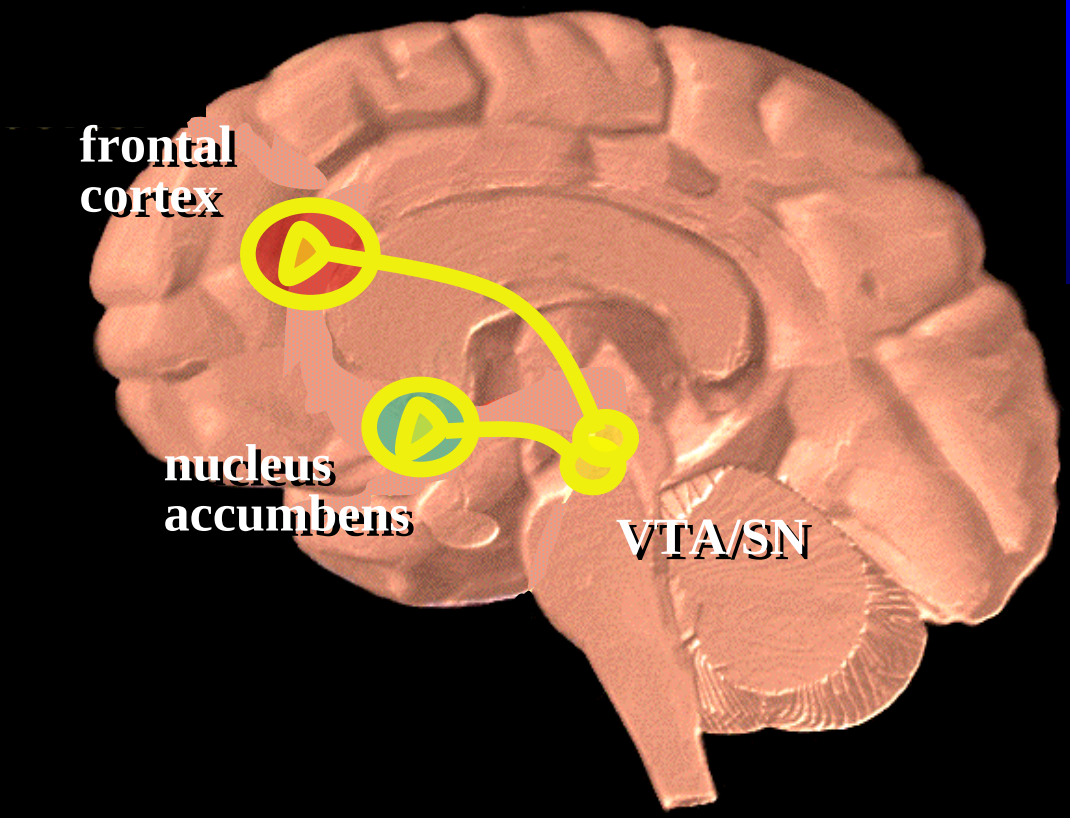
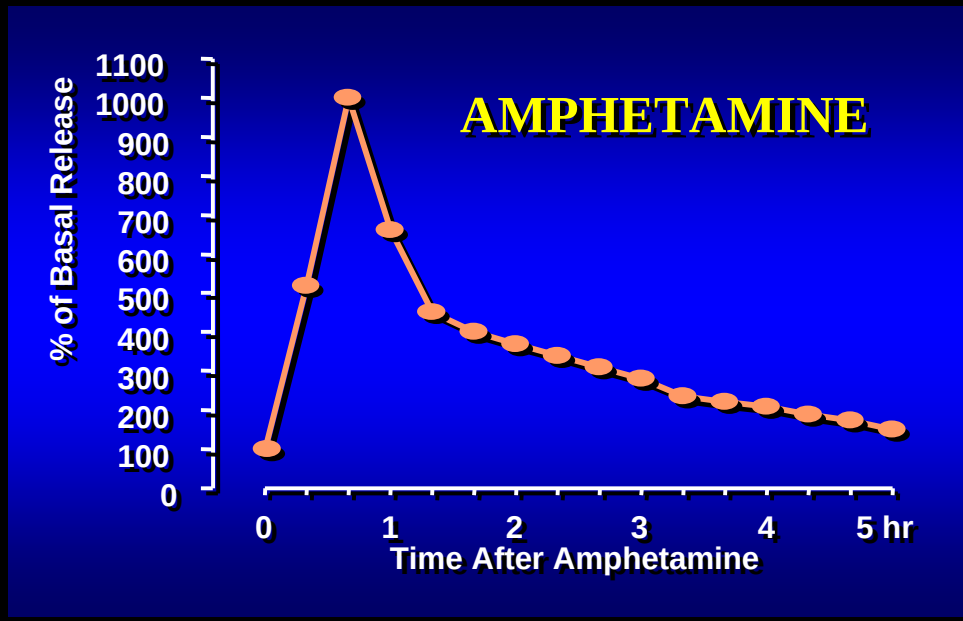
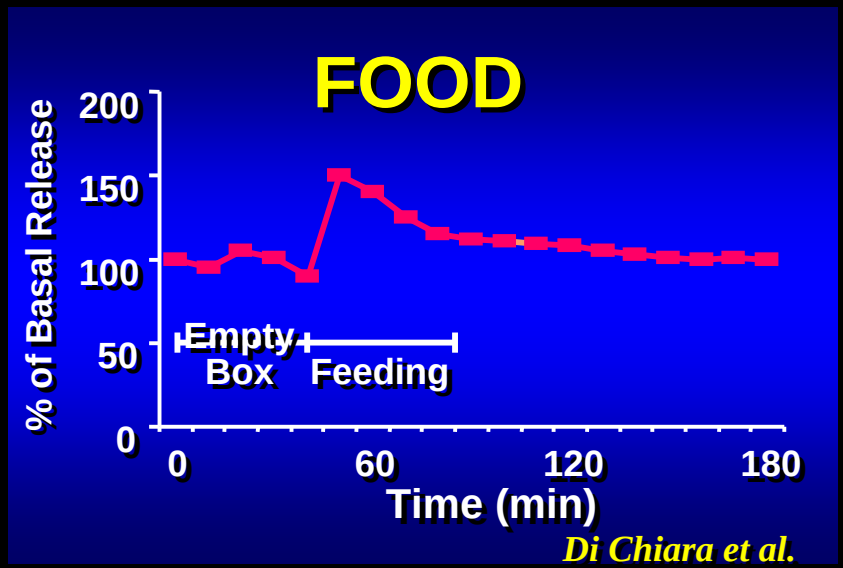

The Neurobiology of Free Will In
ADDICTIVE DISORDERS
NATIONAL INSTITUTES OF HEALTH
DEPARTMENT OF HEALTH & HUMAN SERVICES · USA
Nora D. Volkow, M.D.
Director
National Institute on Drug Abuse

