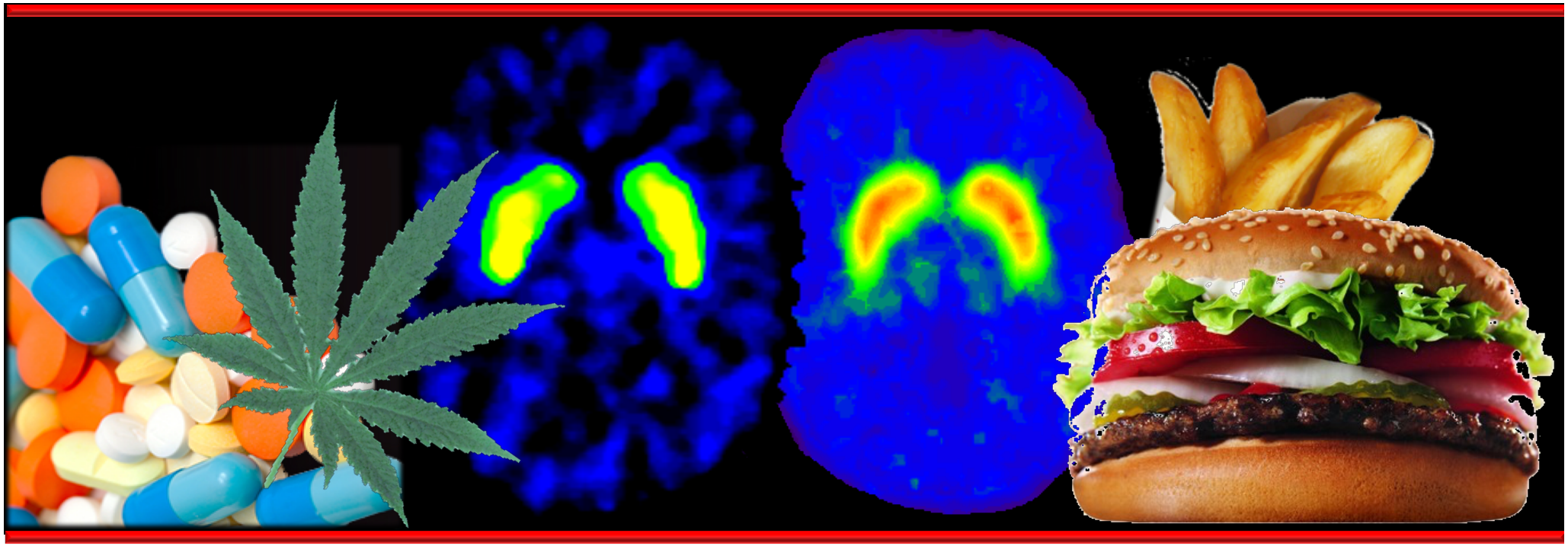
ADDICTION and HABITUATION

Drugs and Food



Nora D. Volkow, M.D.
Director

National Institute on Drug Abuse
Advancing Addiction Science

and

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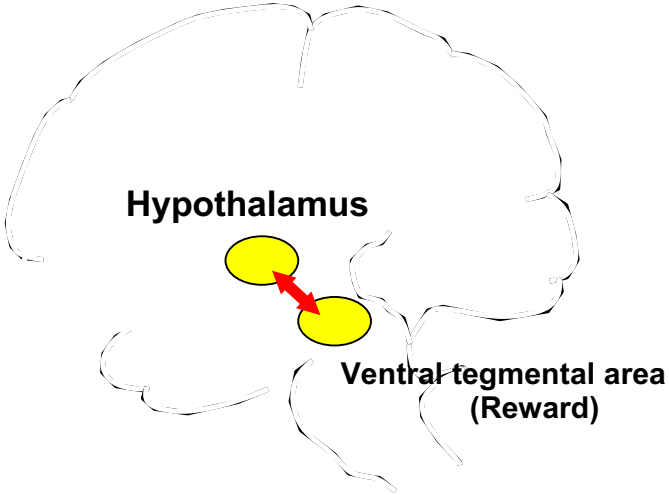
Chief.
Integrative Physiology Section
Laboratory of Biological Modeling

National Institute of Diabetes and Digestive and Kidney Diseases

Brain Signals that Control:

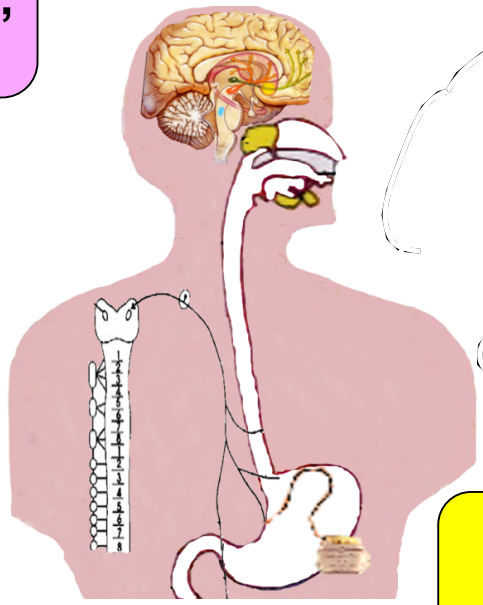
Drug Consumption

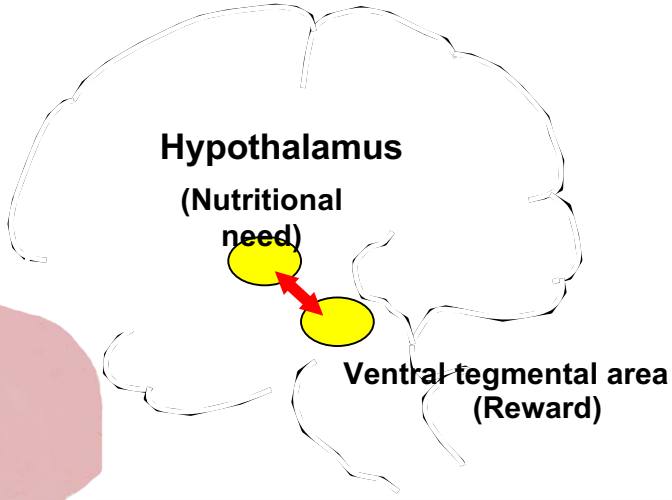
Reward
Dopamine, Cannabinoids, serotonin, opioids



