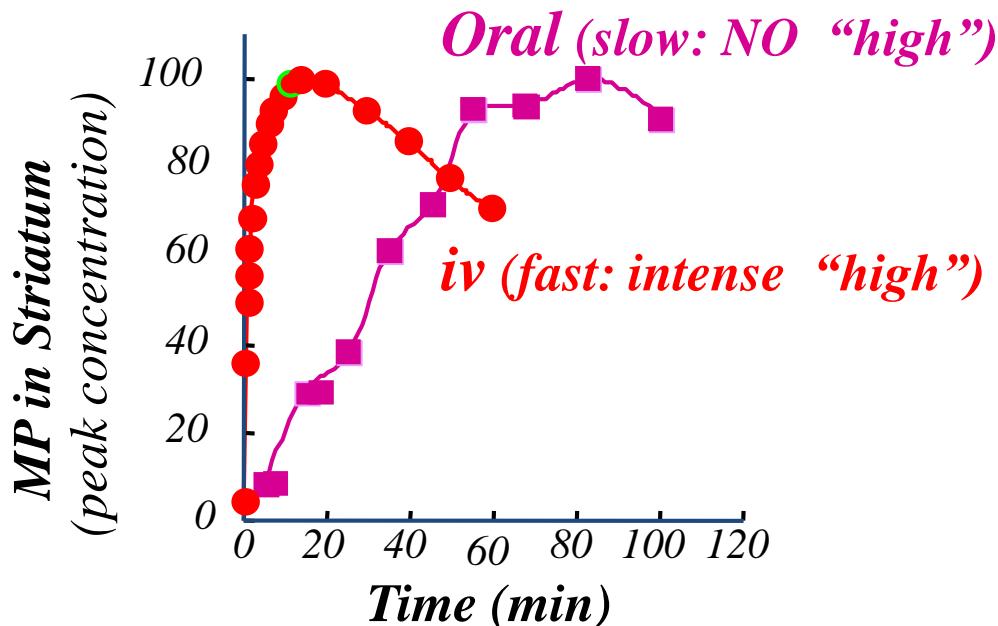


# DA and the Rewarding Effects of Drugs in Humans



*DA increases induced by intravenous but not by oral administration of MPH were associated with the “high”... WHY?*

# Pharmacokinetics of Oral and IV MPH in Baboon Brain

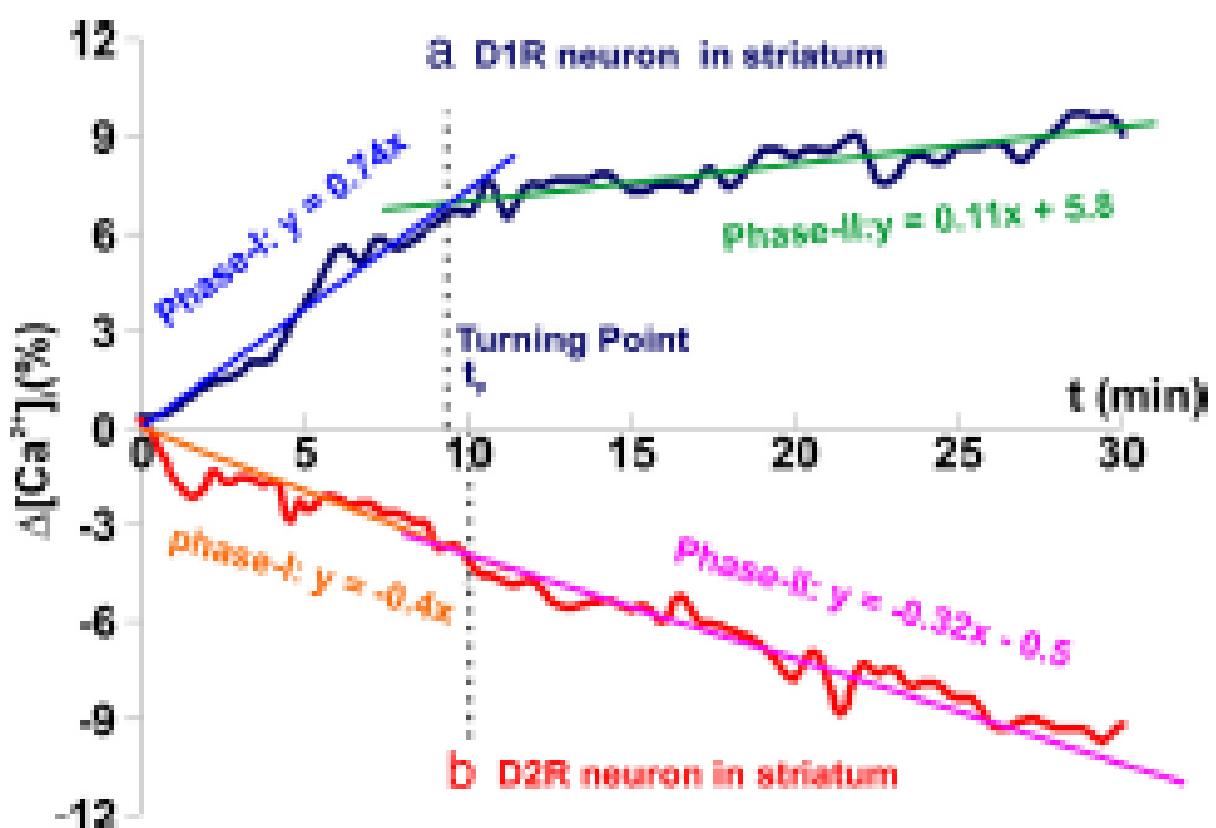
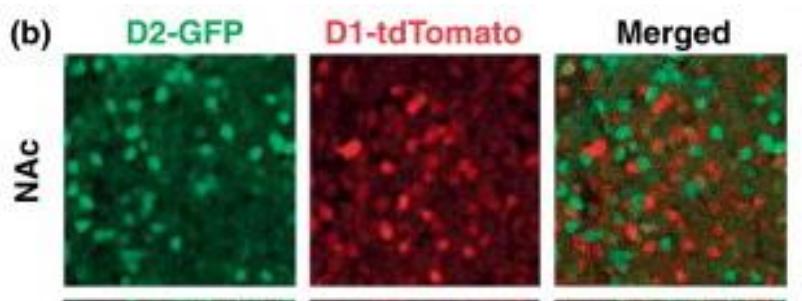
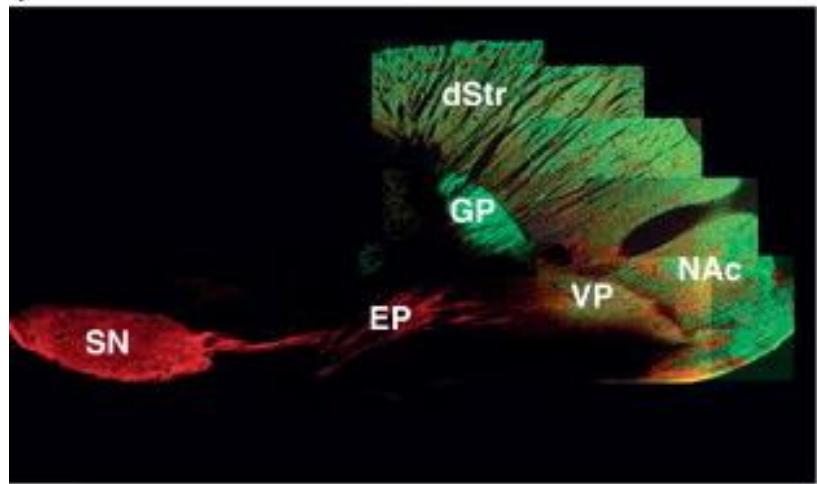


Volkow et al PNAS 2011.

Drug reinforcing effects result from **FAST DA increases emulating phasic DA cell signaling (15-30 Hz)**, which are implicated in ***reward and conditioning*** rather than **tonic DA signaling (2-10 Hz)**, which are implicated in ***cognitive, motivational and motoric systems***.

- D1R are predominantly stimulated by **phasic DA** and
- D2R are stimulated by **phasic and tonic DA**.
- Drug reward **requires stimulation of D1R and is optimal when both D1R and D2R are stimulated**