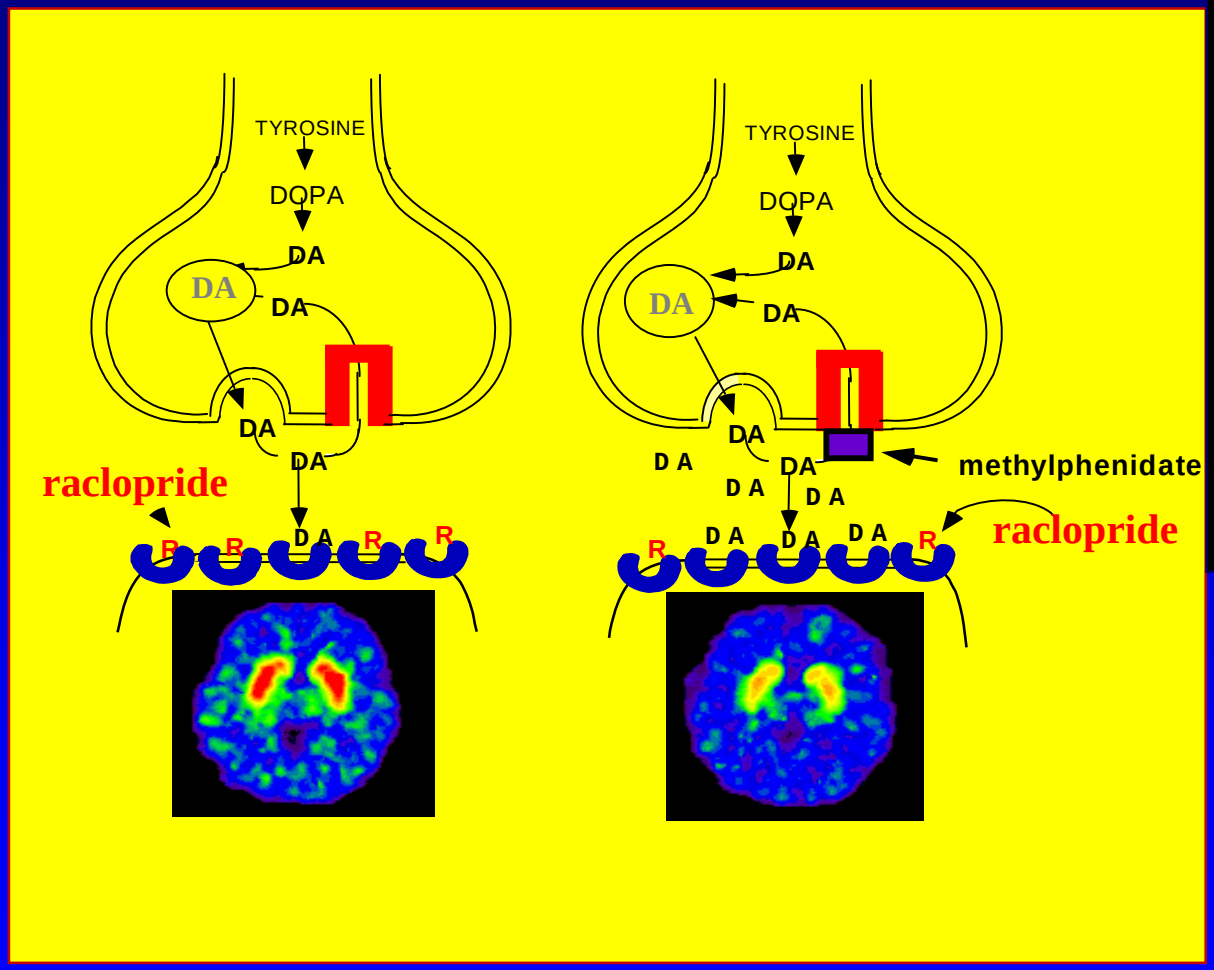
Dopamine Neurotransmission

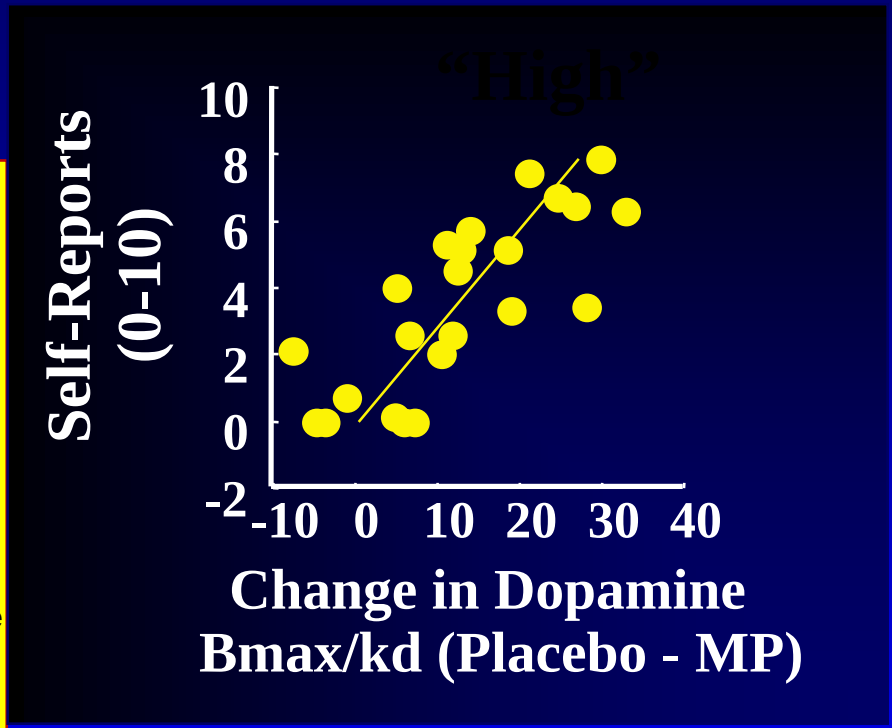






DA and Drug Reinforcement





DA initiates and maintains responses to salient stimuli such as drugs

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

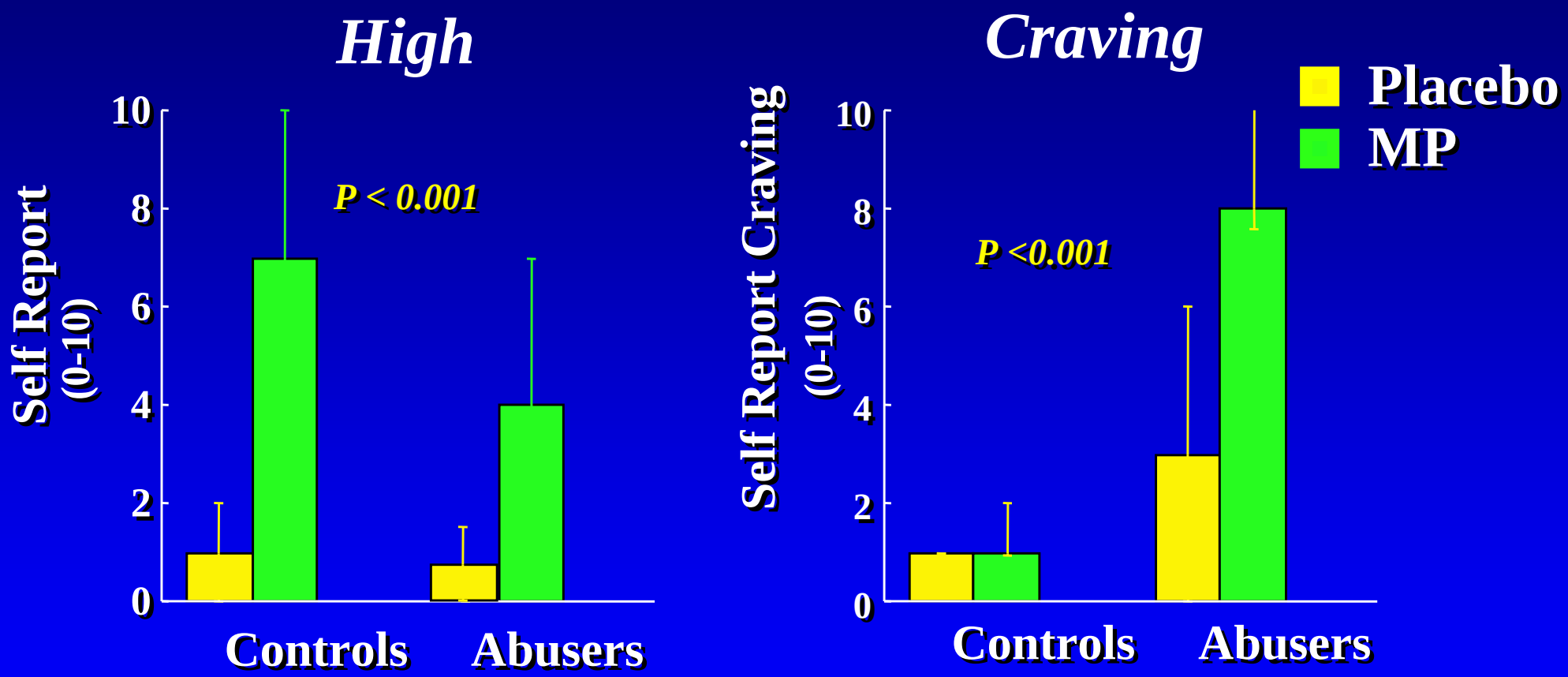
1. Reward Circuit

- In laboratory animals repeated exposure to the drug results in enhanced responses to it (sensitization) that have been hypothesized to underlie addiction.

- Here we tested if, in humans addicted to cocaine, there is an enhancement of DA release and of the reinforcing effects of the drug.

For this purpose we compared the changes in DA and the behavioral effects of intravenous MP between cocaine abusers (n=20) and controls (n=20)

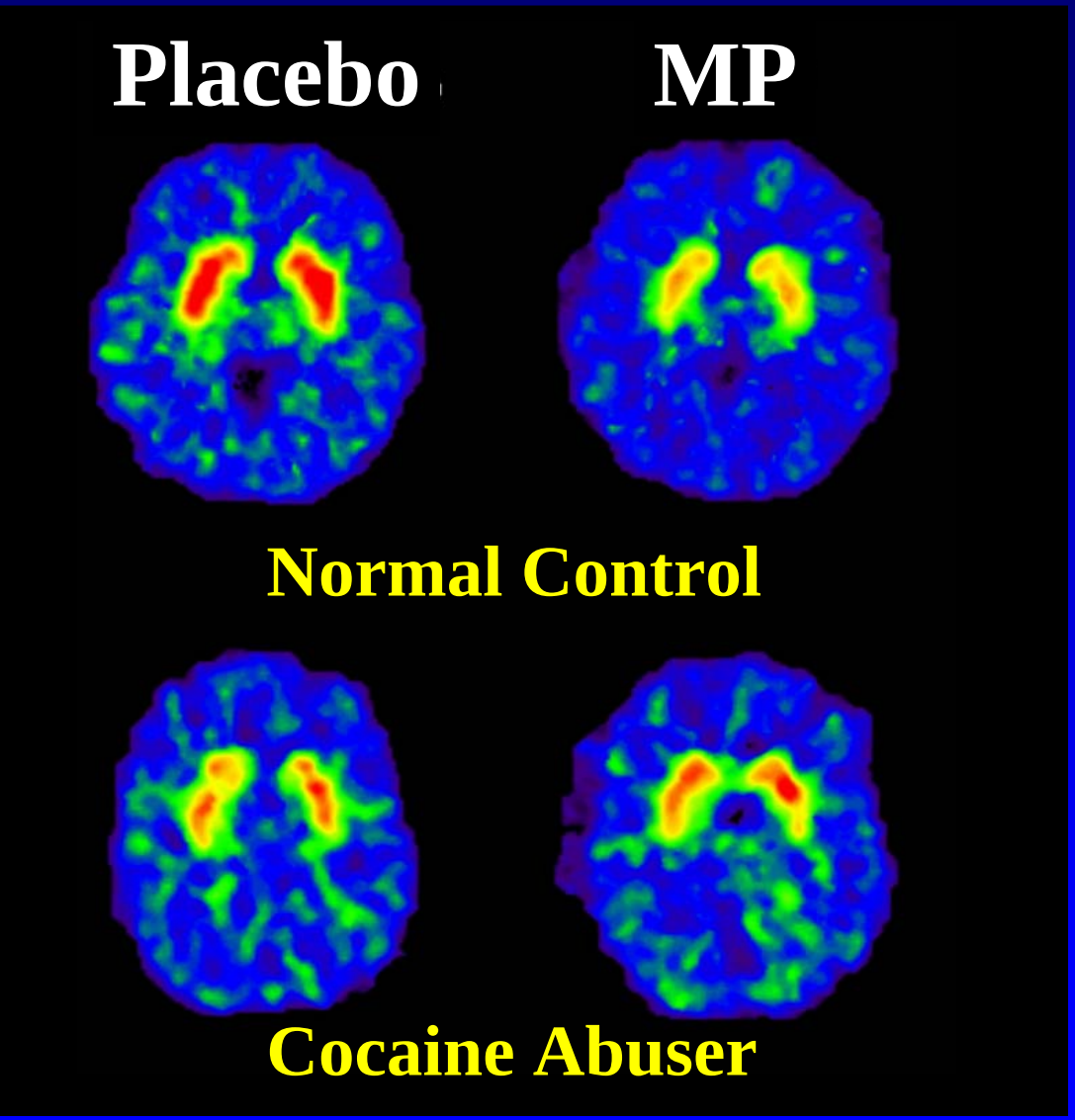
Self Reports of Drug Effects After iv MP in Controls and in Cocaine Abusers

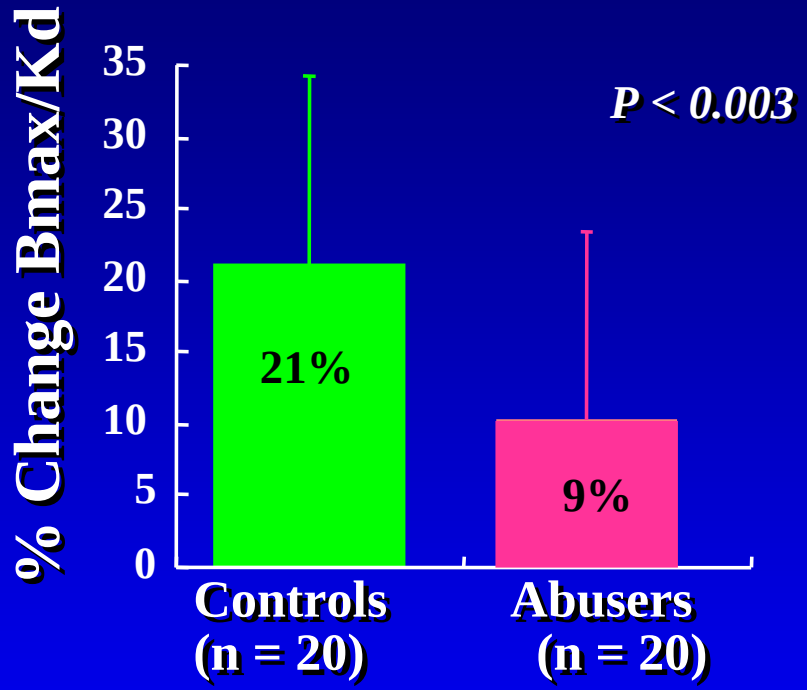


Cocaine abusers showed *decreased* drug induced increases in rewarding responses and enhanced drug craving

Volkow et al., Nature 386:830-833, 1997.