Food Consumption

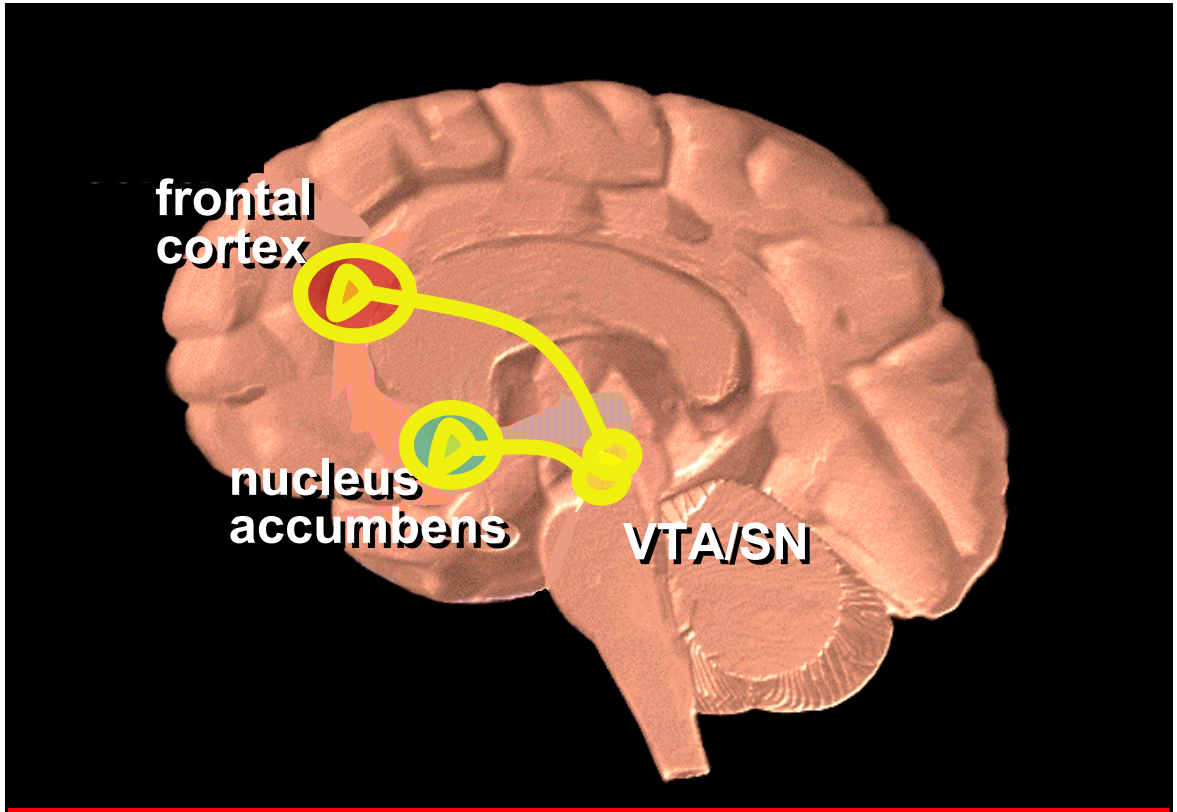
Reward
Dopamine, Cannabinoids, serotonin, opioids