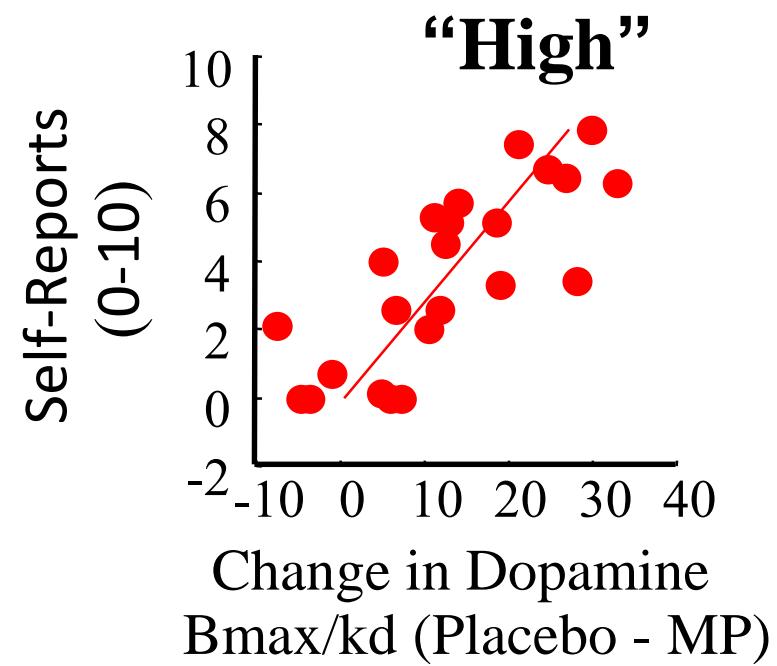
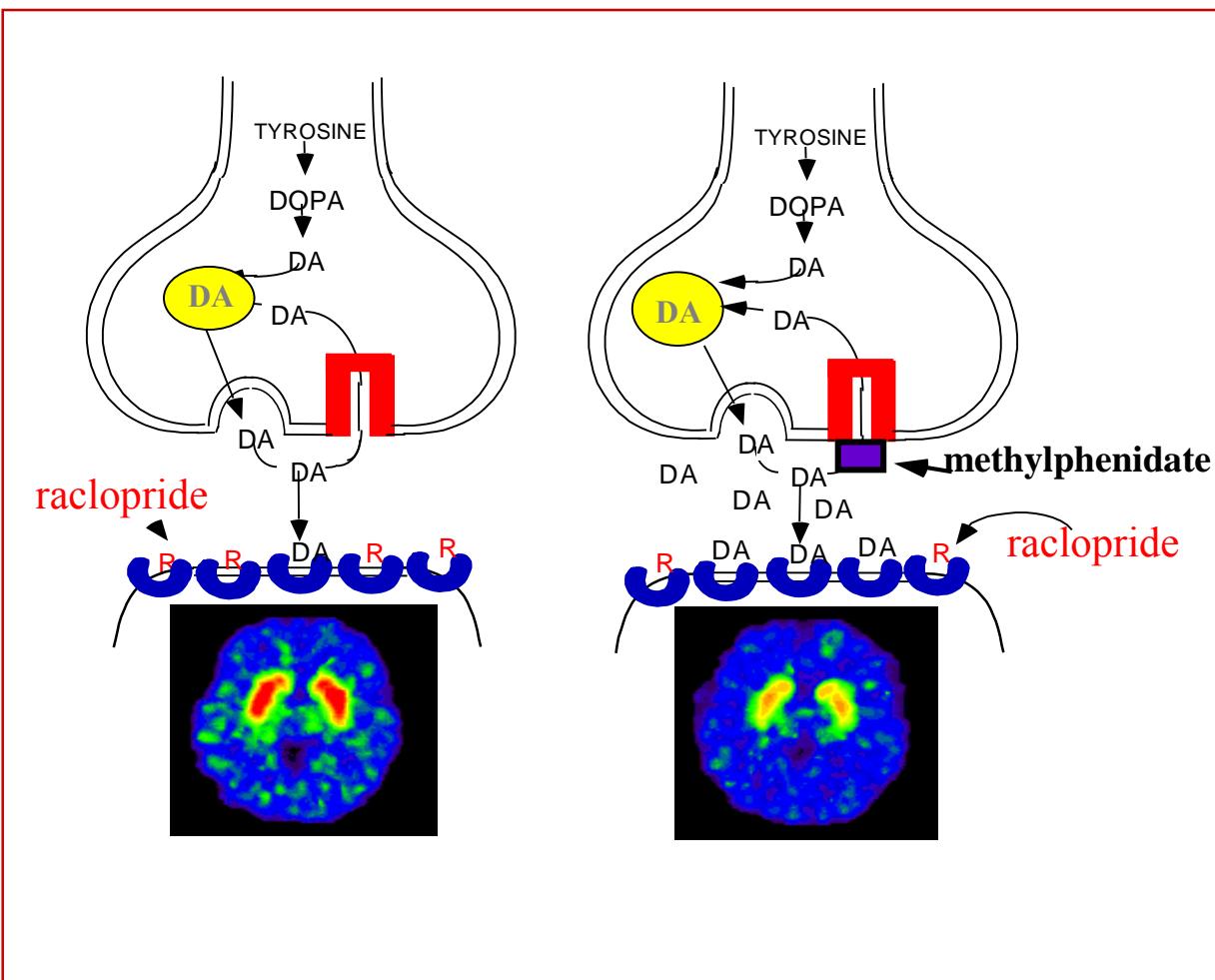
# Cocaine's Rewarding Effects Entail Both Its Fast Stimulation of D1R & A Slower Stimulation of D2R



Luo Z et al., J Neurosci Sept 14, 2011 31(37):13180 –13190.

Smith RJ et al., Current Opinion in Neurobiology 2013, 23:546–552.

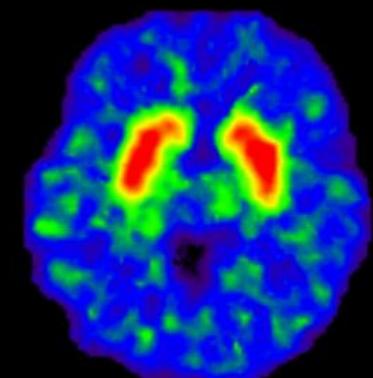
# Reward Circuit in Addiction



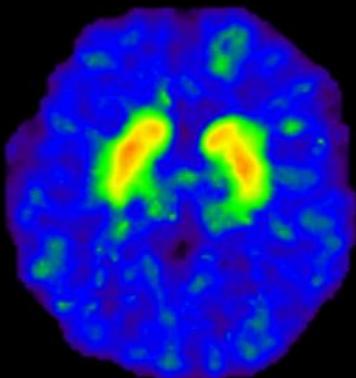
Volkow et al., JPET 291(1):409-415, 1999.

# Methylphenidate-induced Increases in Striatal DA in Controls and in **Detoxified** Cocaine Abusers

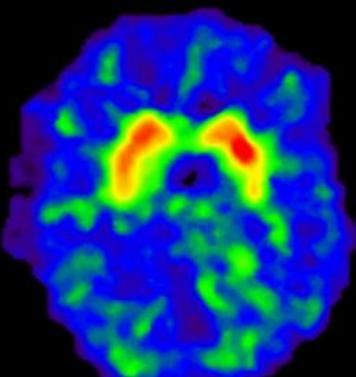
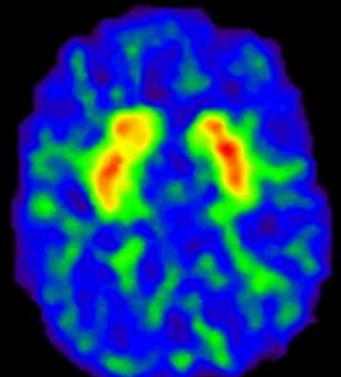
Placebo



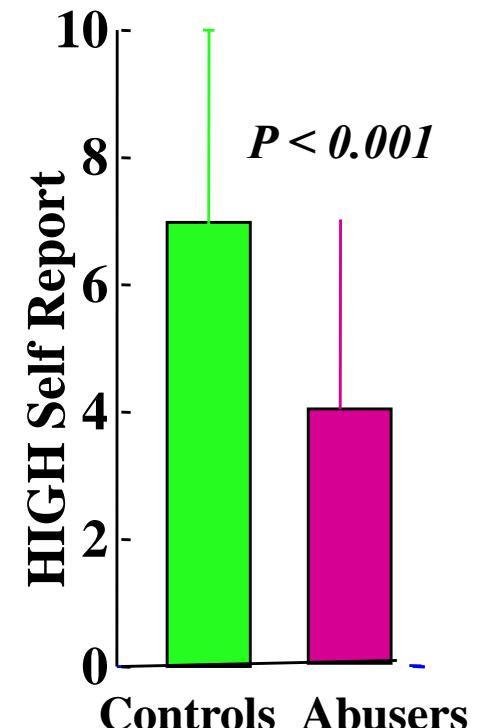
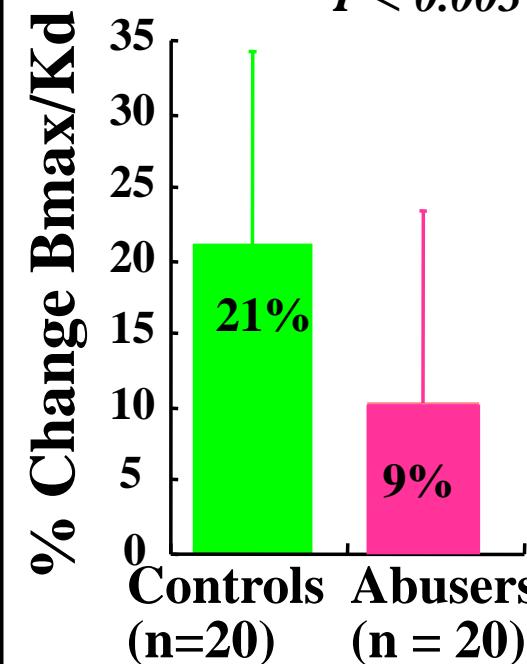
MP