Methylphenidate-induced Increases in Striatal DA in Controls and in Cocaine Abusers



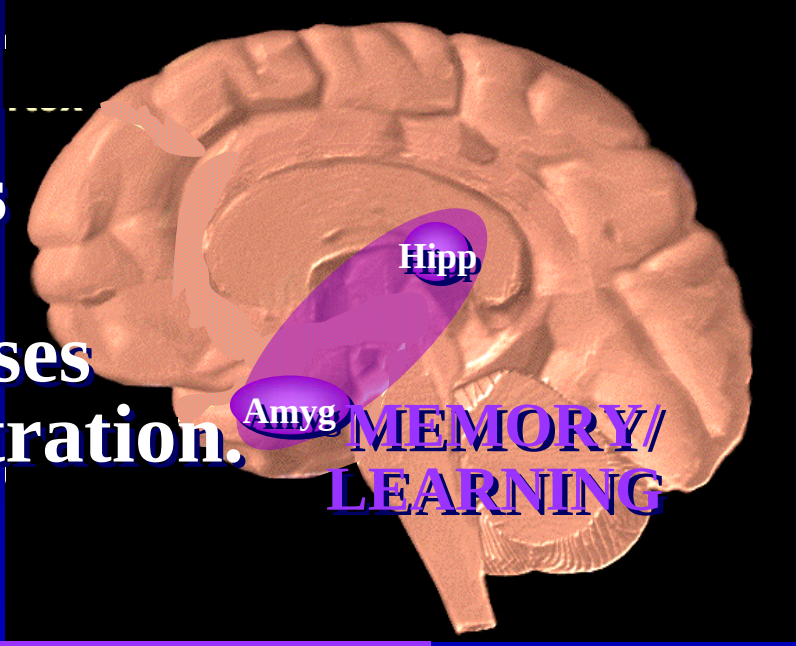


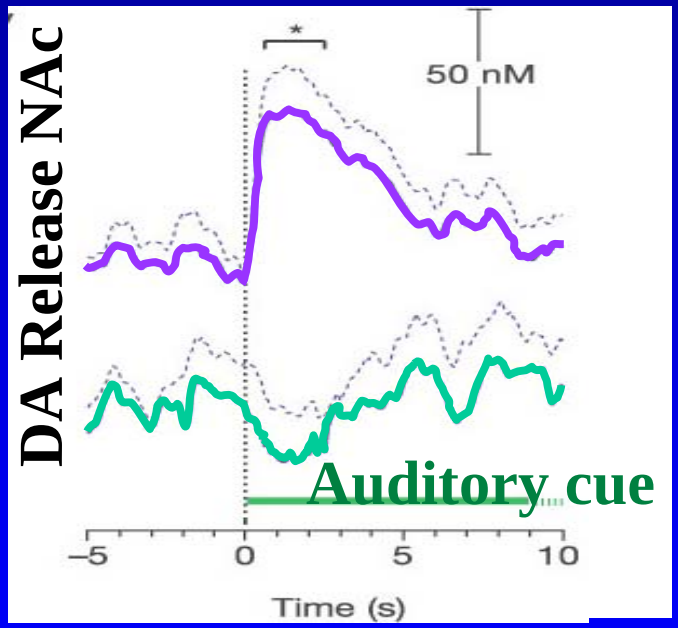
Cocaine abusers showed *decreased* DA increases and reduced reinforcing responses to MP

Volkow et al., Nature 386:830-833, 1997.

2. Memory circuit

- In rats when a neutral stimulus is repeatedly paired with the drug (conditioned), it elicits DA increases and reinstates drug self- administration.





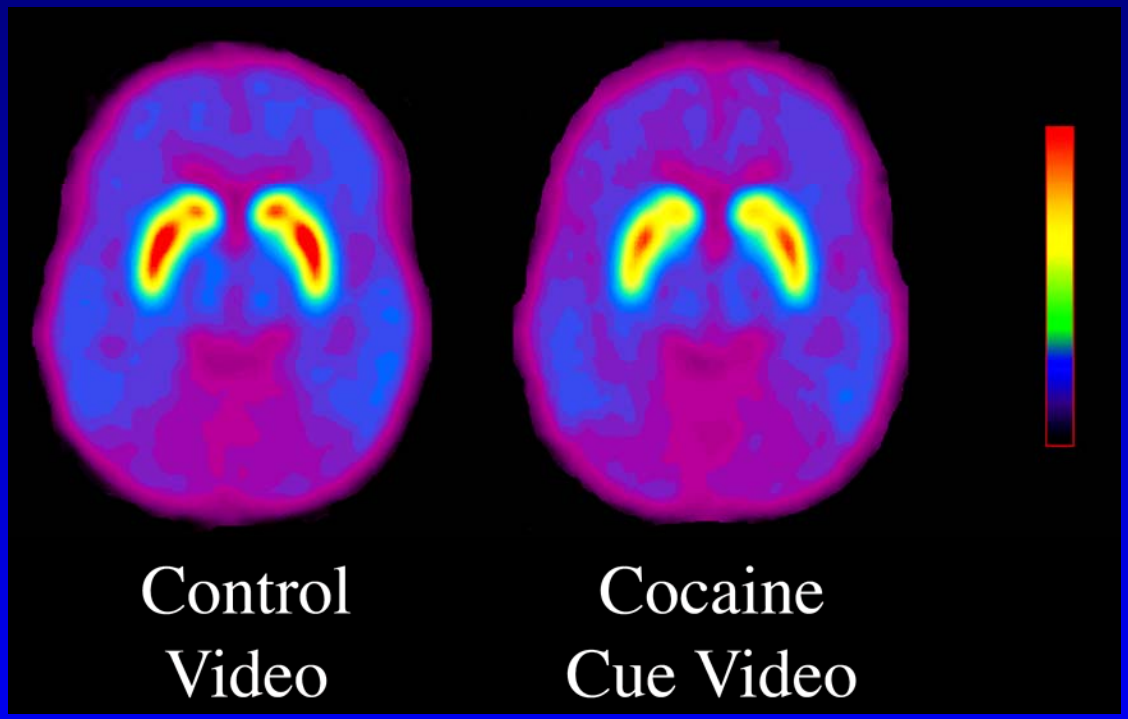
In training the cue **was** paired with cocaine

In training the cue **was not** paired with cocaine

Philipps et al Nature 422, 614-618

Here we tested *if conditioned stimuli increase DA in addicted subjects* and *its relationship to drug craving*

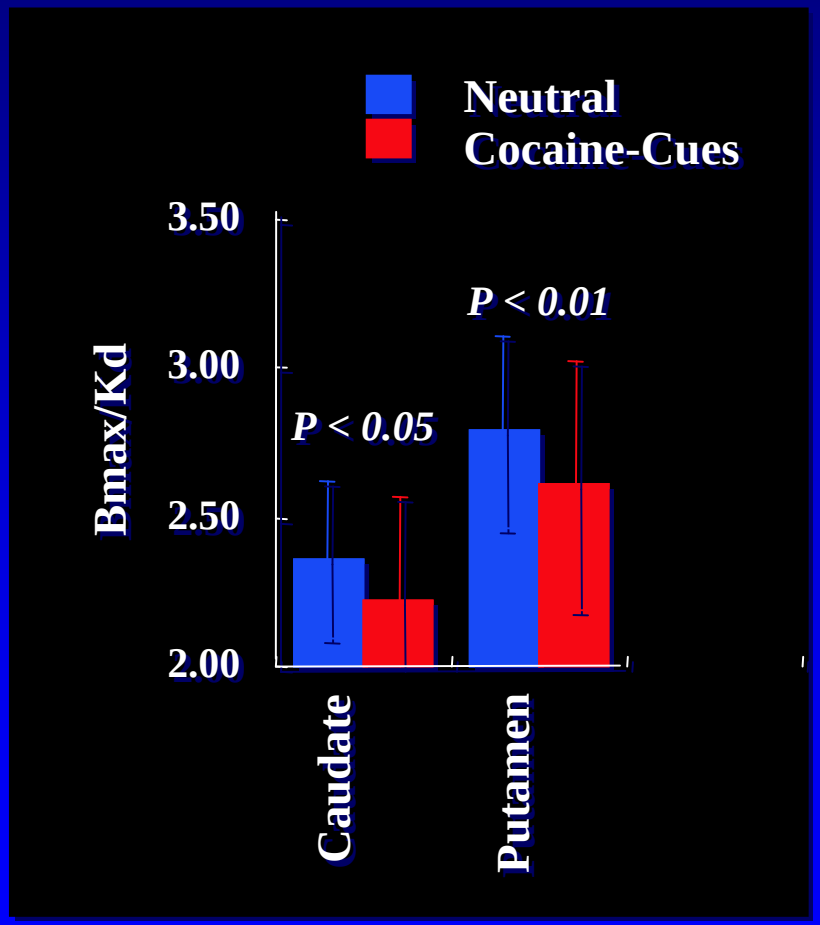
[^{11}C]Raclopride Binding In Cocaine Abusers (n=18) Viewing a Neutral and a Cocaine-Cue Video