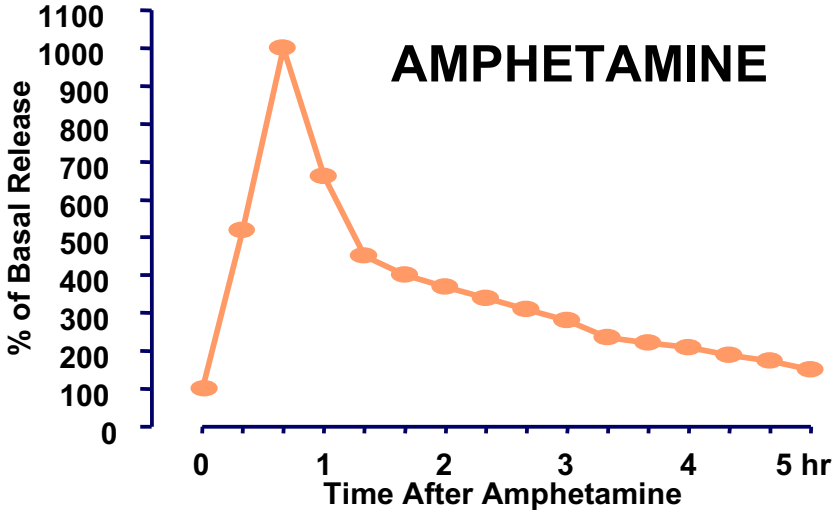


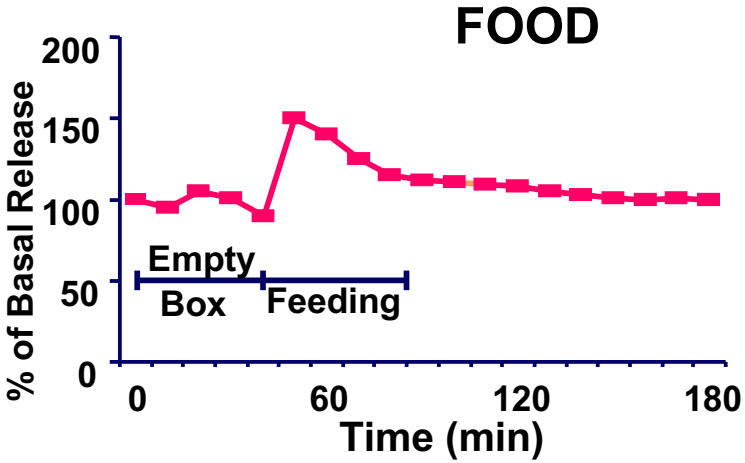


Homeostatic factors
Leptin, Insulin, Ghrelin, PYY

Natural & Drug Reinforcers Increase Dopamine in NAc



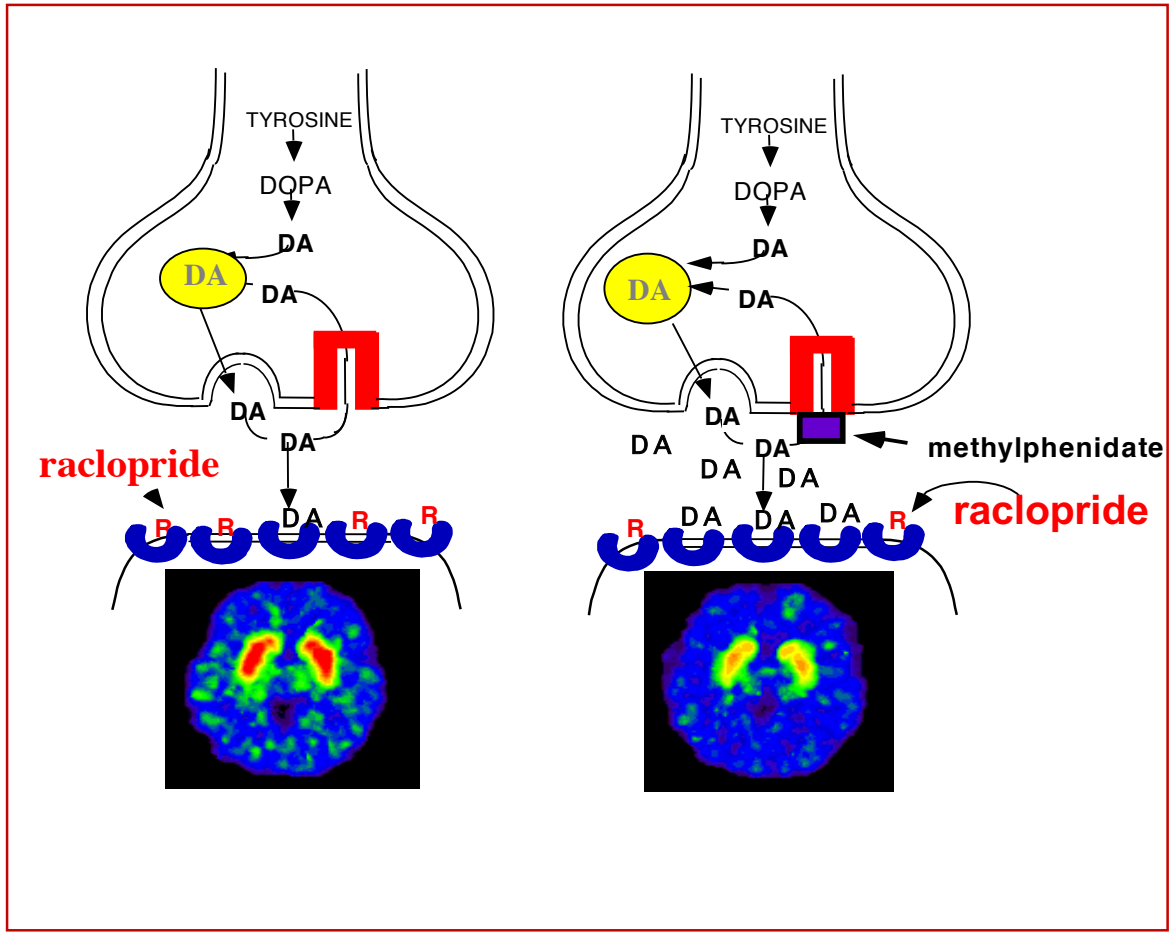


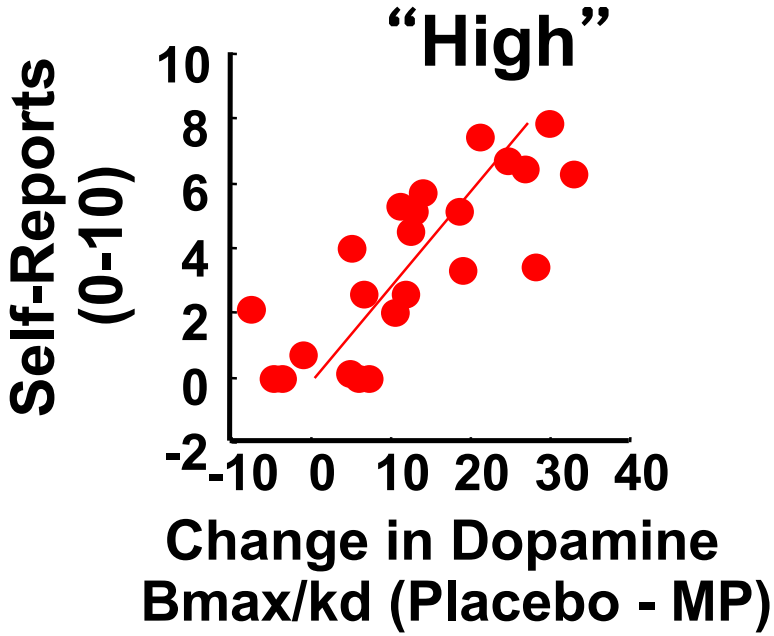


Di Chiara et al.

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

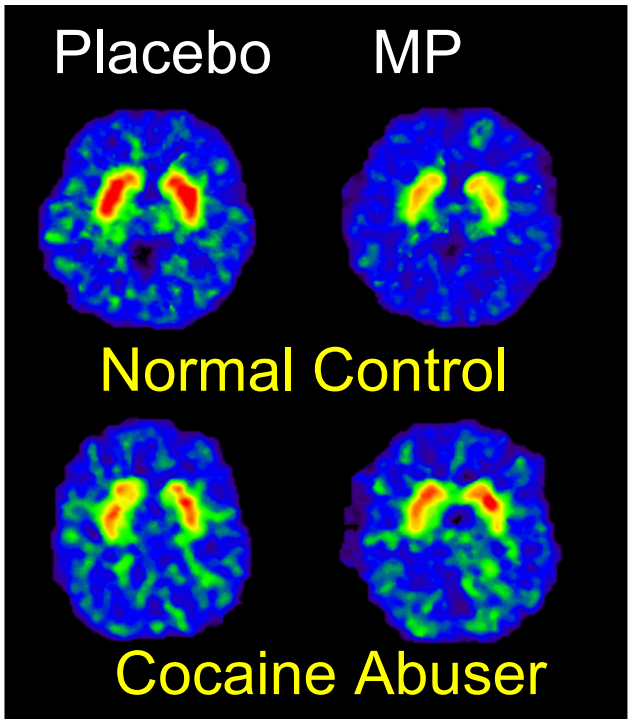
DA and Drug Reinforcement



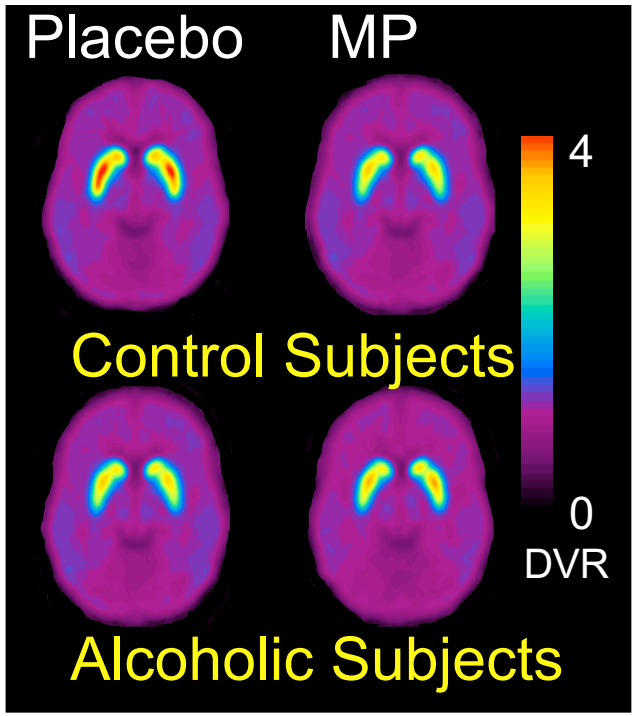


DA initiates and maintains responses to salient stimuli such as drugs

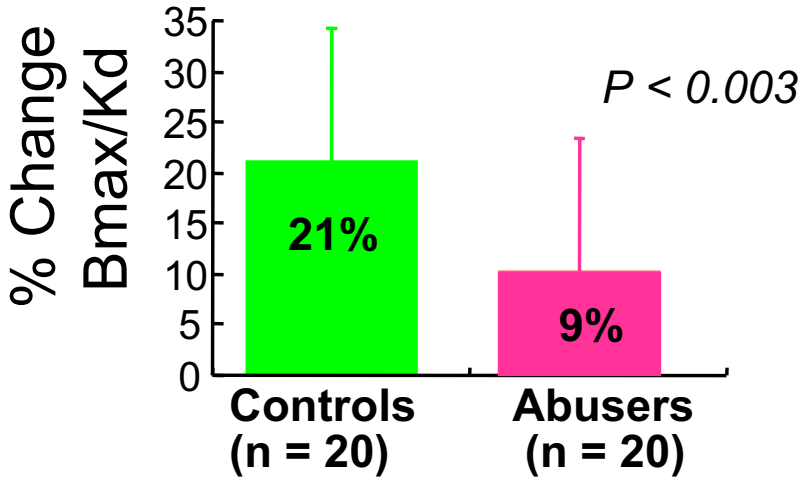
Volkow et al., JPET 291(1):409-415, 1999.

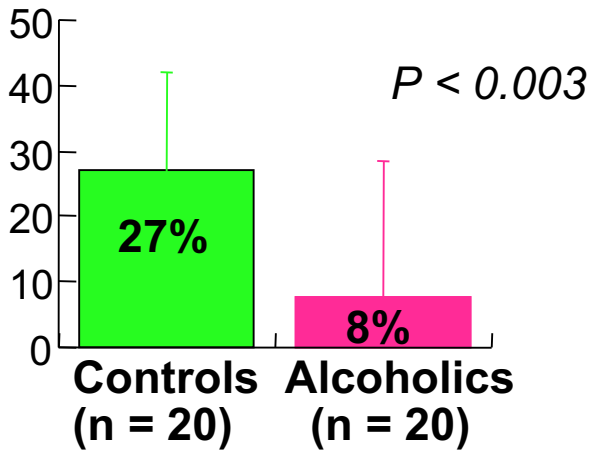


Volkow et al., Nature 386:830-833, 1997.