Normal Control

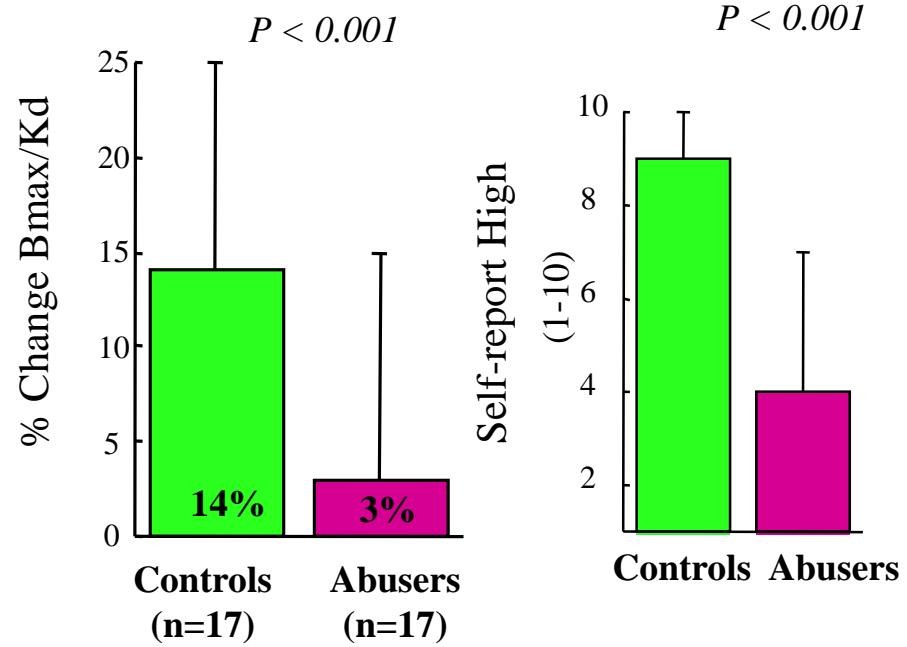
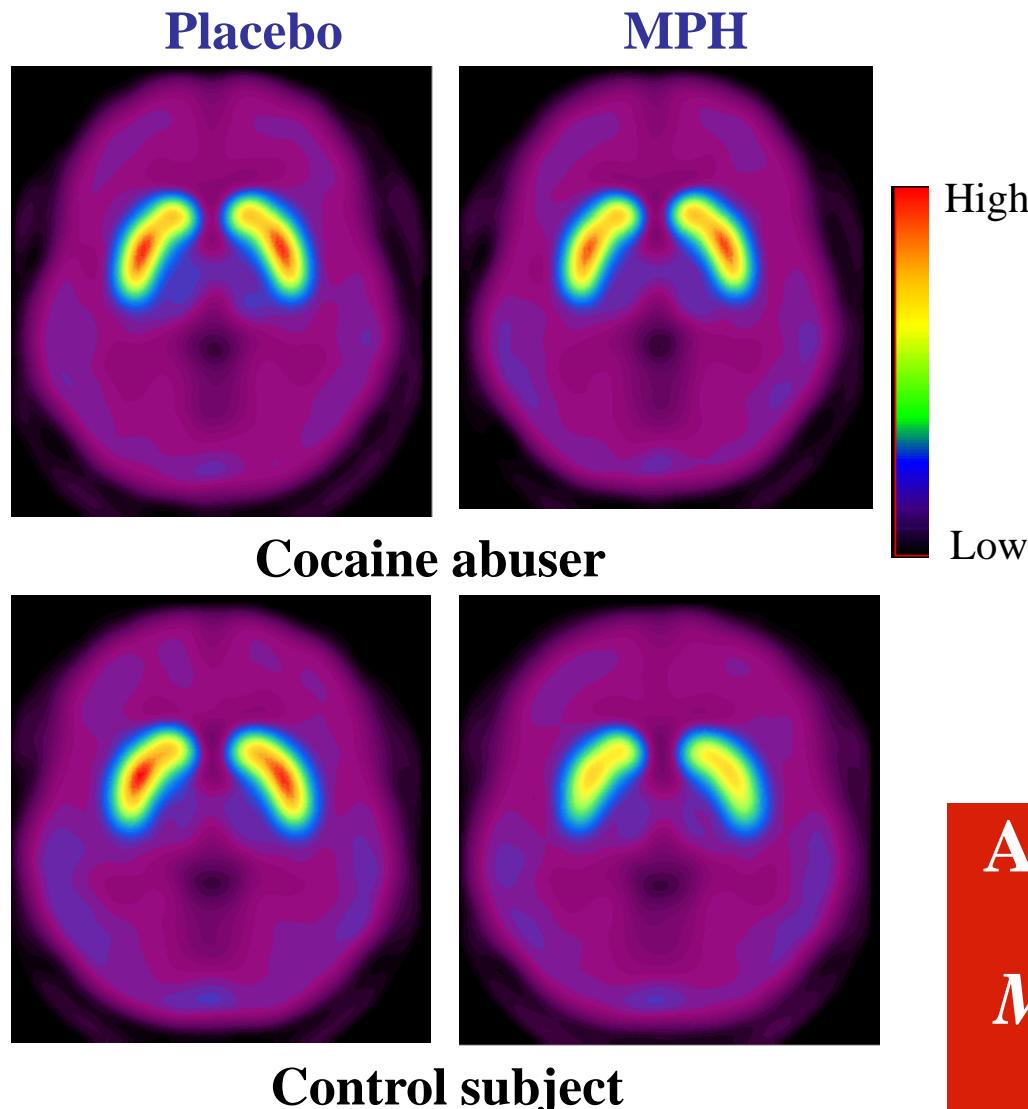


Cocaine Abuser



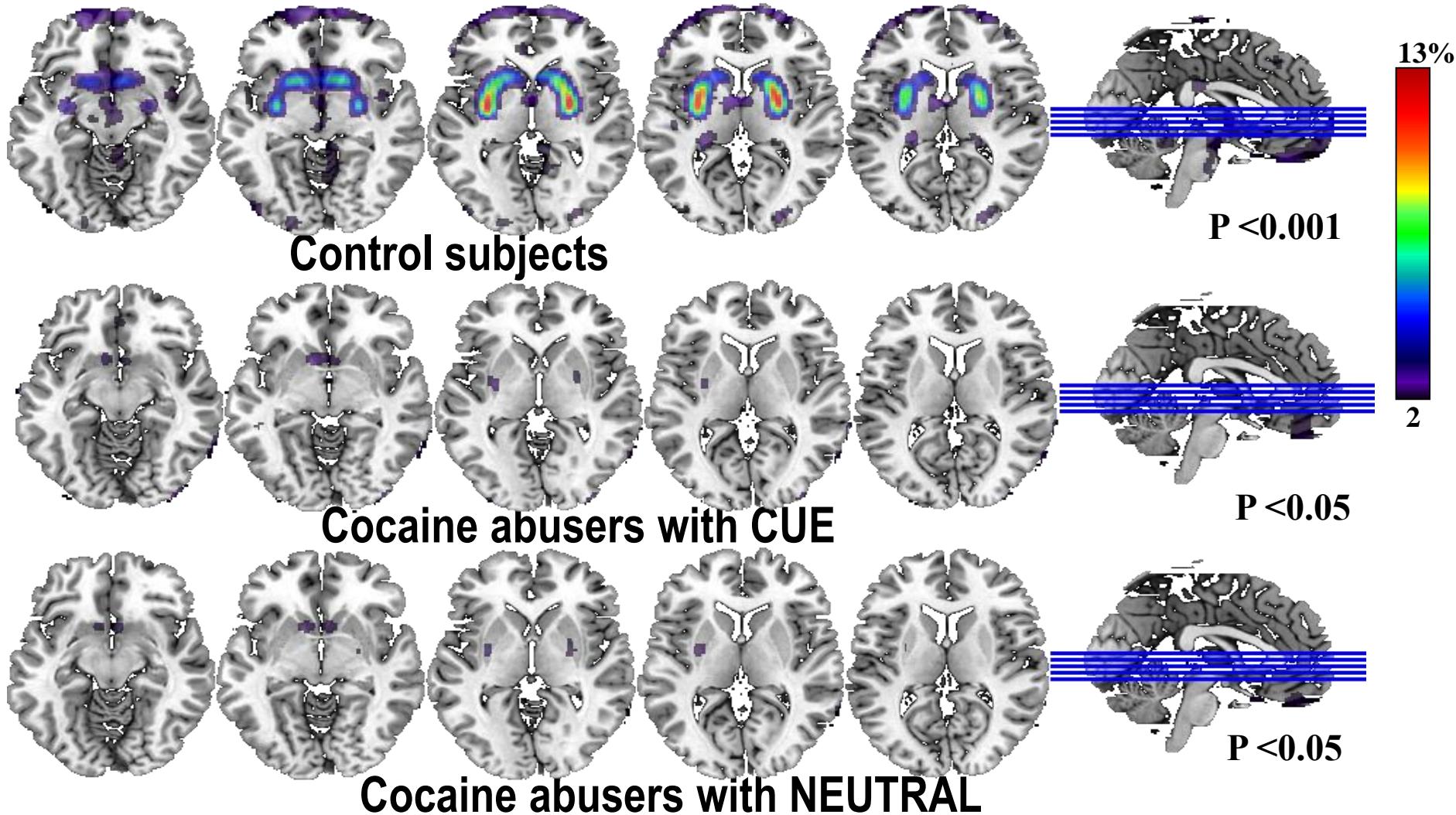
Cocaine abusers showed *decreased* DA increases and reduced reinforcing responses to MP