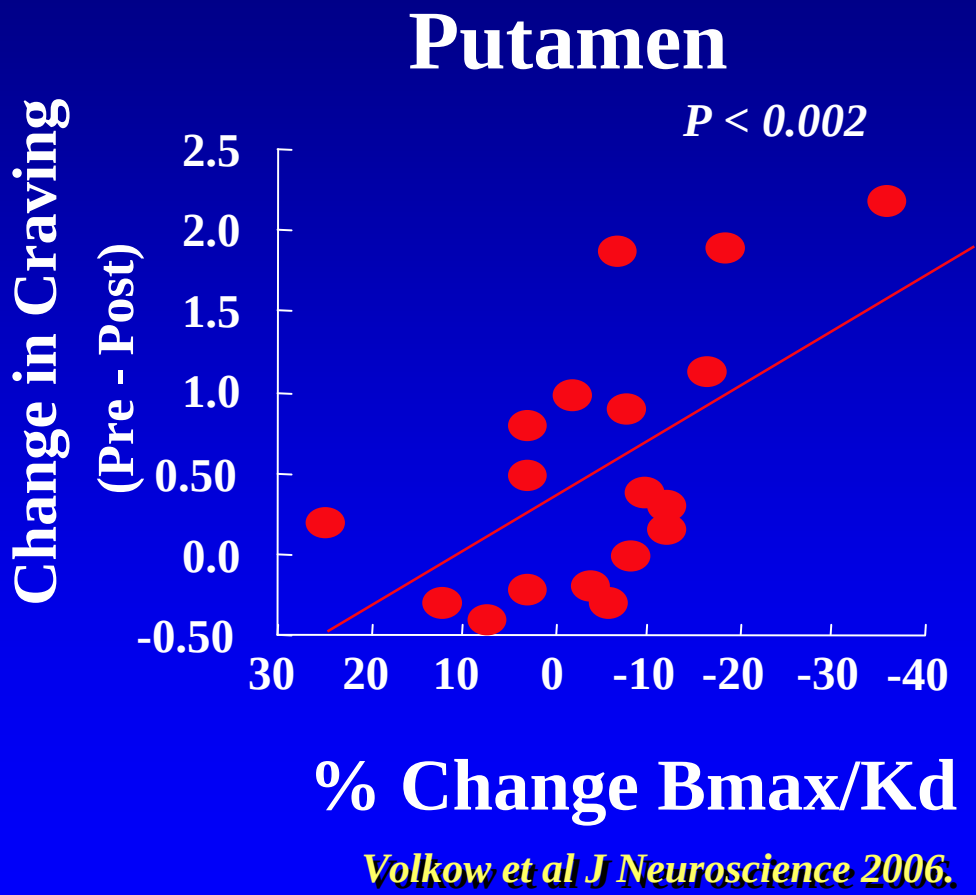


Viewing a video of cocaine scenes decreased specific binding of [11C]raclopride presumably from DA increases

Volkow et al. J Neuroscience 2006.

Relationship between Cue-Induced Decreases in [11C]raclopride Binding and Cocaine Craving

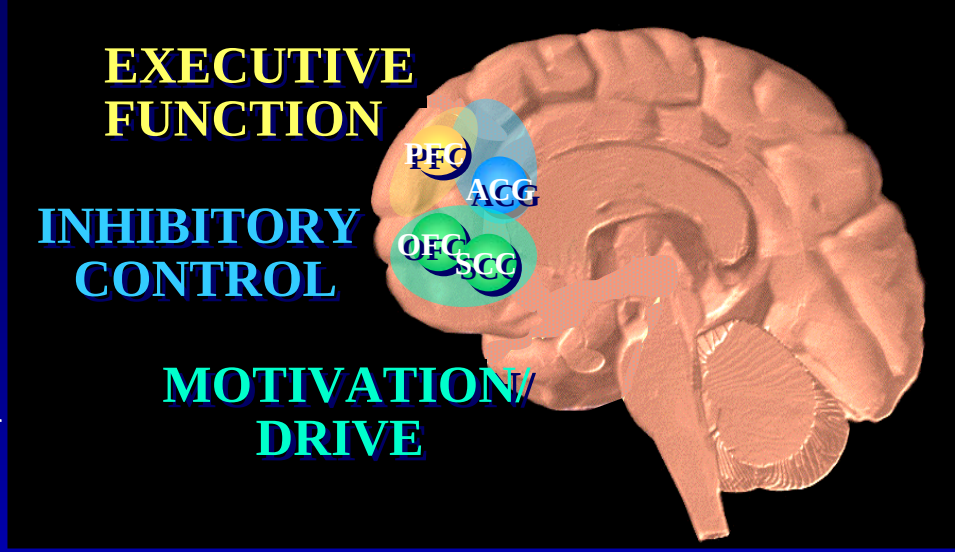




Volkow et al J Neuroscience 2006.

Cue-induced increases in DA were associated with craving

3. Motivation & Executive Control Circuits

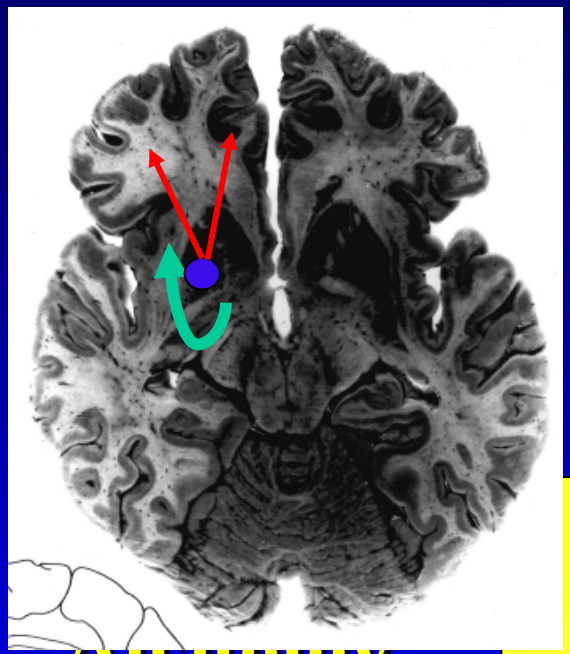


DA is involved not only with reward and prediction of reward but also with motivation and executive function via its regulation of frontal activity.

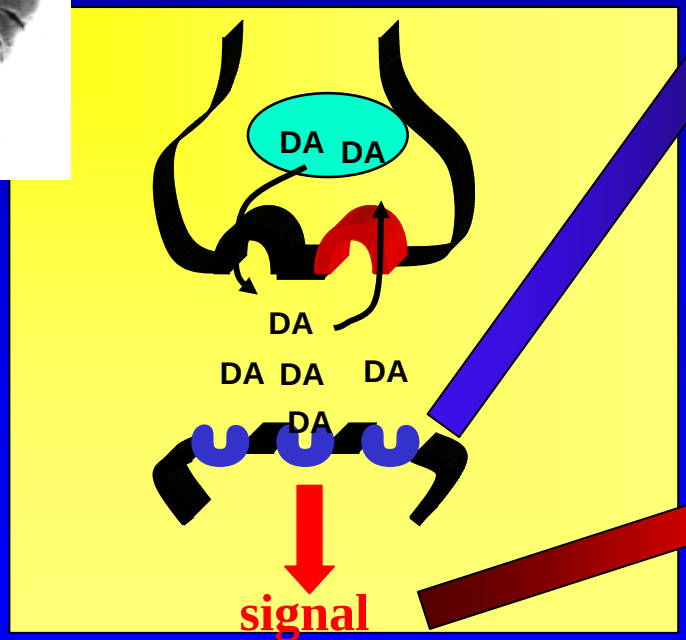
Here we tested if, in addicted subjects, changes in DA function were linked with disruption of frontal activity as assessed by brain glucose metabolism.

We assessed the relationship between DA markers and frontal activity in cocaine (n=20) and in methampethamine abusers (n =20) and controls