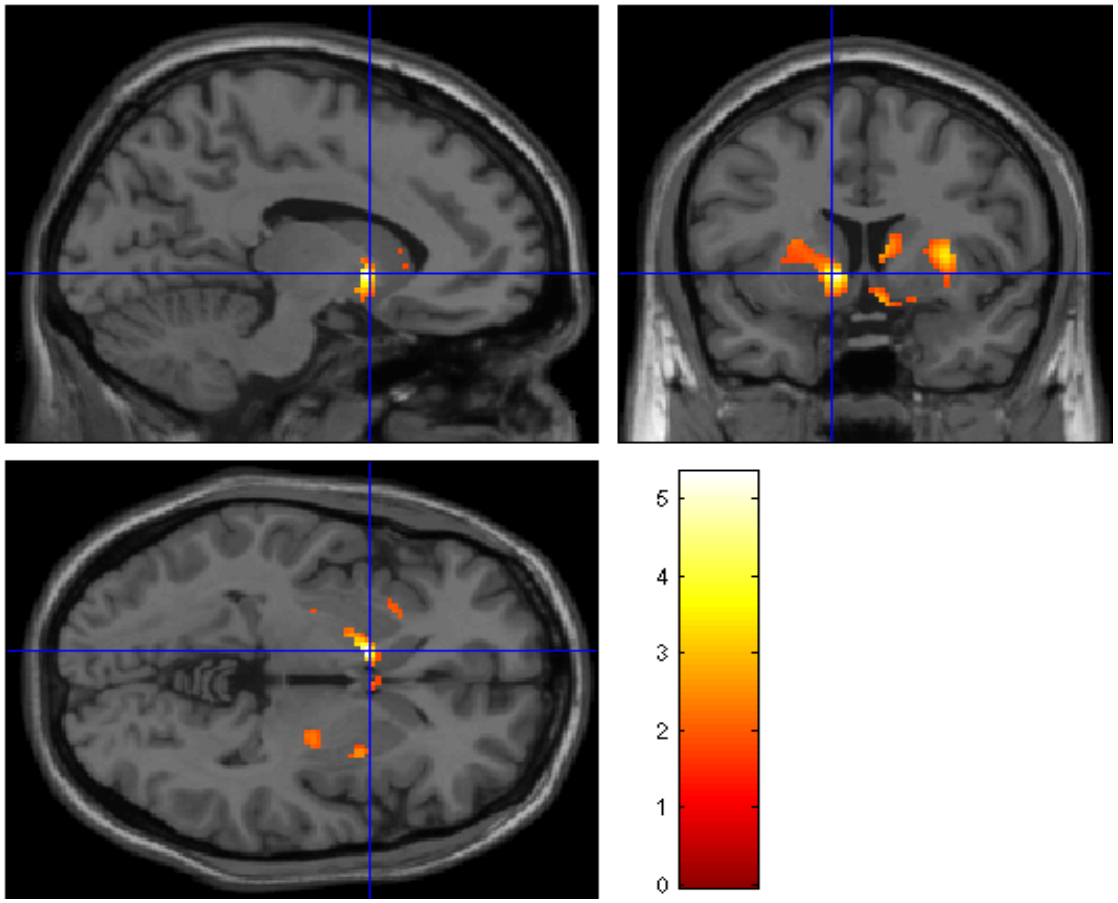
Volkow, ND et al., Neurosc 27:12700-6, 2007.

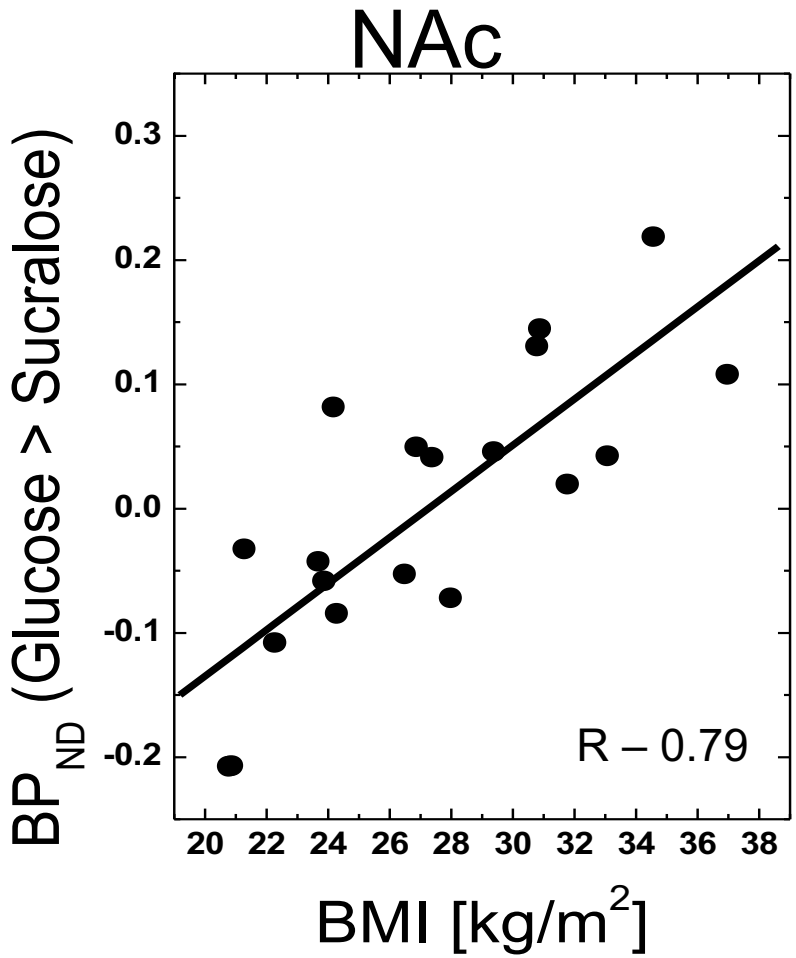




Cocaine abusers and alcoholics showed blunted DA increases to MP

Glucose triggered DA changes in NAc & BMI



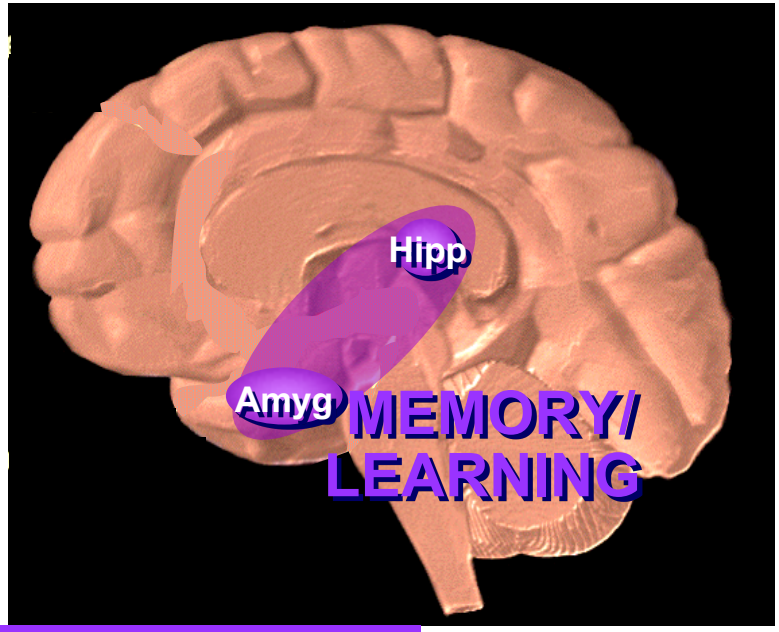


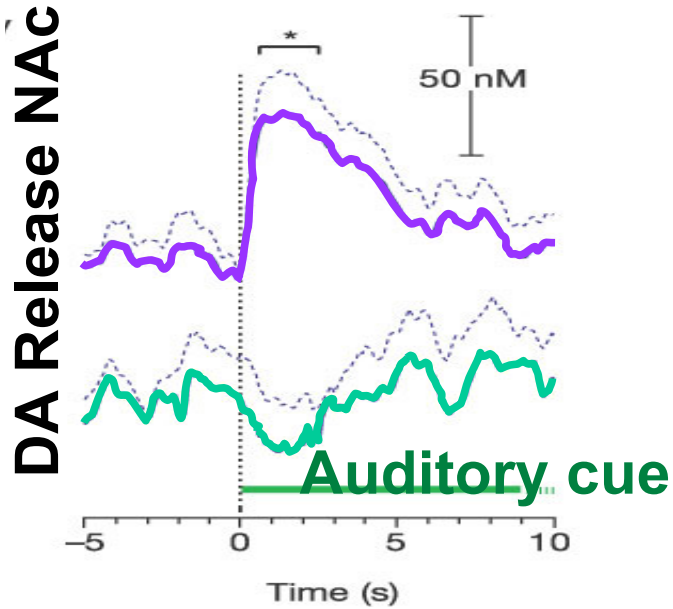
DBP*: corrected for changes in blood glucose levels (glucose – sucralose)
Within PET acquisition (0-60min)

Wang G-J et al., PLoS ONE 2014; 9(7): e101585.