# Reactivity of Dopamine System To Drug Consumption in Actively Using Addicted Subjects



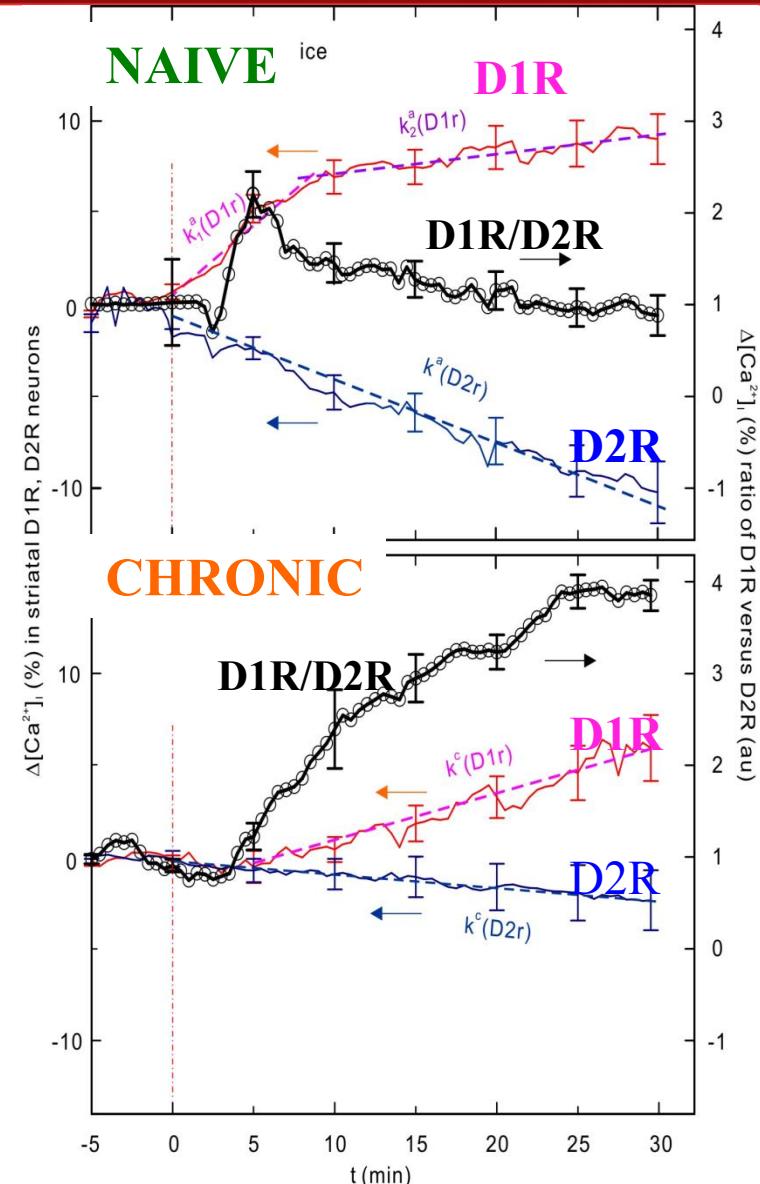
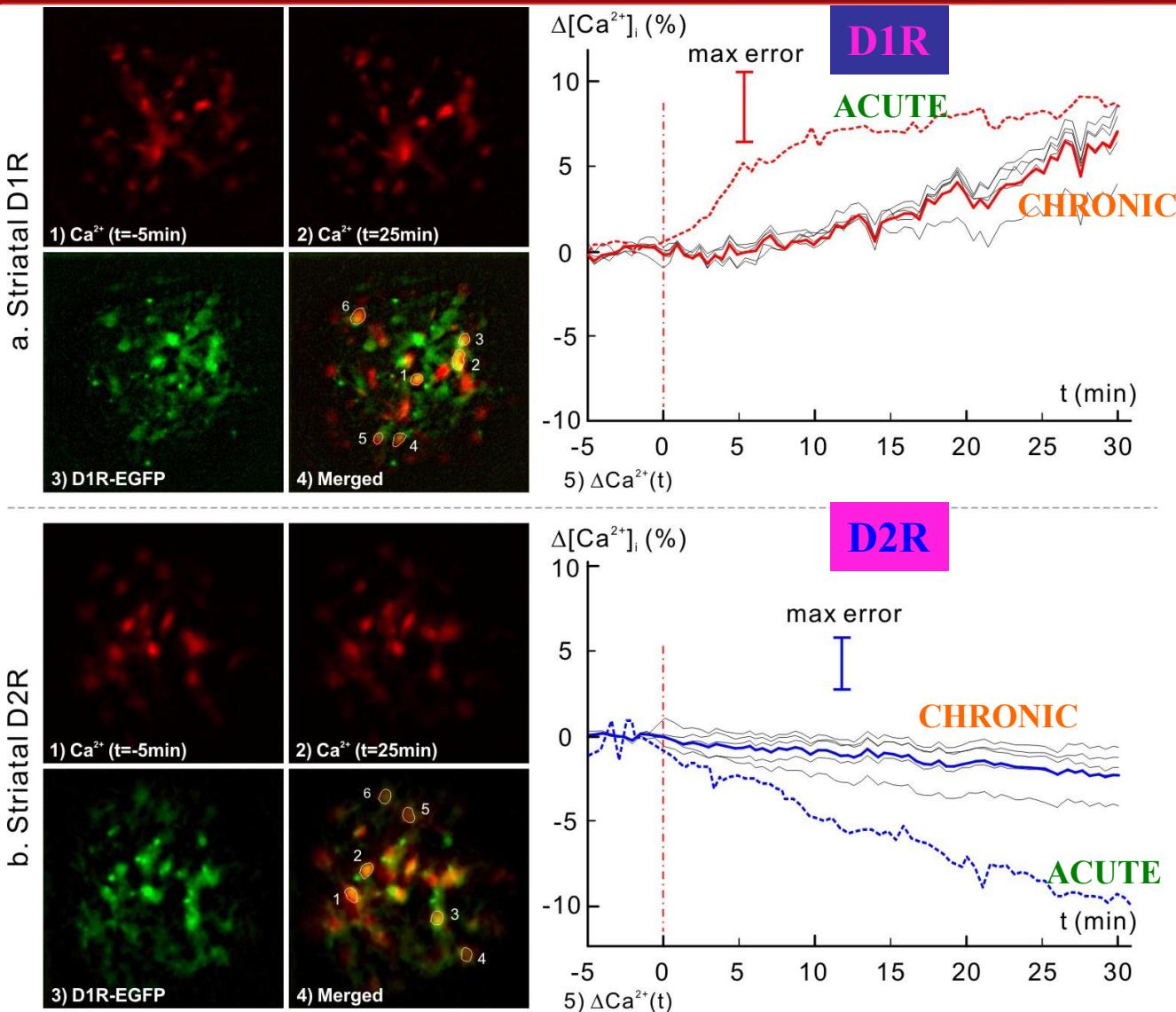
Active cocaine abusers showed a marked *reduction* in MPH-induced DA increases and in its reinforcing effects

# MP-Induced DA Change Controls vs Cocaine Abusers (with and without cues)



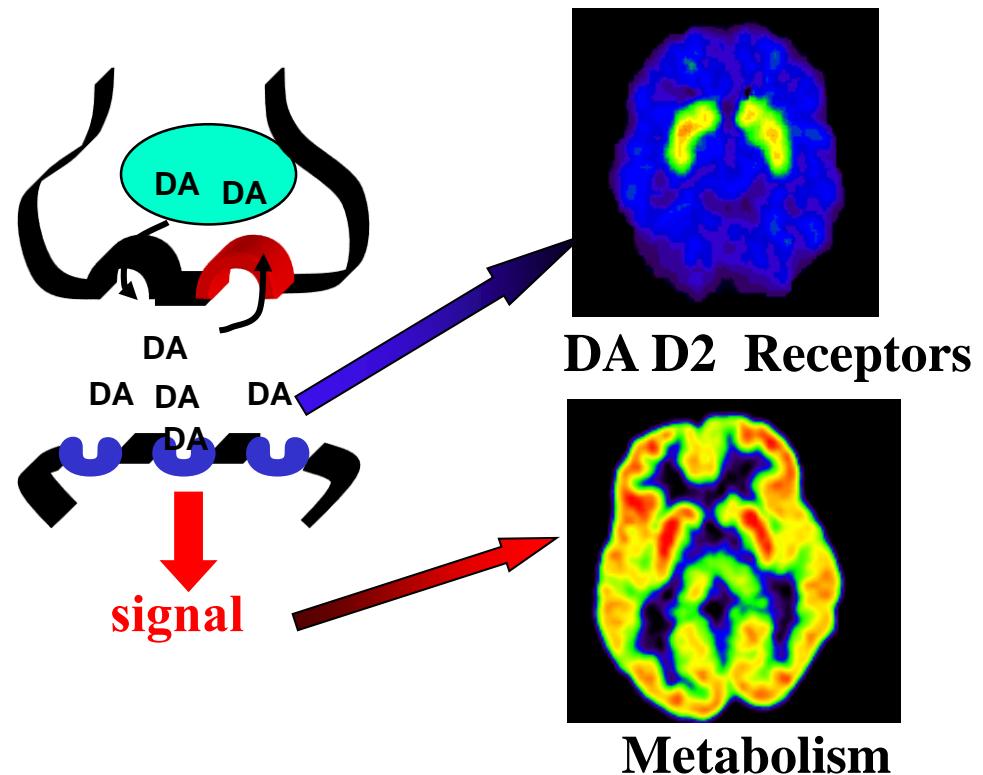
*MP increased DA in controls ( $p<0.001$ ) whereas in cocaine abusers the effects were minimal and only significant in VS ( $p<0.05$ )*