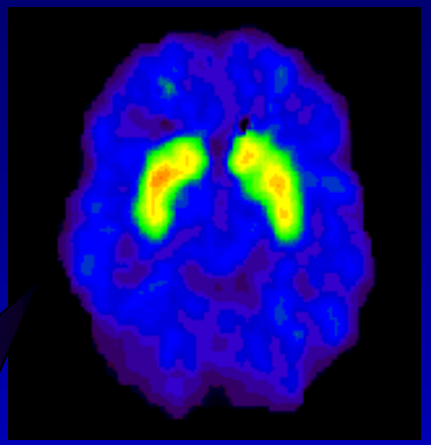
Dopamine Measures Obtained



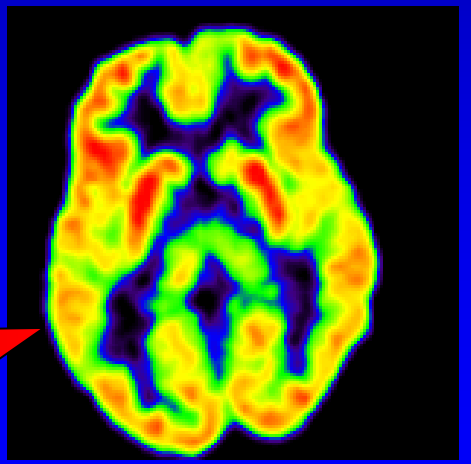
Anatomy



Dopamine Synapse



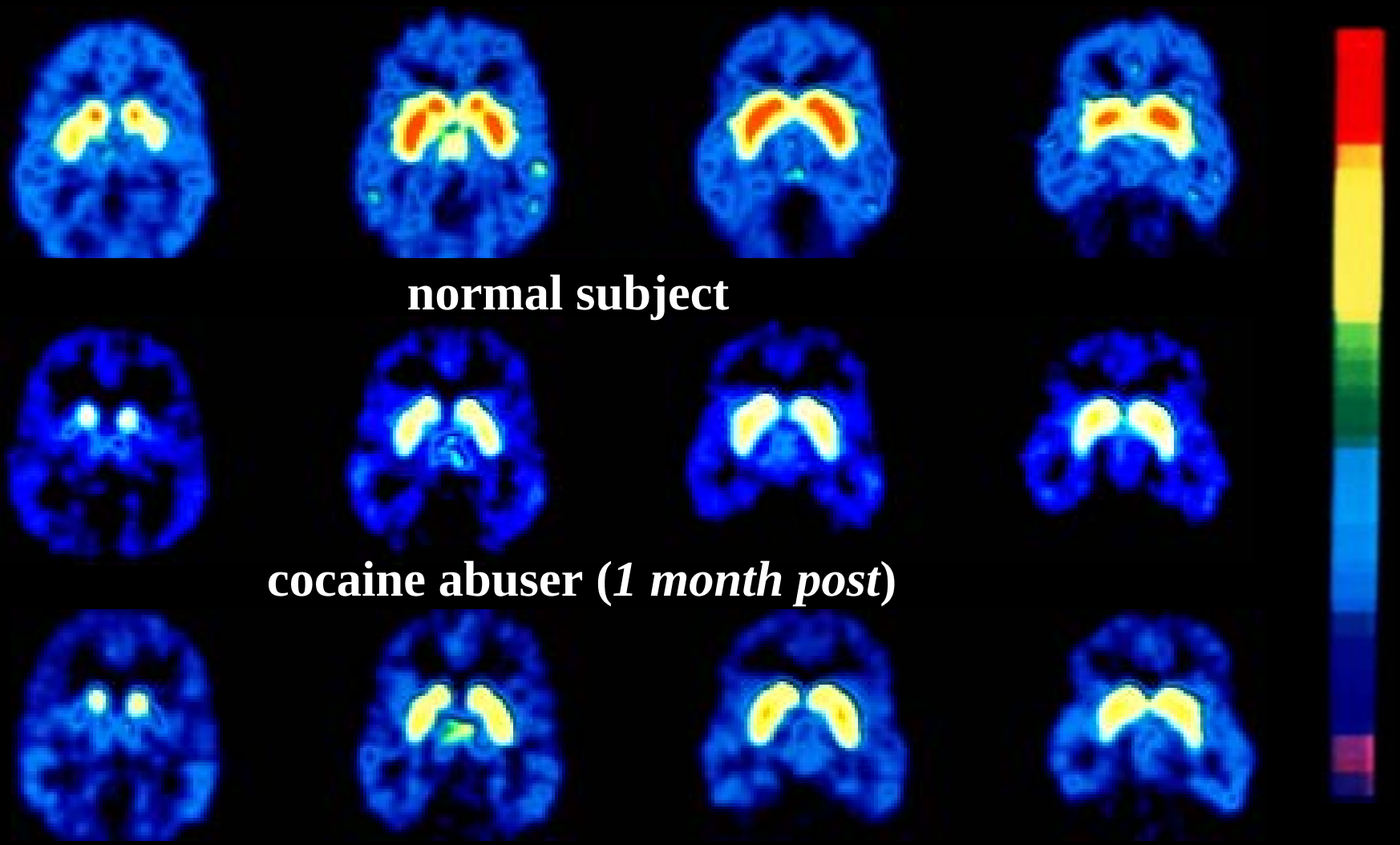
DA D2 Receptors



Metabolism

Adapted from: Volkow et al., J Clin Invest 111(10):1444-1451, 2003.

Effect of Cocaine Abuse on Dopamine D2 Receptors



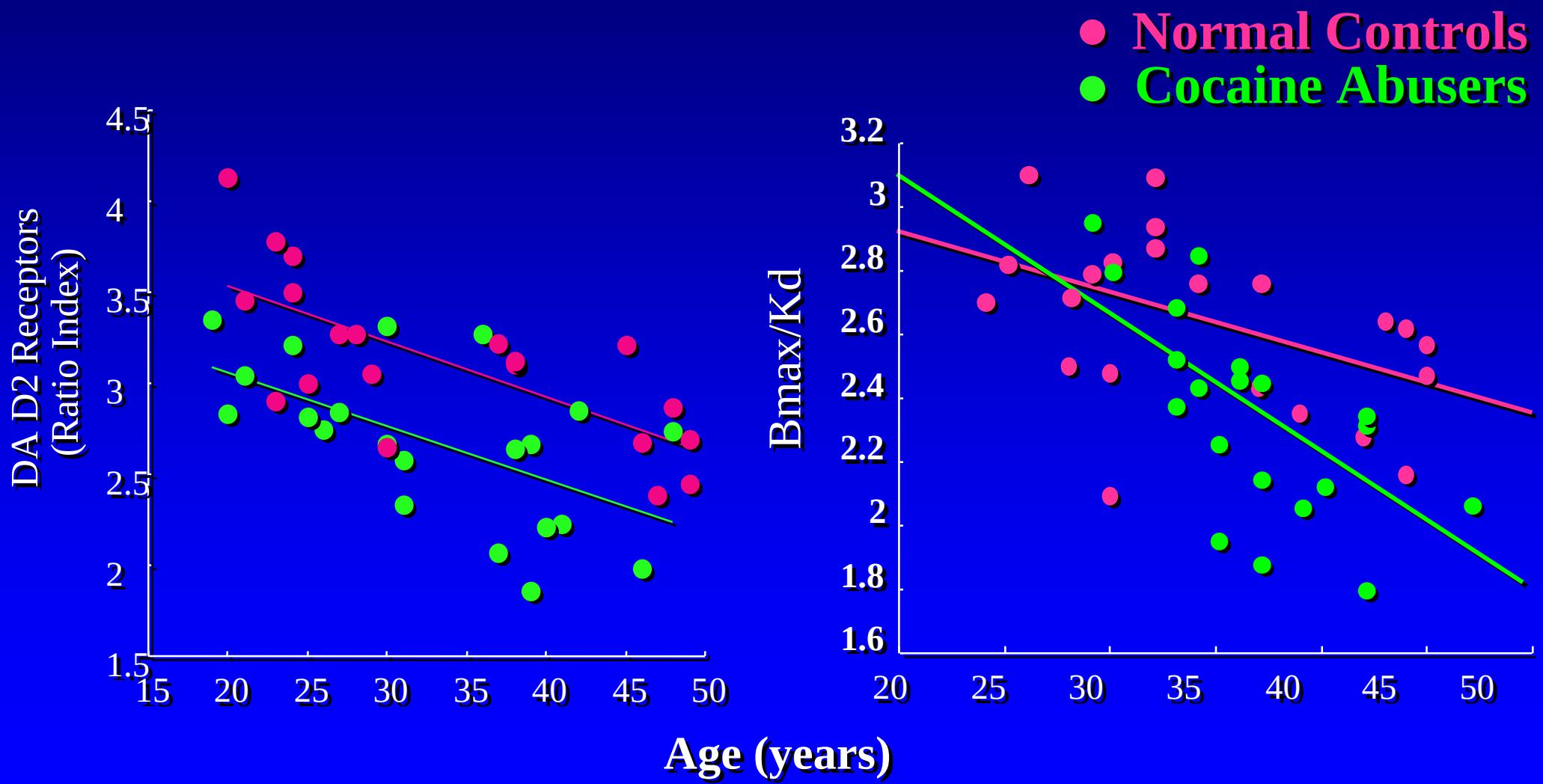
normal subject

cocaine abuser (*1 month post*)

cocaine abuser (*4 months post*)

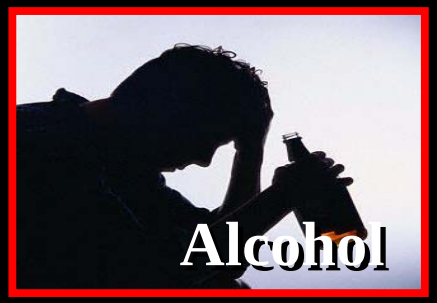
Volkow et al., Synapse 14(2): 169-177, 1993.

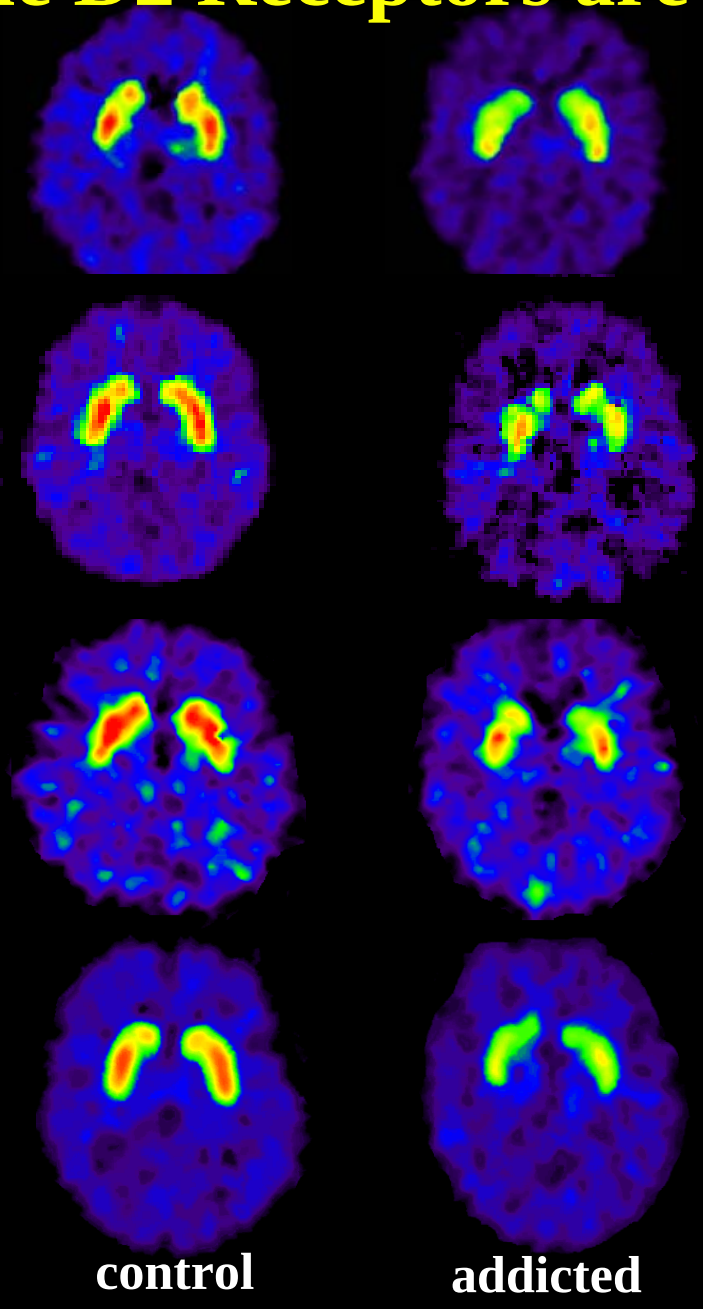
DA D2 Receptors in Controls and in Cocaine Abusers (NMS)

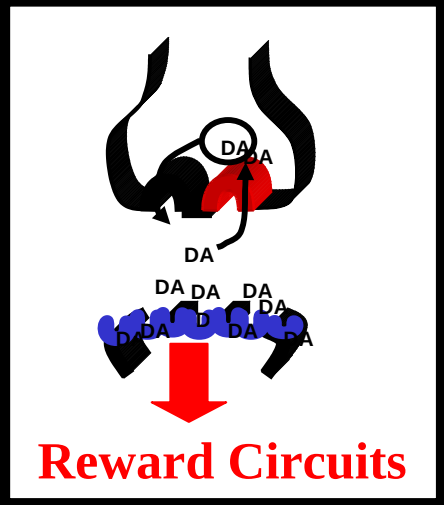


Volkow et al., Neuropsychopharmacology 14(3):159-168, 1996.