Memory circuit

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





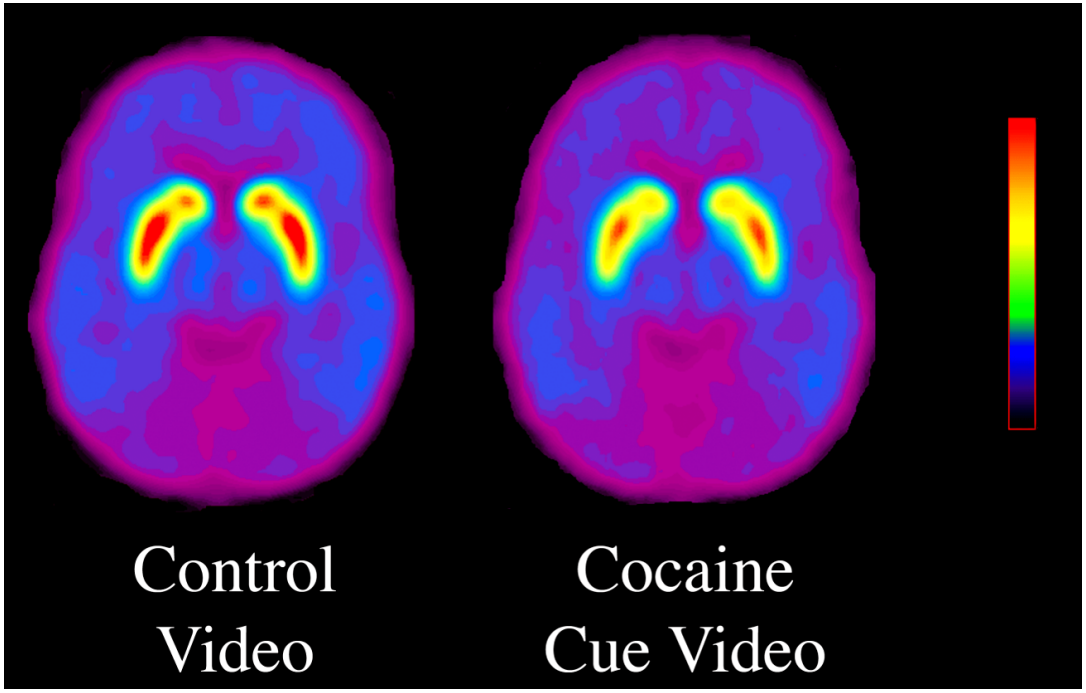
In training the cue **was** paired with cocaine

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*

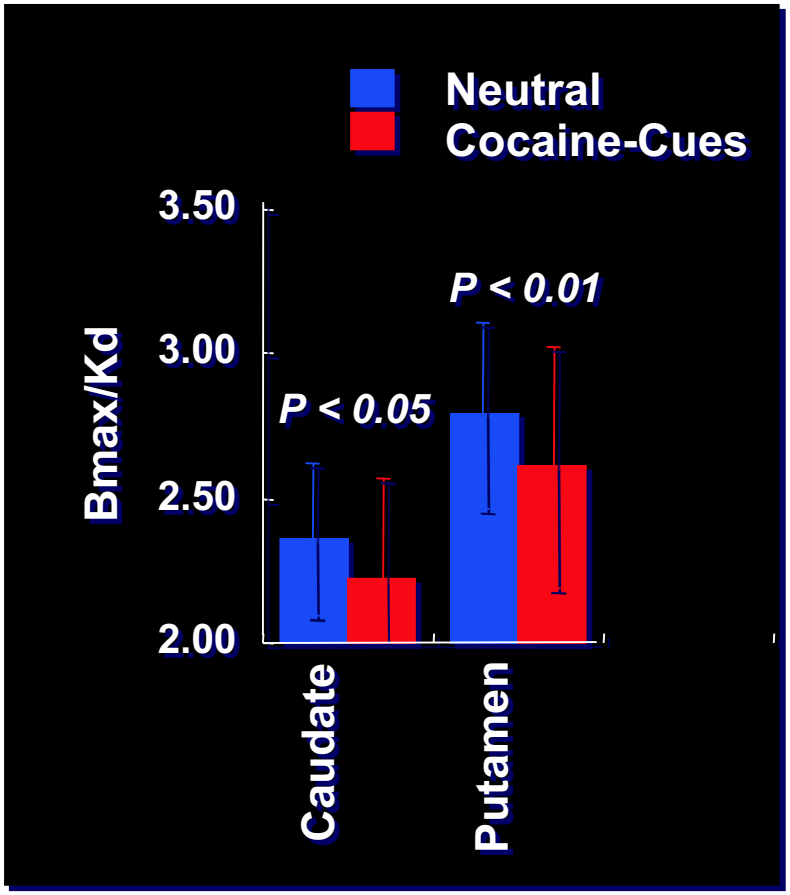
[^{11}C]Raclopride Binding In Cocaine Abusers (n=18) Viewing a Neutral and a Cocaine-Cue Video

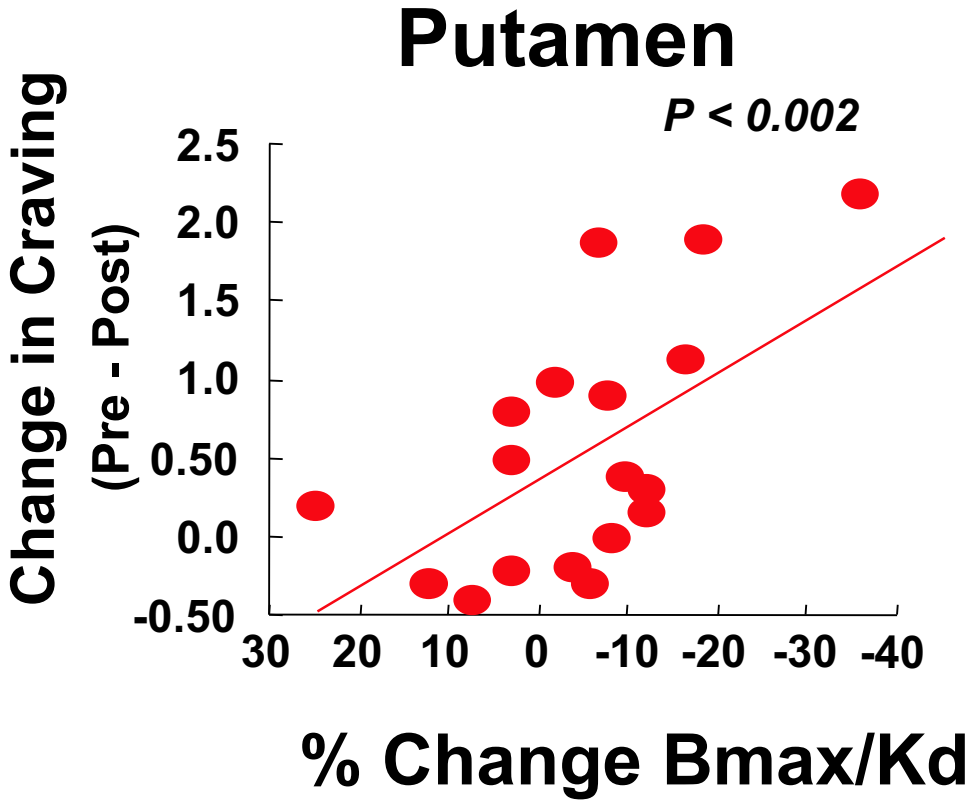


Viewing a video of cocaine scenes decreased specific binding of [11C]raclopride presumably from DA increases

Volkow et al J Neuroscience 2006.