# Effects Of Chronic Cocaine In D1R and D2R Signaling During Intoxication

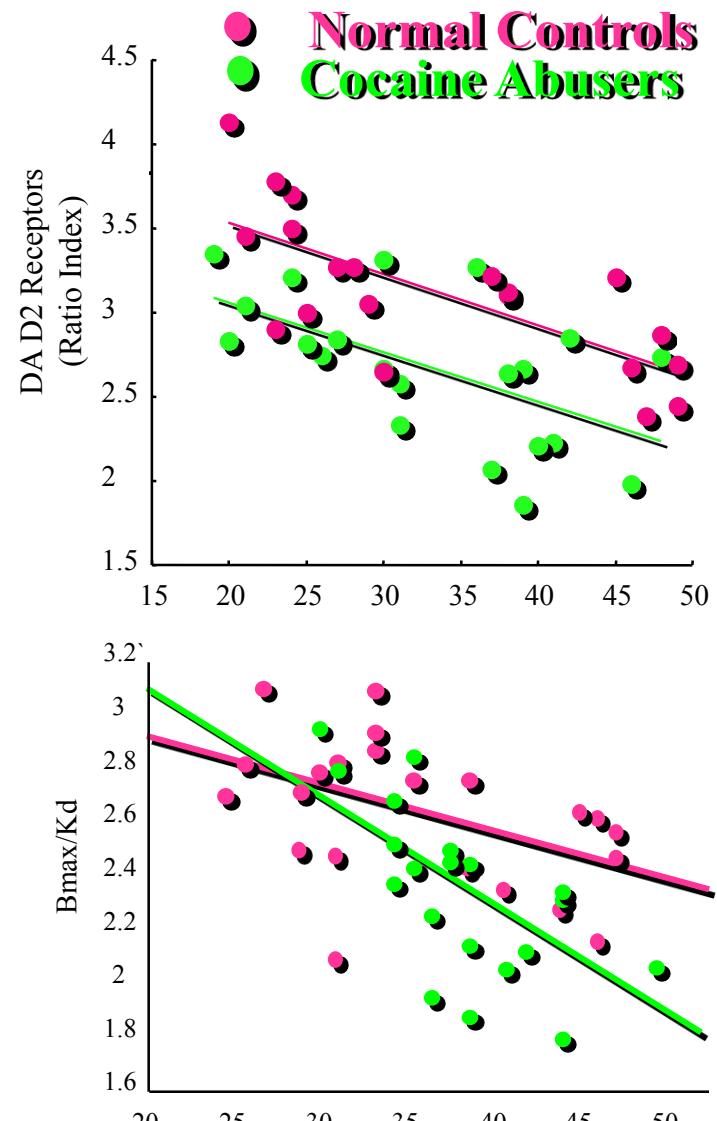
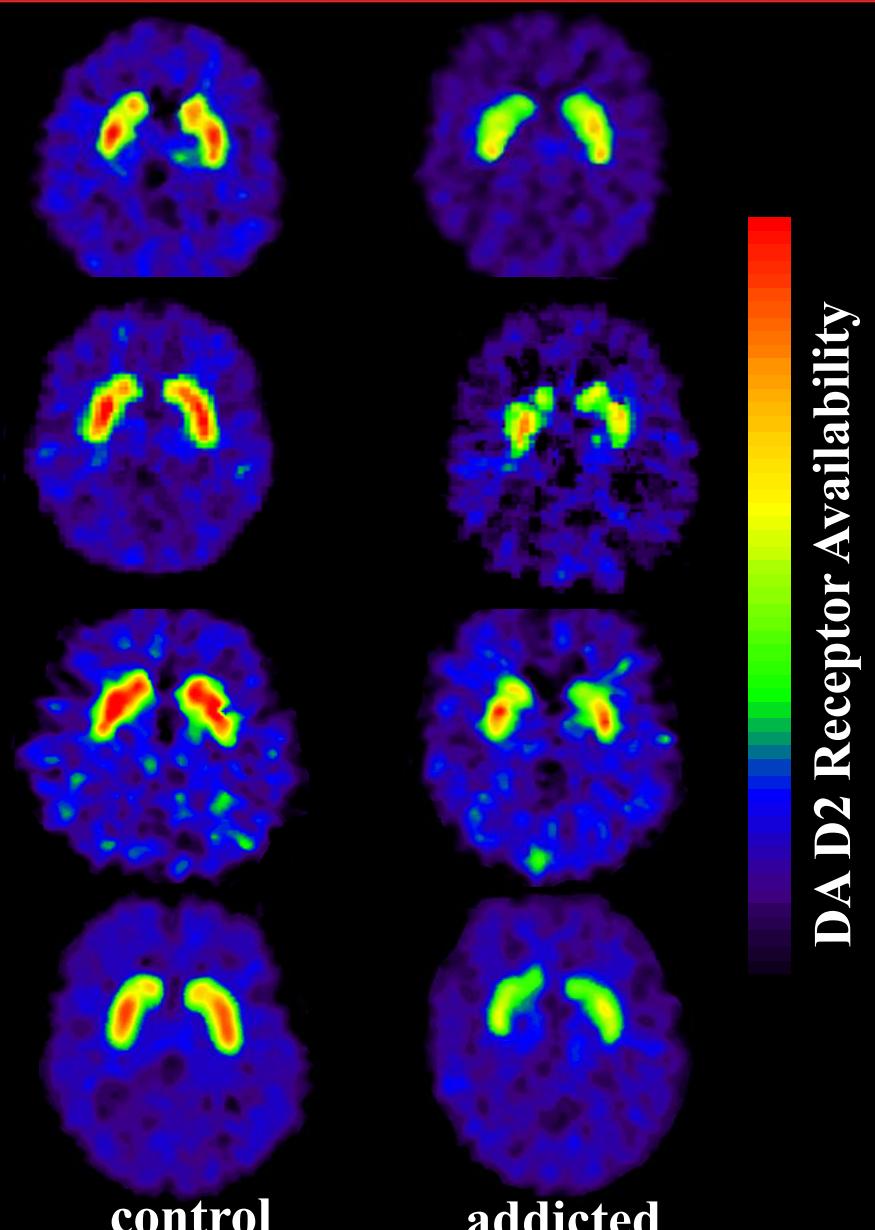


# Motivation & Executive Control Circuits

Here we tested if, in addicted subjects, changes in DA function were linked with disruption of frontal activity as assessed by multiple tracer studies that evaluated in the same subject dopamine D2 receptors and brain glucose metabolism (marker of brain function).

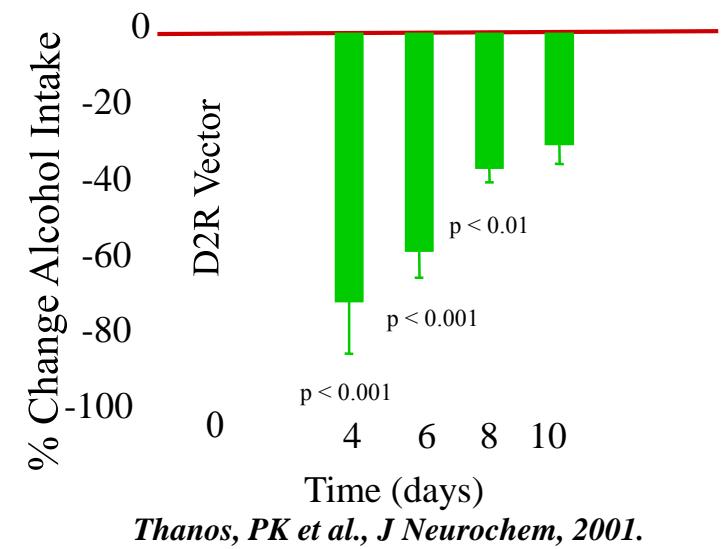
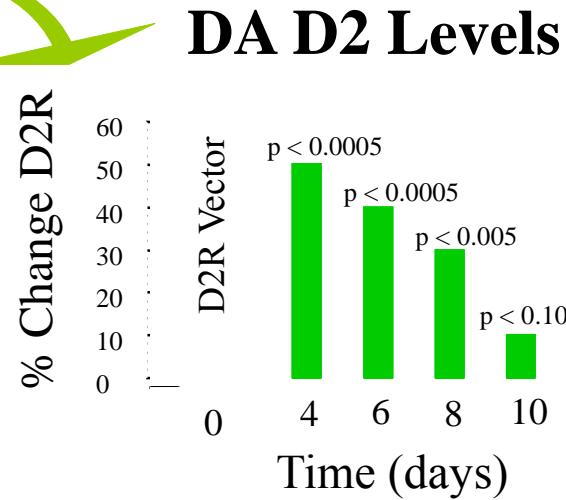
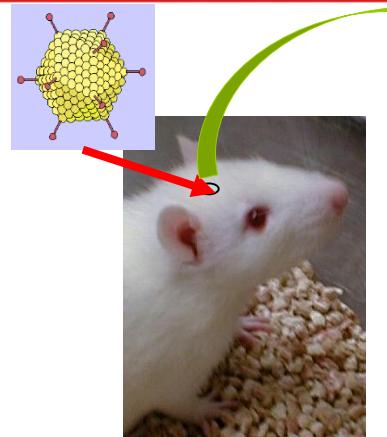


# Dopamine D2 Receptors are Lower in Addiction

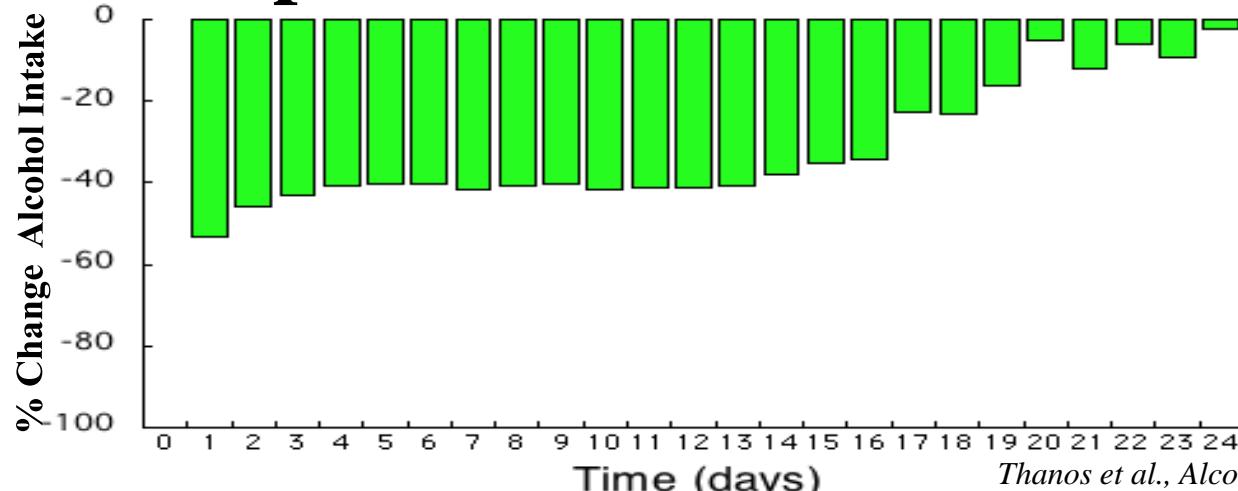


Volkow et al., Neuro Learn Mem 2002.