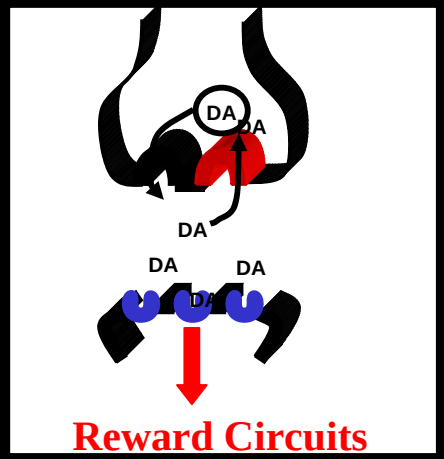
Dopamine D2 Receptors are Lower in Addiction







Non-Drug Abuser

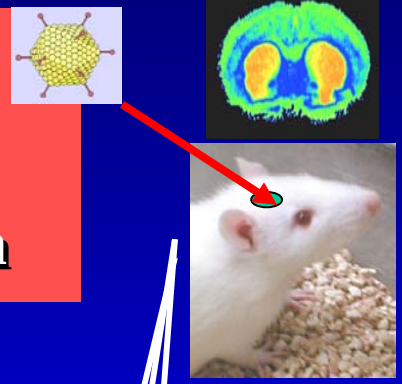


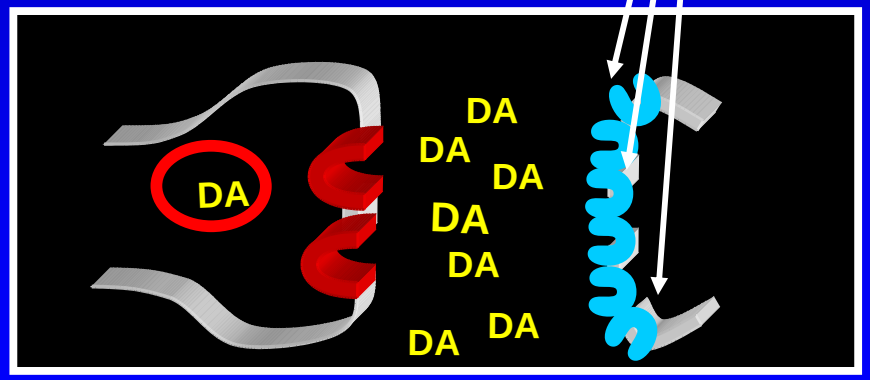
Drug Abuser

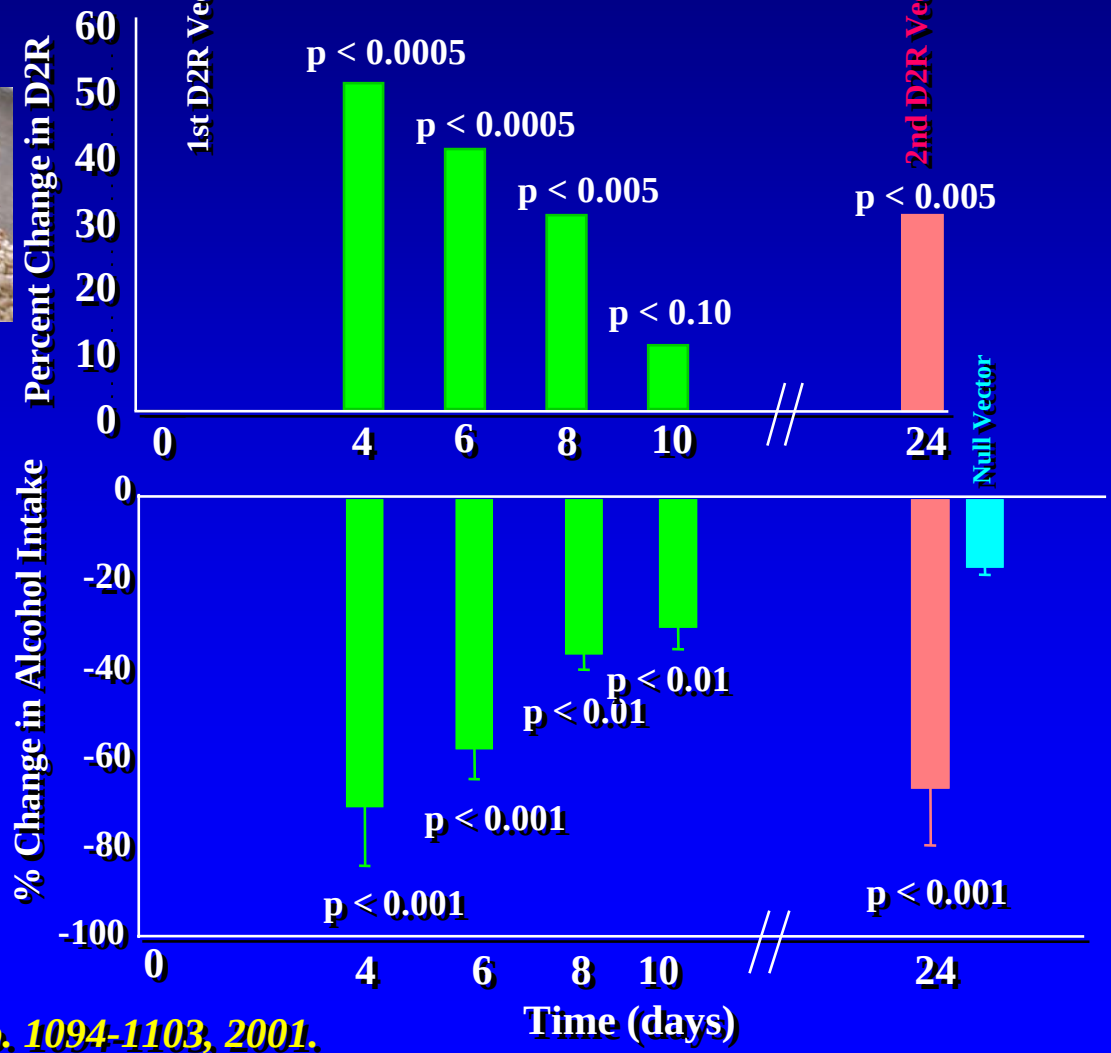
Adapted from Volkow et al., Neurobiology of Learning and Memory 78:610-624, 2002.

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

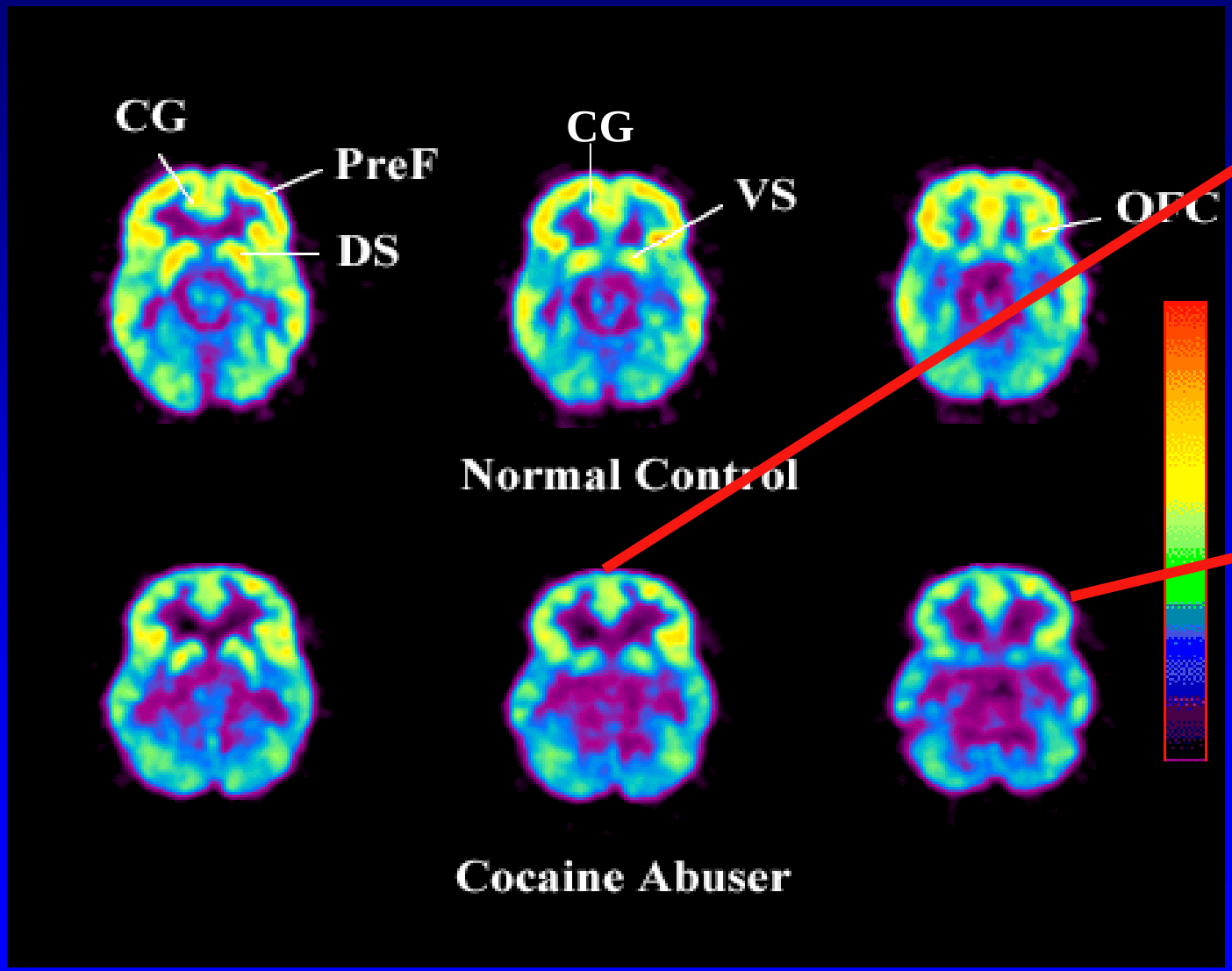


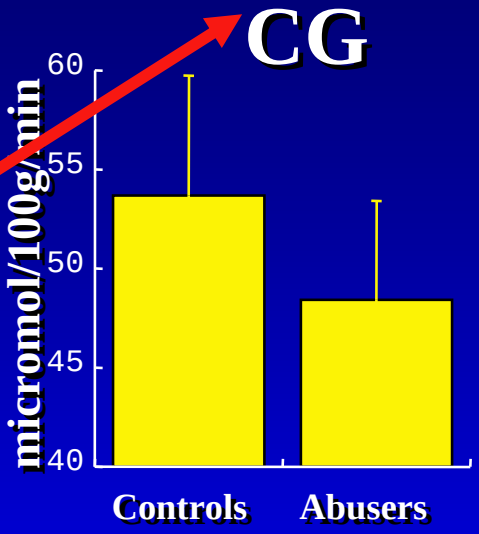




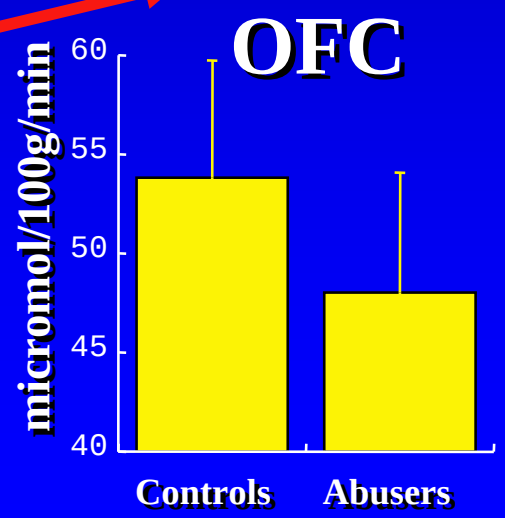
Thanos, PK et al., J Neurochem, 78, pp. 1094-1103, 2001.