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

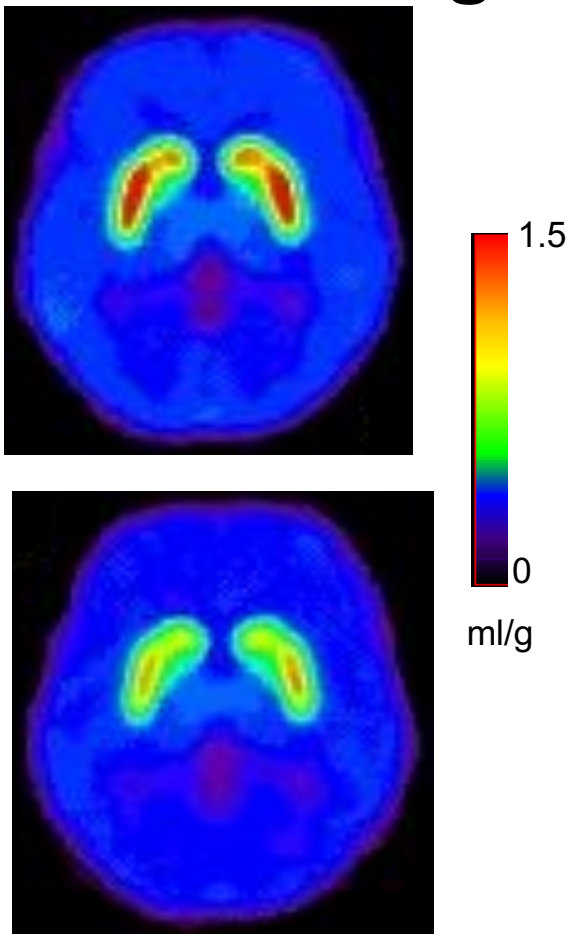




Volkow et al J Neuroscience 2006.

Cue-induced increases in DA were associated with craving

[^{11}C]Raclopride Binding in Food Deprived (15-18 hours) Controls (n=16) During Neutral and Food Cues



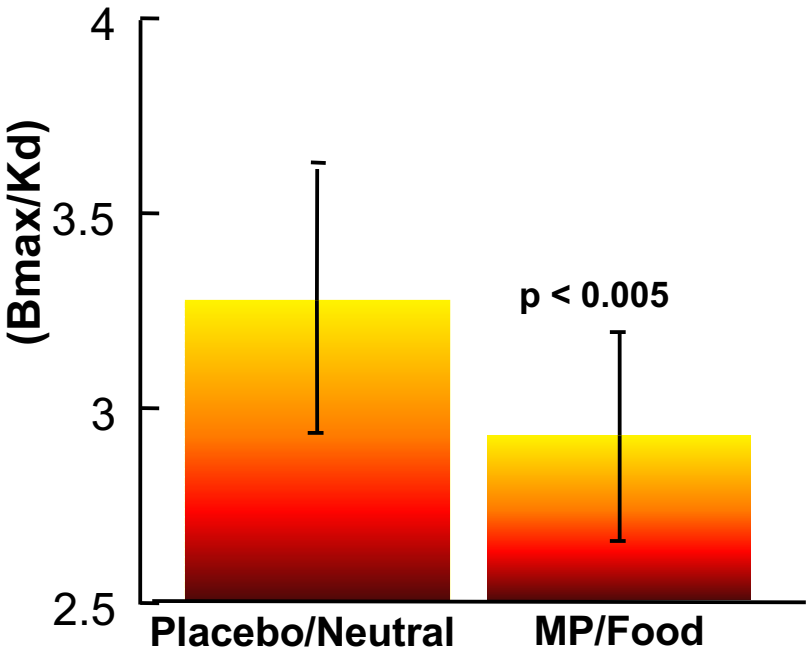
Neutral: **Subjects were asked to describe their family genealogy.**

Food Cue:

Volkow, et al., Synapse 2002.

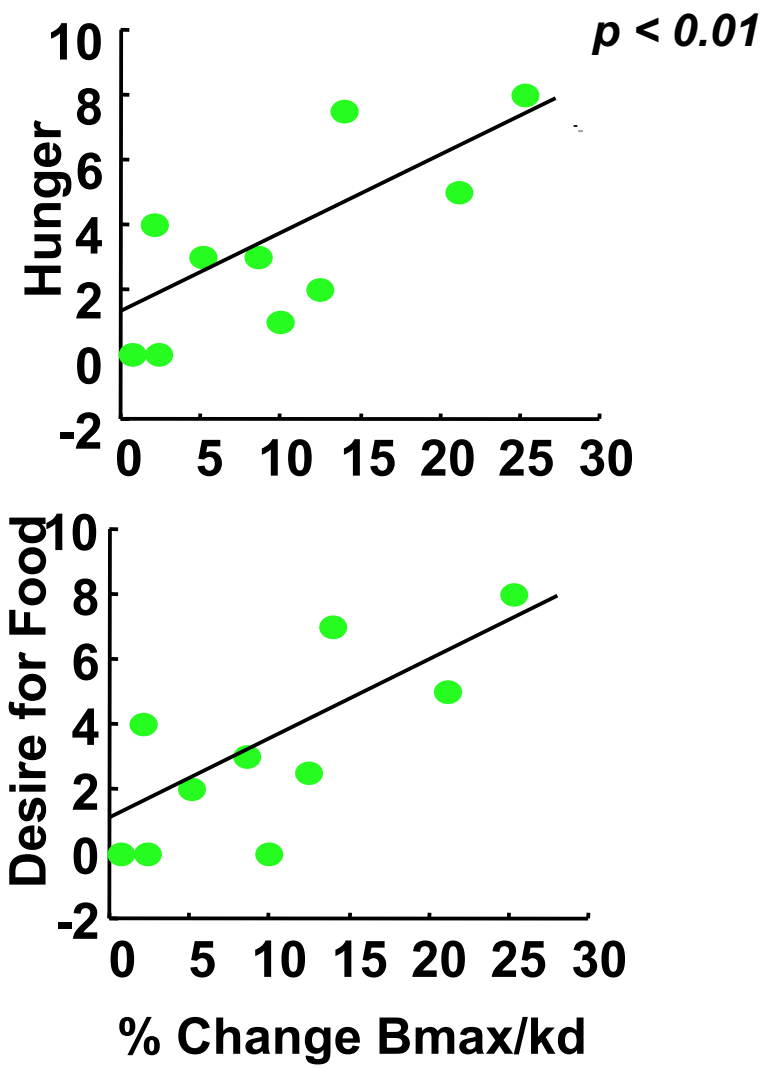
Bmax/Kd decreased with exposure to food-cues

[^{11}C]Raclopride Binding in Food Deprived Controls During Neutral and Food Cues

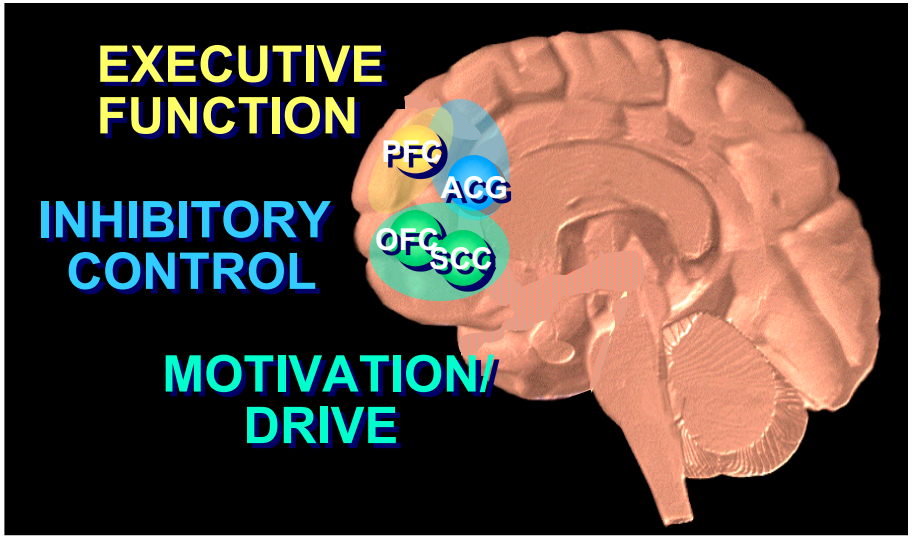


Bmax/Kd decreased with exposure to food-cues presumably from DA increases

Source: Volkow, et al., Synapse 2002.