# D2R Overexpression in Sprague Dawleys



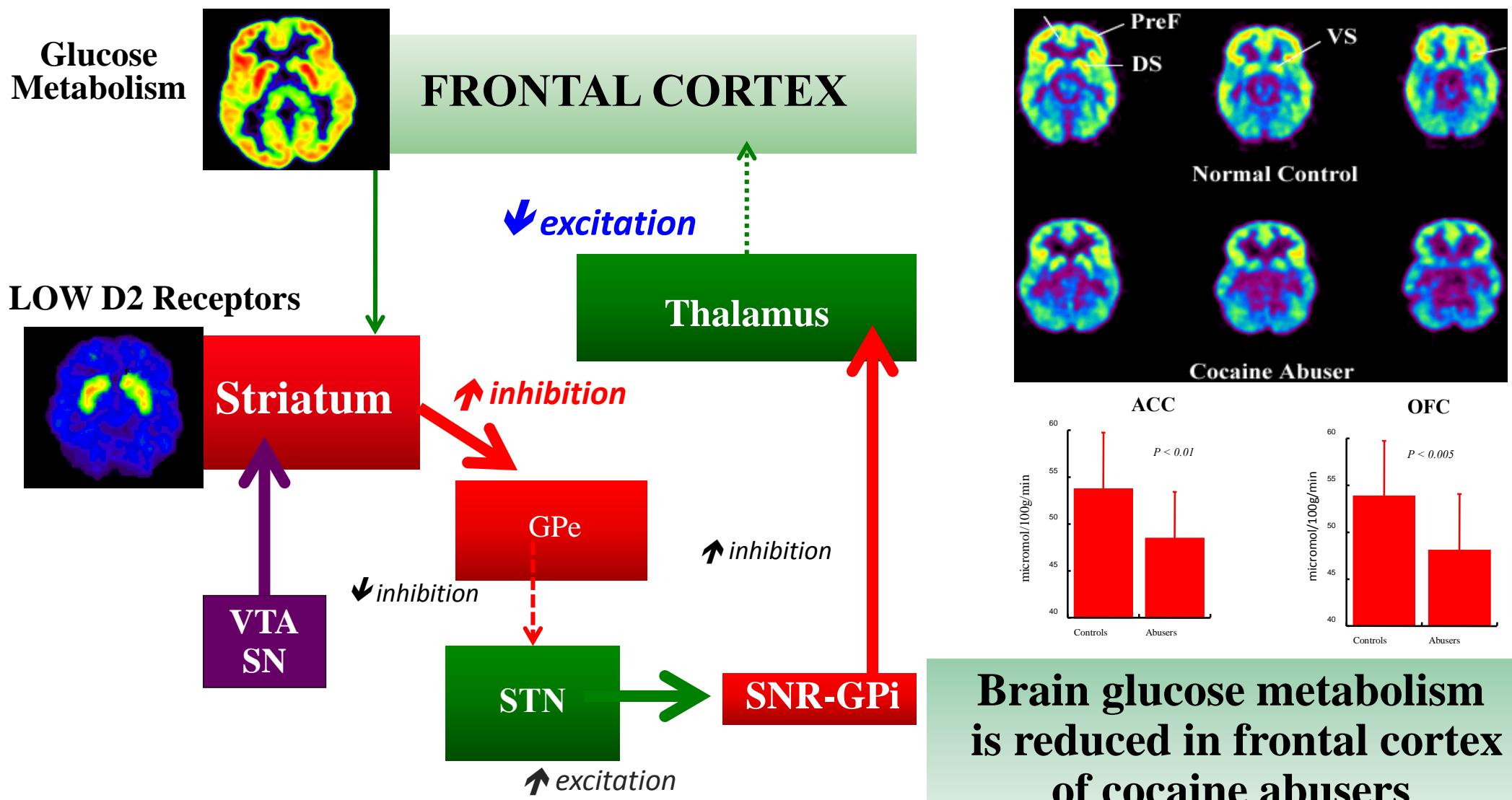
## D2R Overexpression In Alcohol Preferring Rats



*Thanos et al., Alcohol Clin Exp Res.*

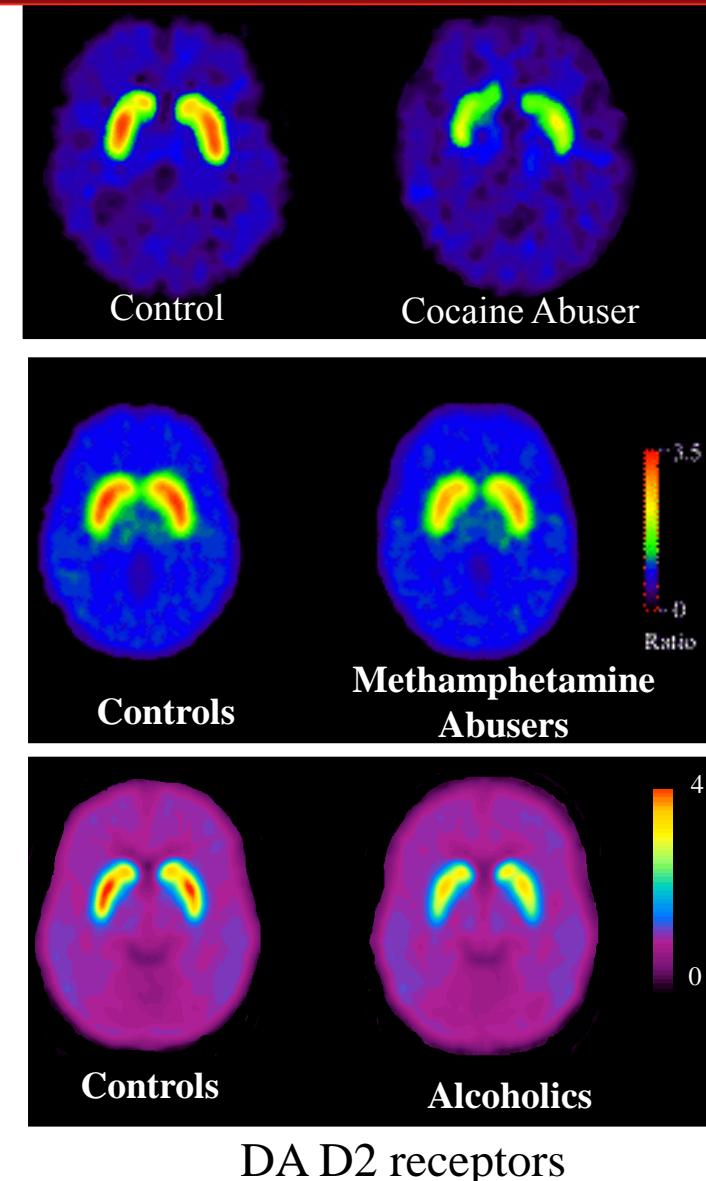
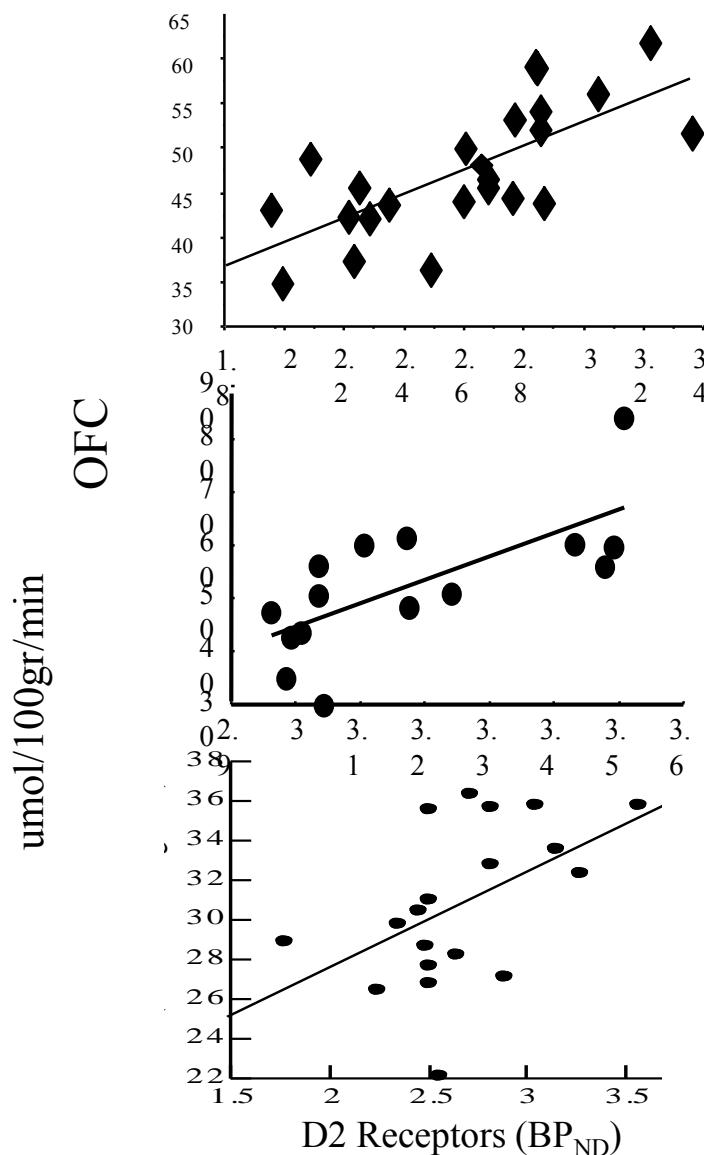
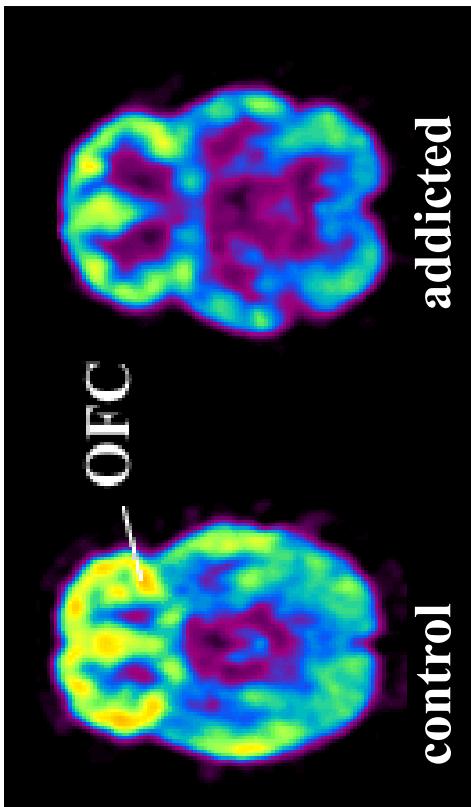
*Over-expression of D2 receptors in rats markedly reduces alcohol intake*