Brain Glucose Metabolism
in Cocaine Abusers (n=20) and Controls (n=23)





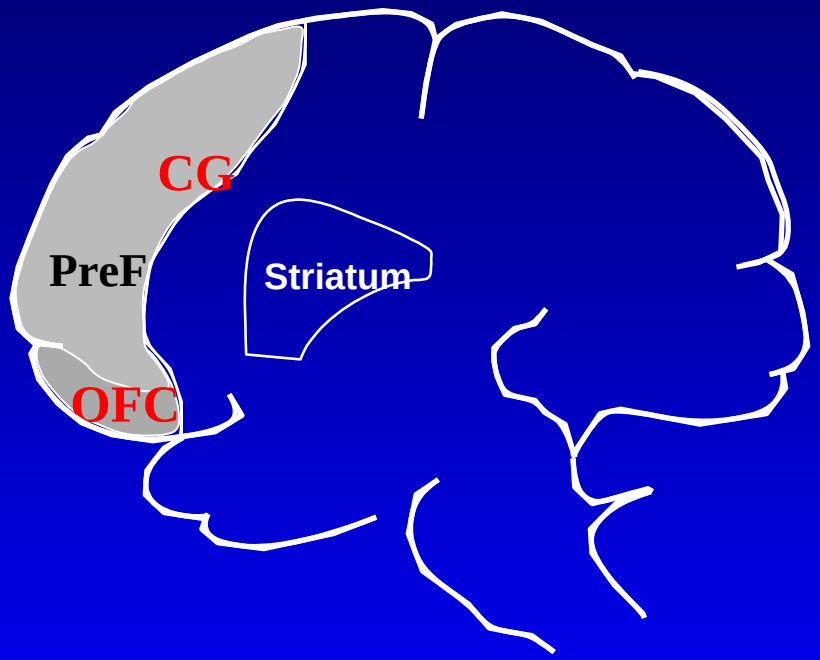
P < 0.01

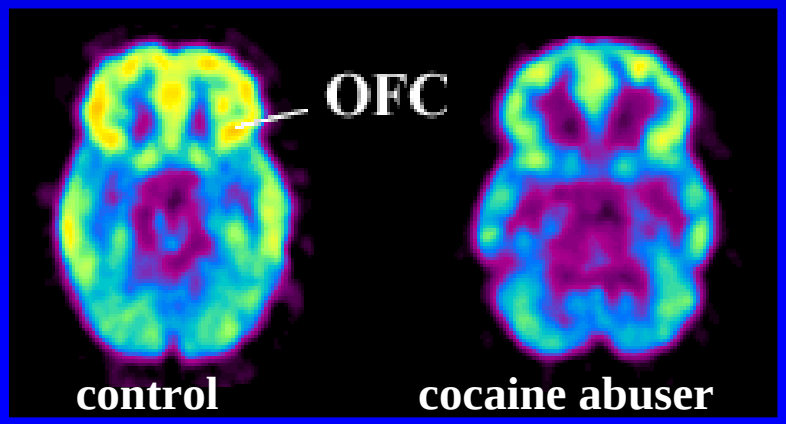


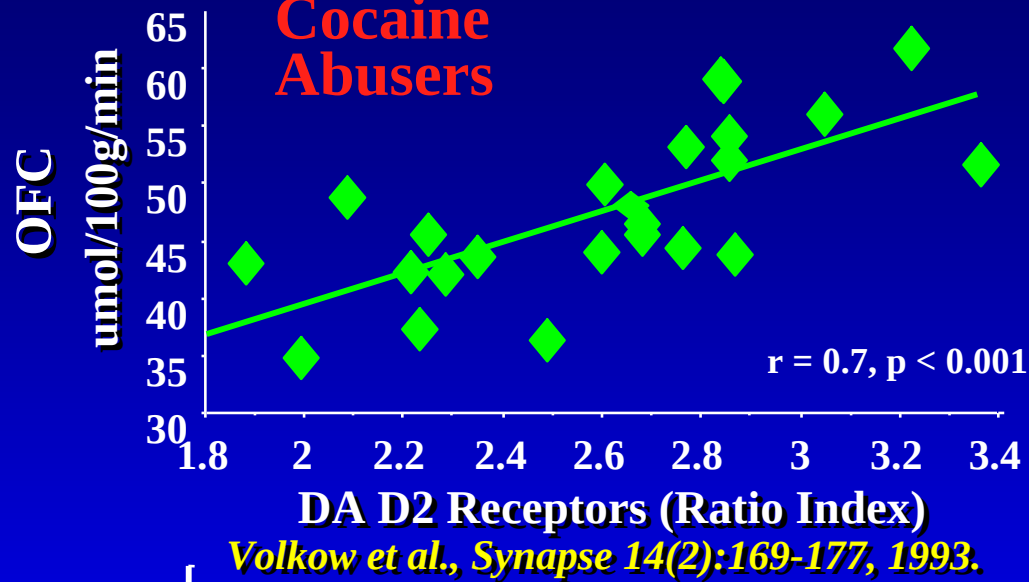
P < 0.005

Volkow et al., AJP 156:19-26, 1999.

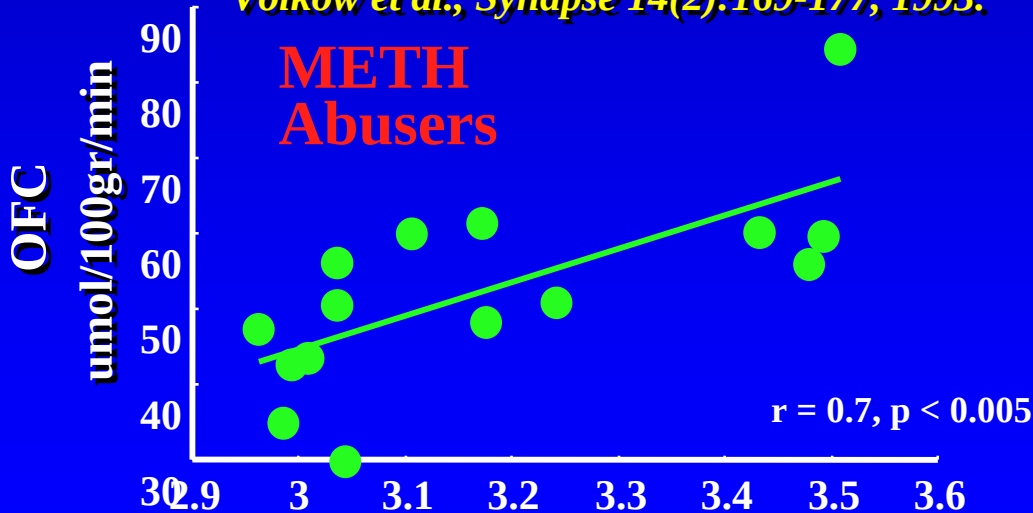
Correlations Between D2 Receptors in Striatum and Brain Glucose Metabolism





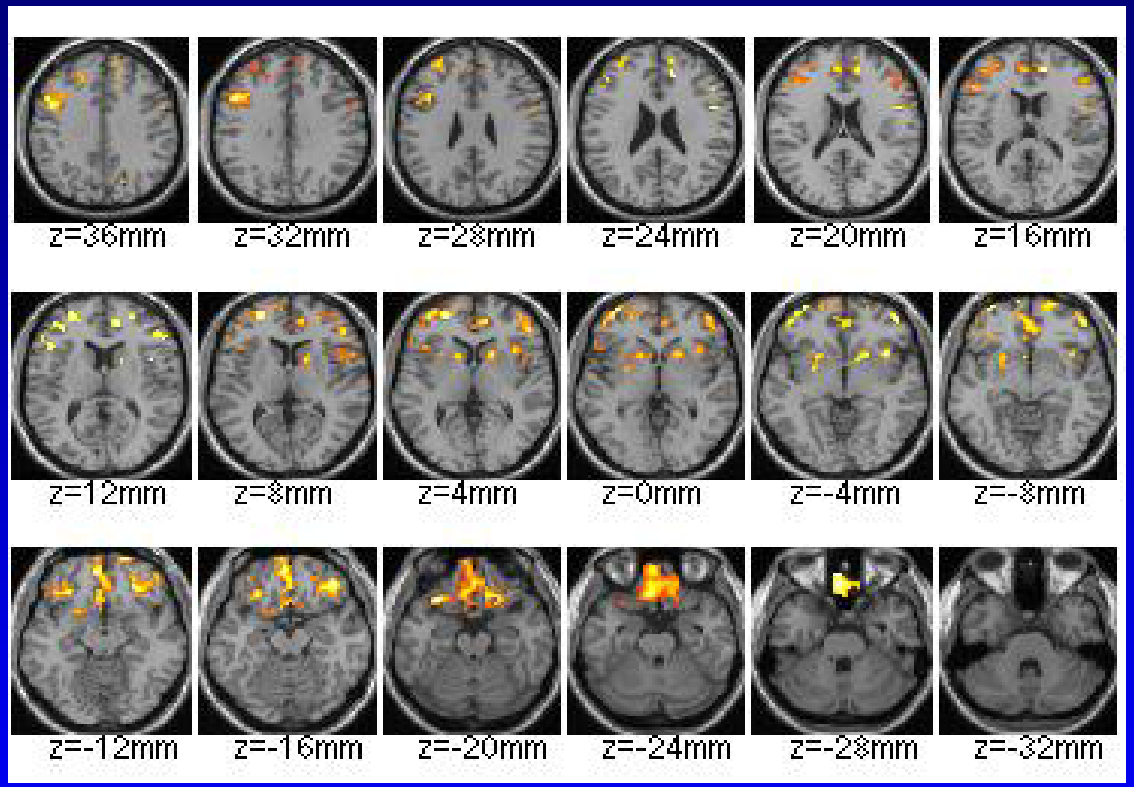


Volkow et al., Synapse 14(2):169-177, 1993.