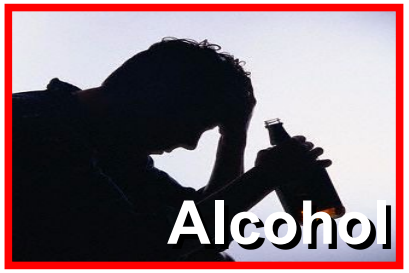
Motivation & Executive Control Circuits

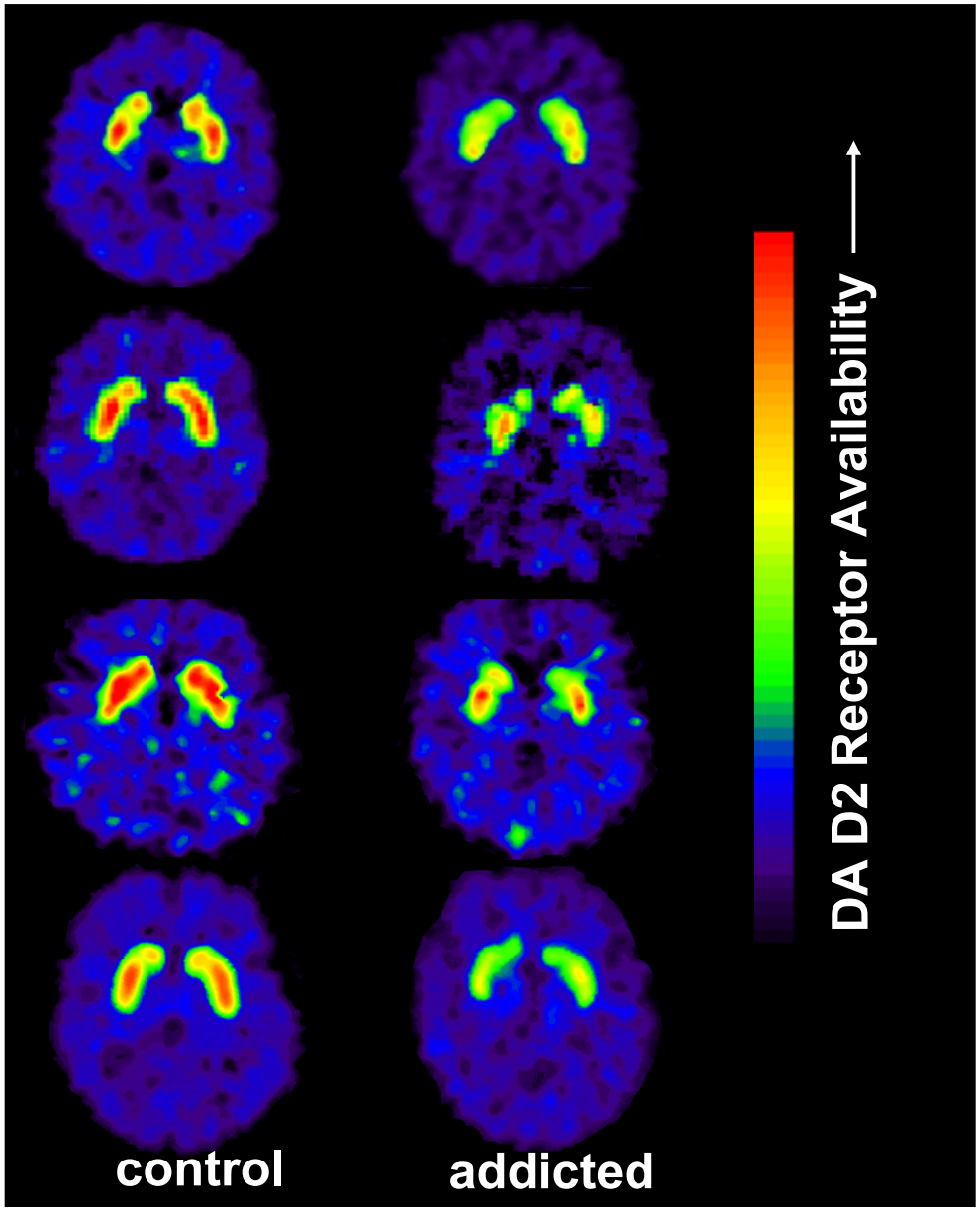


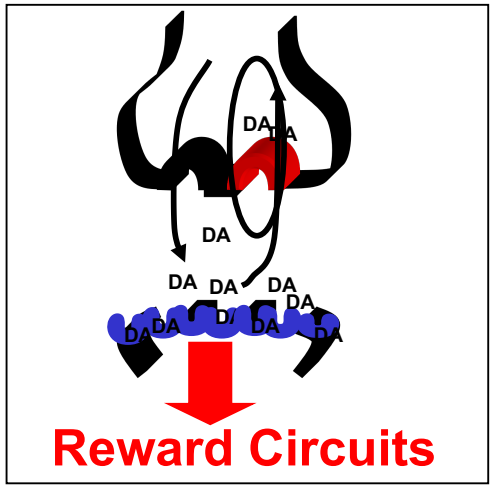
- DA is involved not only with reward and prediction of reward but also with motivation and executive function via its regulation of frontal activity
- Here we tested if, in addicted subjects, changes in DA function were linked with disruption of frontal activity as assessed by brain glucose metabolism

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

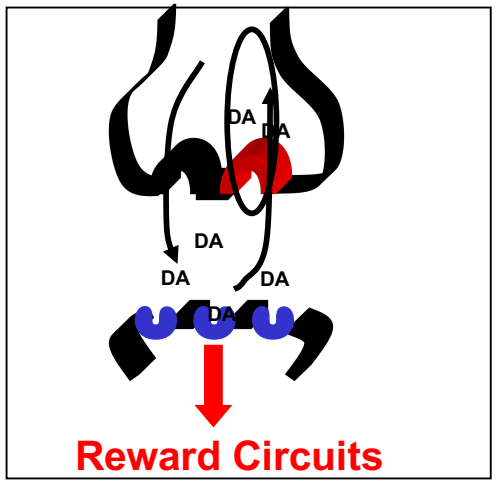
Dopamine D2 Receptors are Lower in Addiction