# Expected Consequences of Reduced Striatal D2R Signaling in Indirect Pathway

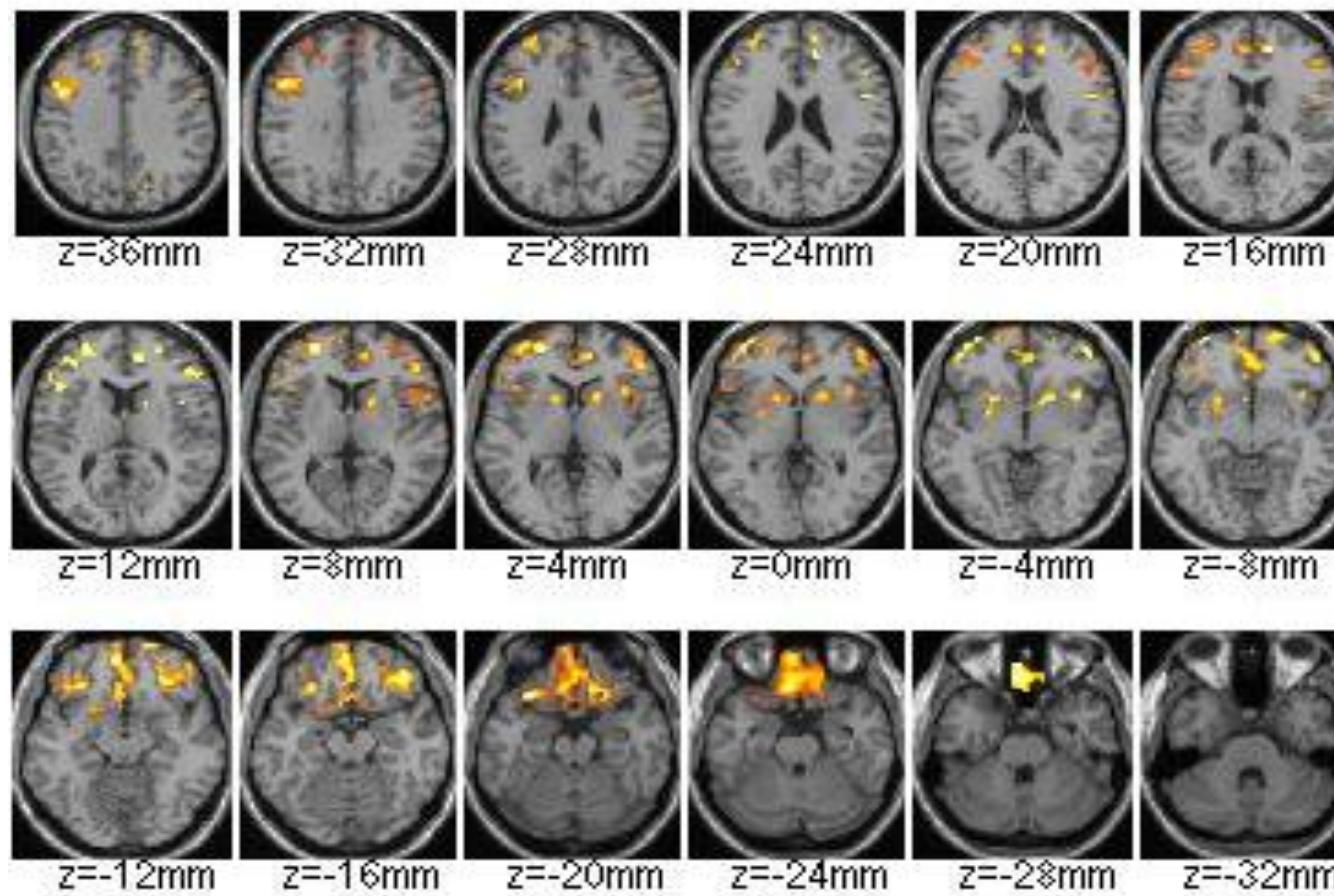


# Relationship Between Brain Glucose Metabolism and Striatal D2 Receptors

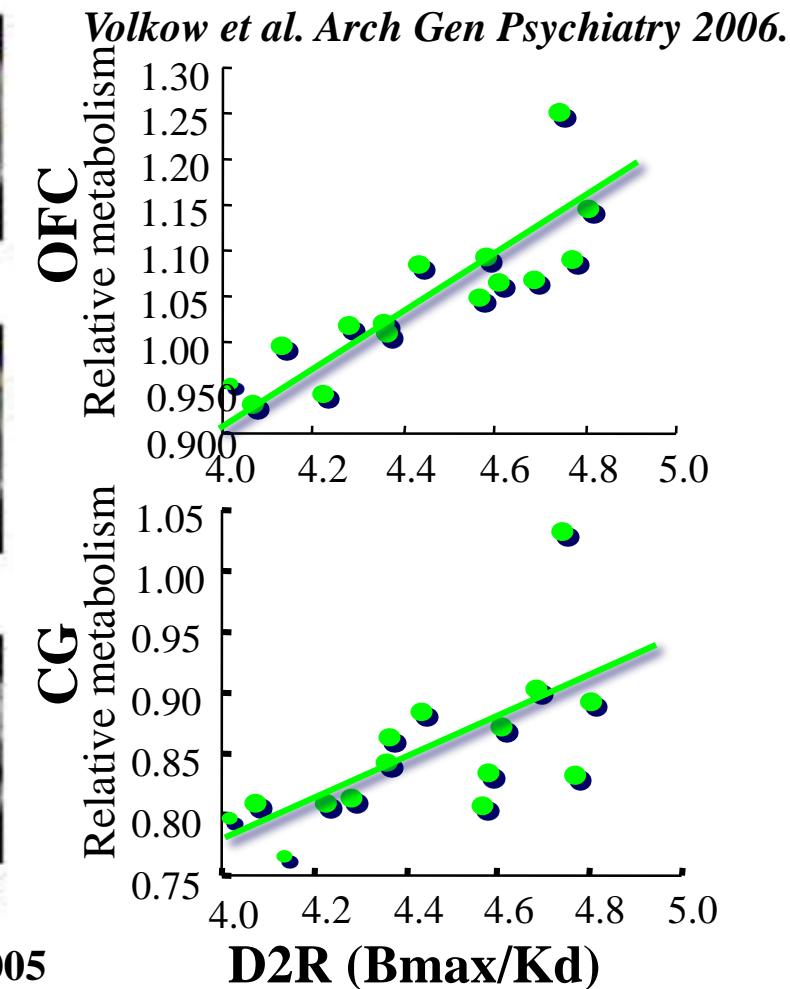
Brain glucose metabolism



# DA D2 Receptors and Relationship to Brain Metabolism in Subjects with Family History for Alcoholism

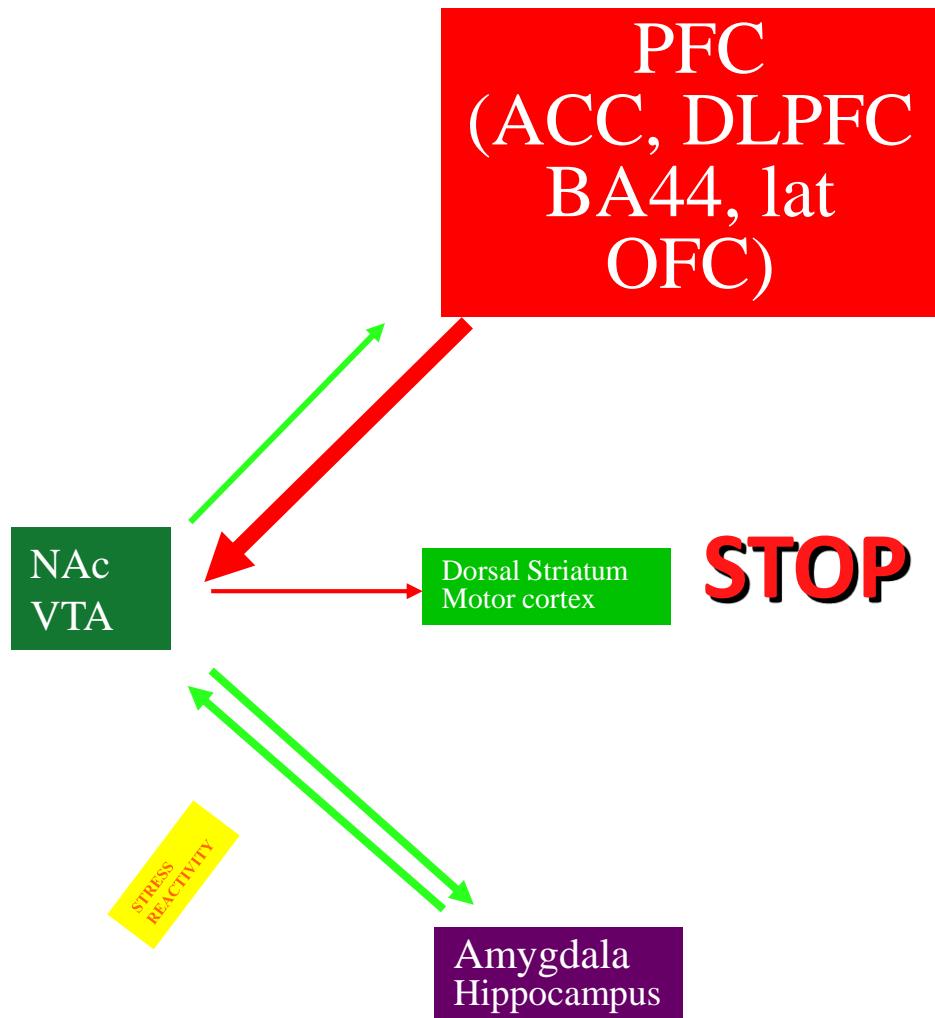


Correlations between Metabolism and D2R  $P < 0.005$



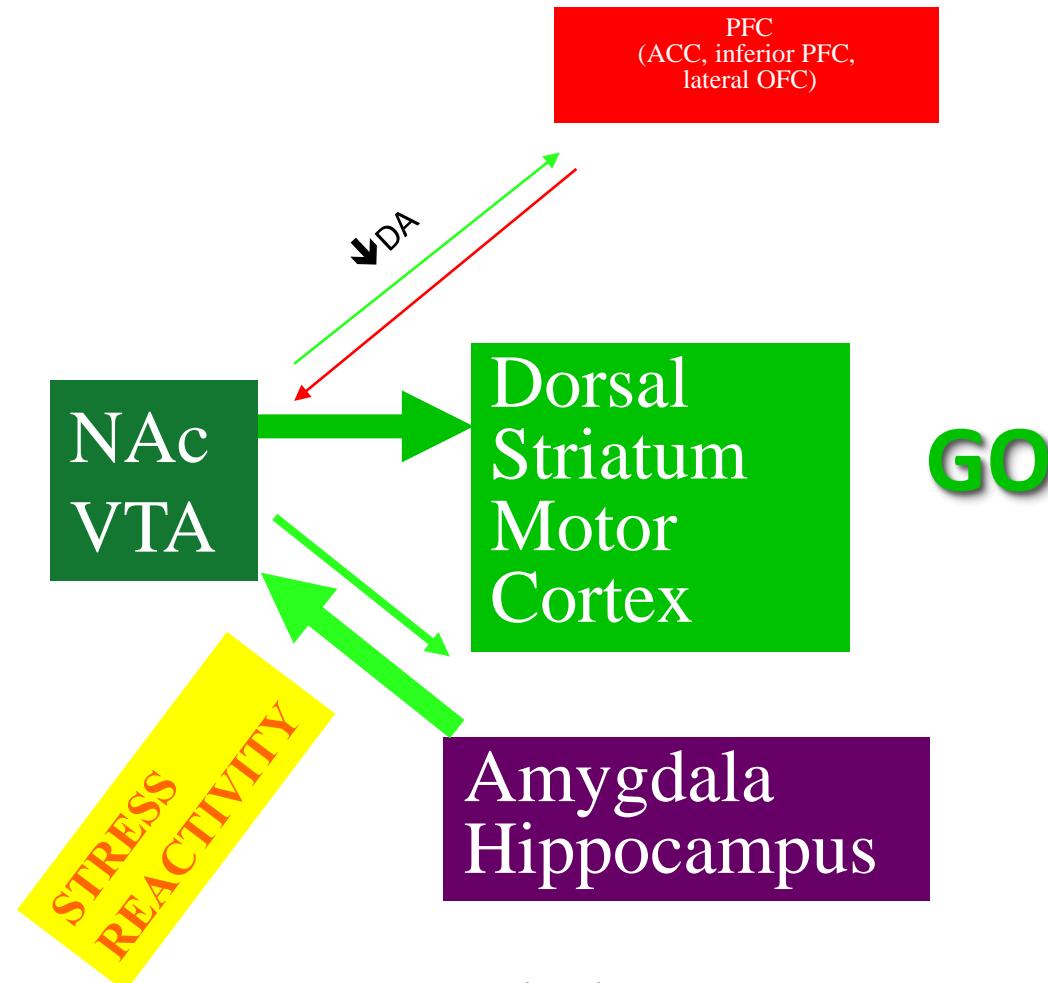
*D2R were associated with metabolism in PREFRONTAL regions  
the disruption of which results in impulsivity and compulsivity*

# Non-Addicted Brain



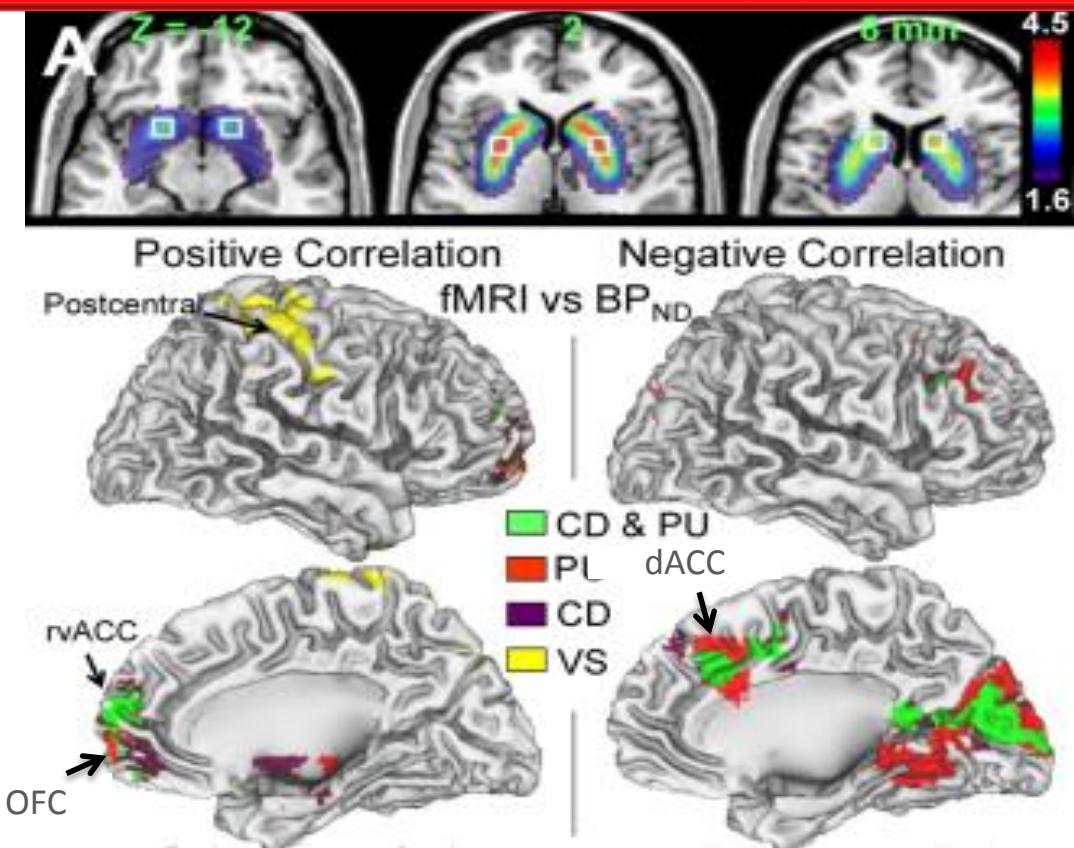
*Controlled behavior*

# Addicted Brain



*Automatic behavior*

# Striatal D2R (PET) and Brain Reactivity (fMRI) to Drug & Food Cues in Cocaine Abusers (n=20)

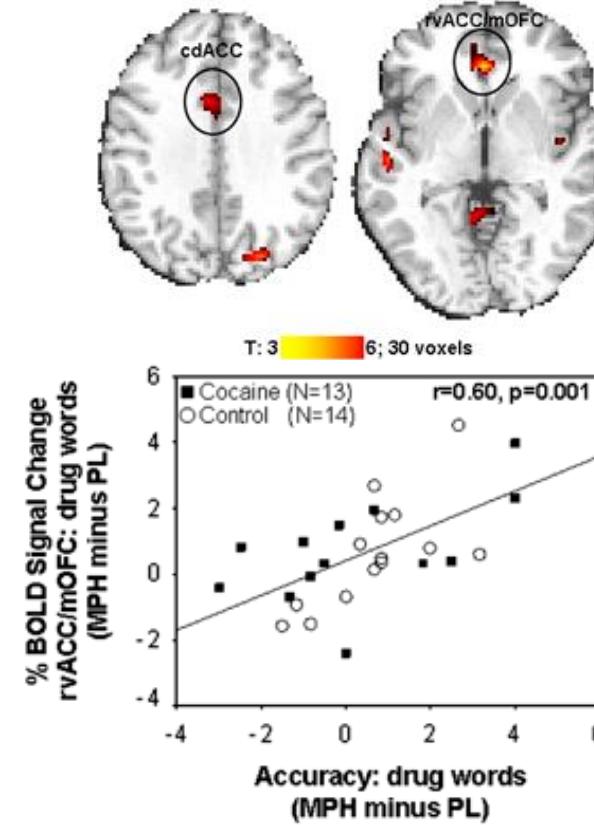


Striatal D2R receptors correlated positively with Cue reactivity in rvACC and OFC and negatively in dACC