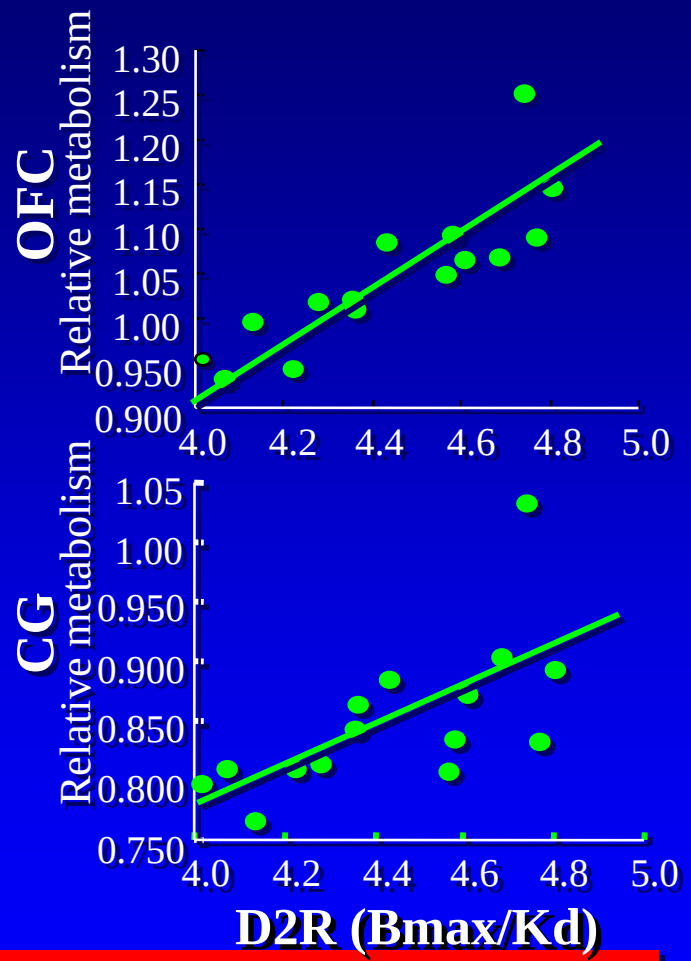
Volkow et al., AJP 158(3):377-382, 2001.

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



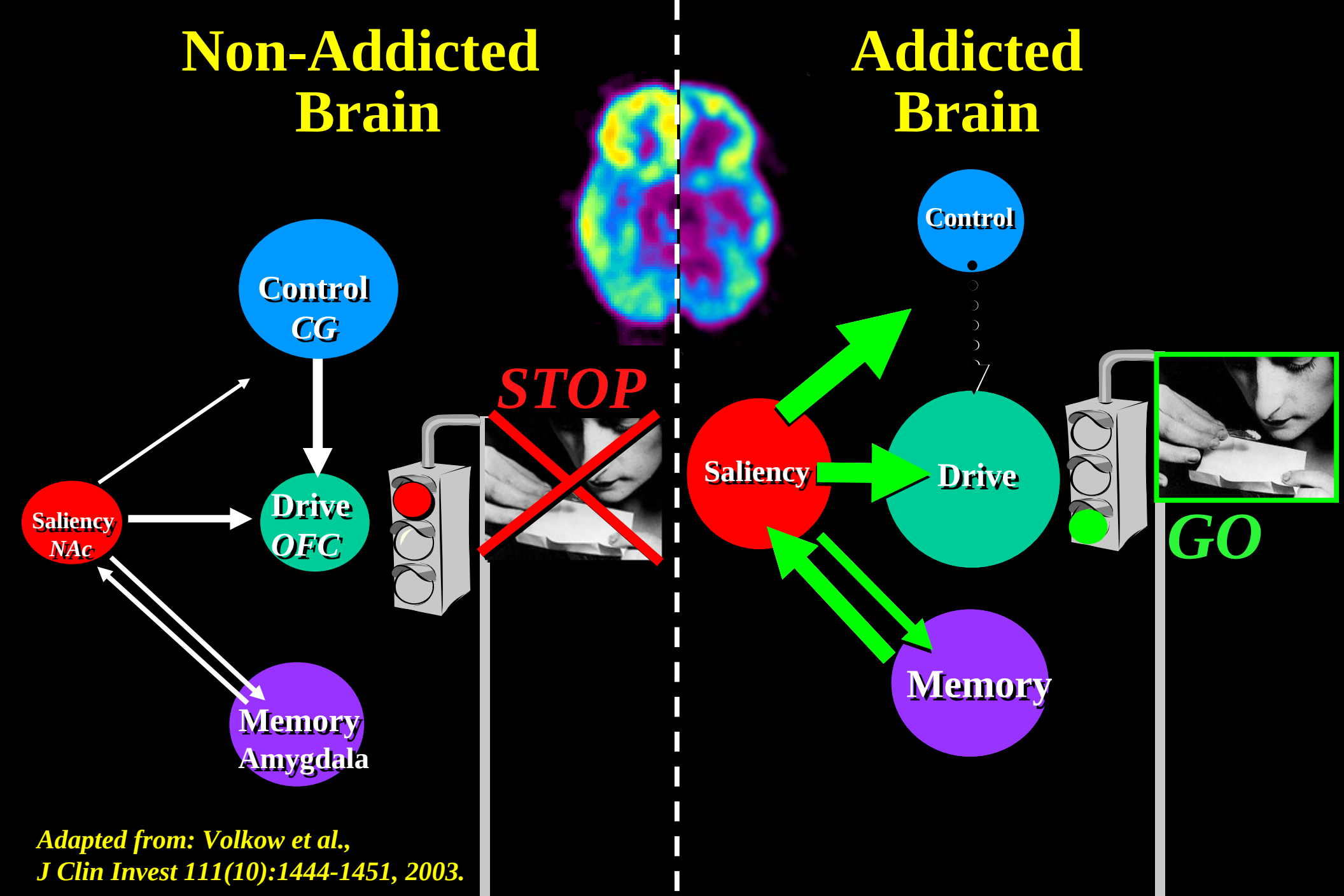
Correlations between Metabolism and D2R

P <0.005

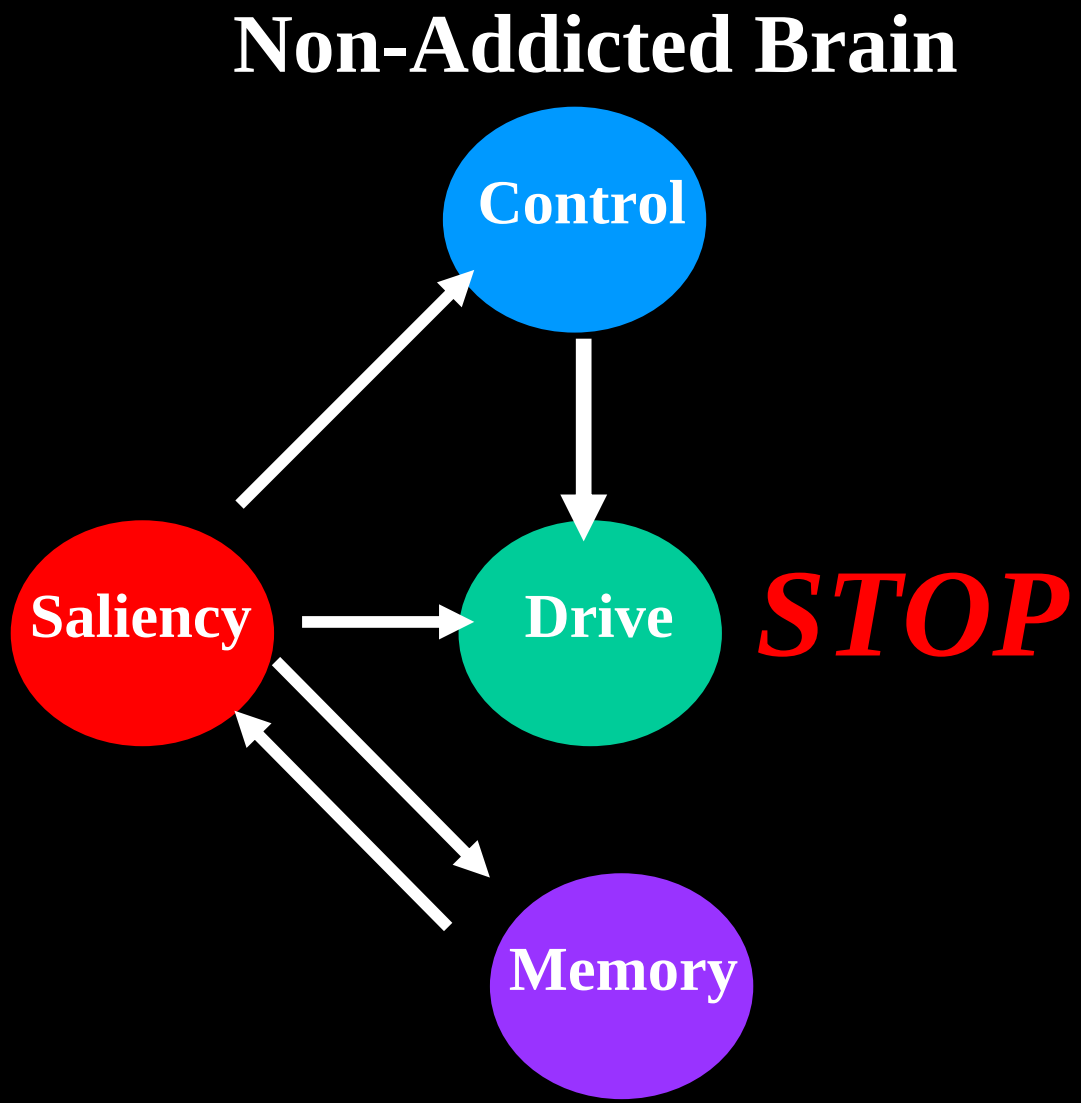


DA D2R were associated with metabolic activity in OFC, CG and dorsolateral prefrontal cortex

Volkow et al. Arch Gen Psychiatry 2006.


Non-Addicted Brain
Addicted Brain
Control
CG
Saliency
NAc
Drive
OFC
Memory
Amygdala
STOP
Control
Saliency
Drive
Memory
GO
Adapted from: Volkow et al.,
J Clin Invest 111(10):1444-1451, 2003.

Medications for Relapse Prevention



- Strengthen reinforcing effects of non-drug reinforcers
- Strengthen inhibitory control
- Strengthen prefrontal-striatal communication
- Interfere with conditioned memories (craving)
- Counteract stress responses that lead to relapse

Adapted from: Volkow et al., J Clin Invest 111(10):1444-1451, 2003.

Brookhaven PET Group

F. Telang, R. MacGregor, P. Carter, D. Schlyer, C. Shea, J. Gatley, S. Dewey, C. Redvanly, P. King

L. Caligiuri, G-J Wang, M. Franceschi, Y-S Ding, J. Logan, N. Volkow, J. Fowler, R. Ferrieri, C. Wong

(not shown) D. Alexoff, C. Felder, N. Pappas, D. Franceschi, N. Netusil, V. Garza, R. Carciello, D. Warner, M. Gerasimov