*Tomasi et al., Human Brain Mapping, 2014.*

# Methylphenidate Decreases Impulsivity in Cocaine Abusers & Normalizes Cingulate Activity during Drug Stroop Test

Methylphenidate > Placebo



Correlation between activation in ventral ACC and OFC and change in accuracy (MPH minus placebo)

*Goldstein & Volkow Neuropsychopharmacology, 2010.*



David Alexoff, Karen Apelskog, Helene Benveniste, Anat Biegon, Elisabeth Caparelli, Pauline Carter, Stephen Dewey, Congwu Du, Richard Ferrieri, Joanna Fowler, Andrew Gifford, Rita Goldstein, Nils Hanik, Fritz hennm Jacob Hooker, Bud Jayne, Kun-eek Kil, Sunny Kim, Payton King, Nelly Klein, Hai-Dee Lee, Jean Logan, Jeming Ma, Martine Mirrione, Lisa Muench, Alicia Reid, Colleen Shea, Wynne Schiffer, Hanno Schieferstein, Matthias Schonberger, David Schlyer, Mike Schueller, Elena Shumay, Peter Thanos, Dardo Tomasi, Frank Telang, Paul Vaska, Nora Volkow, Gene-Jack Wang, Donald Warner, Chris Wong, Youwen Xu, Wei Zhu

<http://www.bnl.gov/CTN/>: supported by DOE-OBER and NIH