Non-Drug Abuser

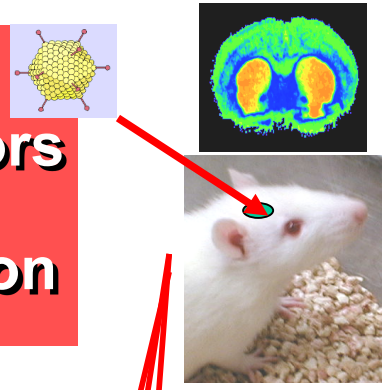


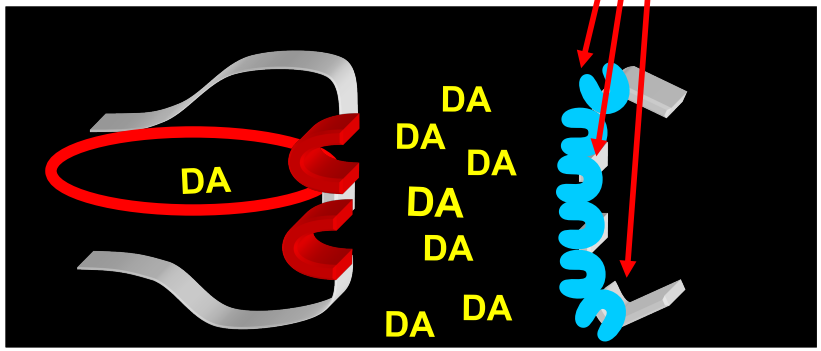
Drug Abuser

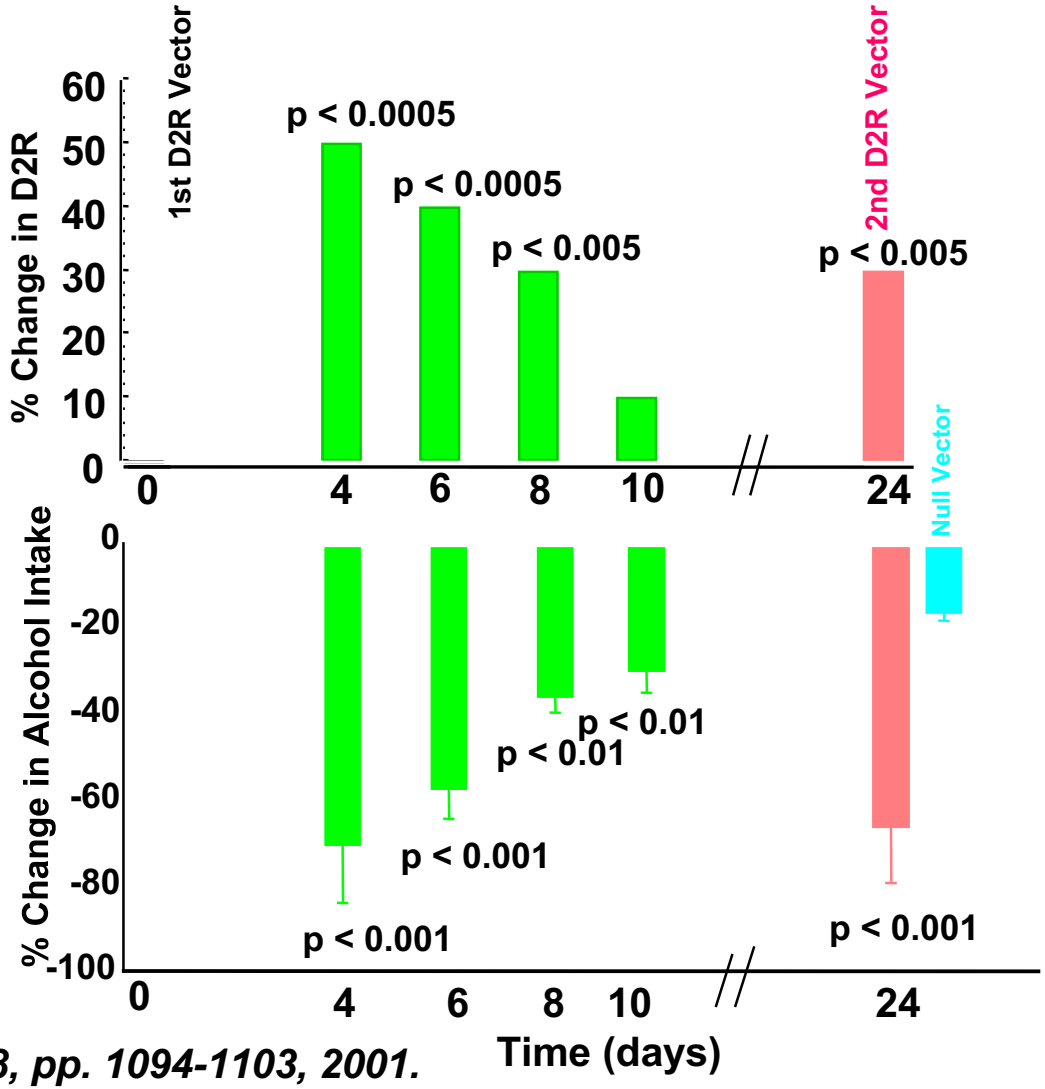
Adapted from Volkow et al., Neurobiology of Learning & Memory 78:610-624, 2002.

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





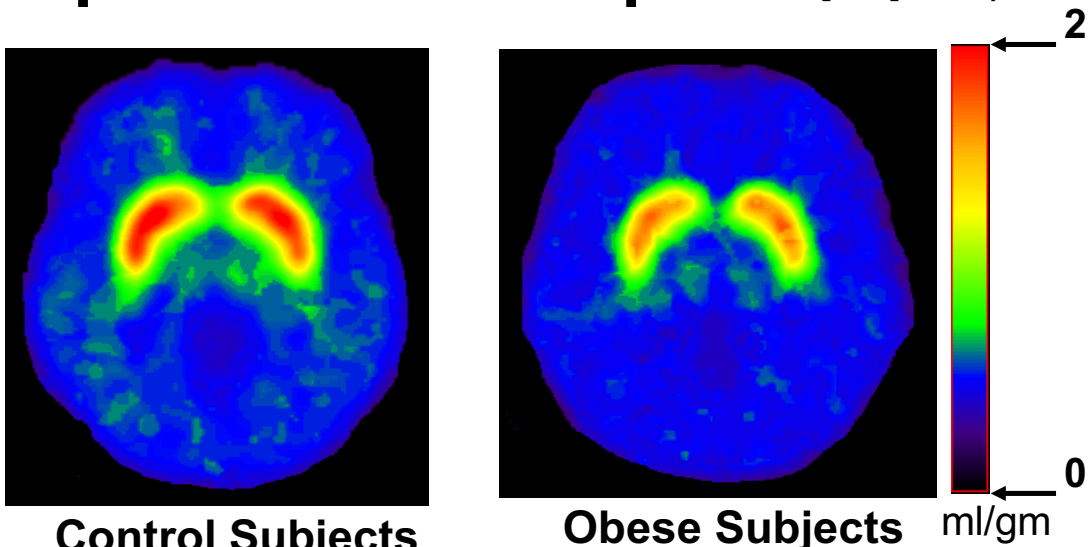


Thanos, PK et al., J Neurochem, 78, pp. 1094-1103, 2001.

Obesity

Compulsive overeating shares many of the same characteristics as drug addiction

Dopamine D2 Receptors [^{11}C]raclopride

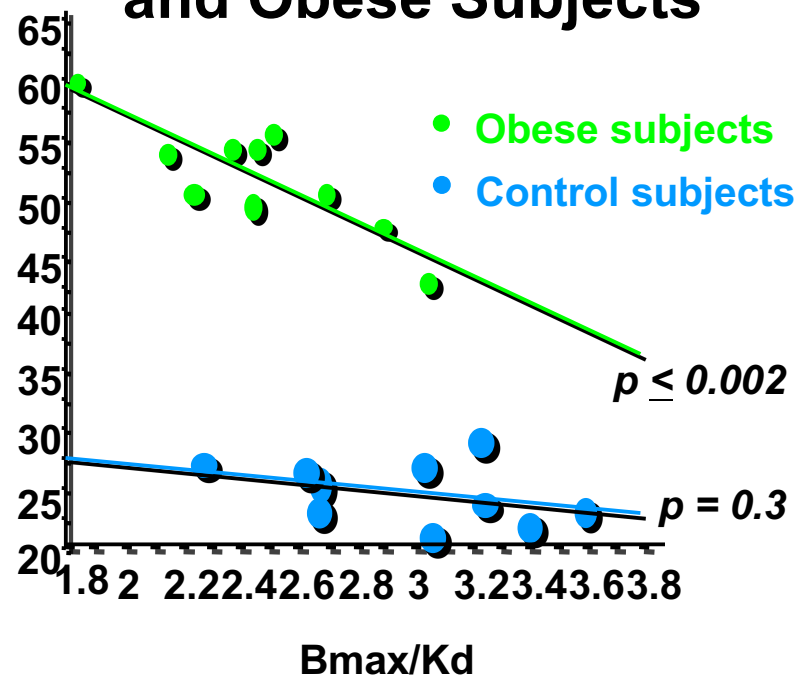


Control Subjects
2.99 (Sd 0.41)

Obese Subjects
2.47 (Sd 0.36)

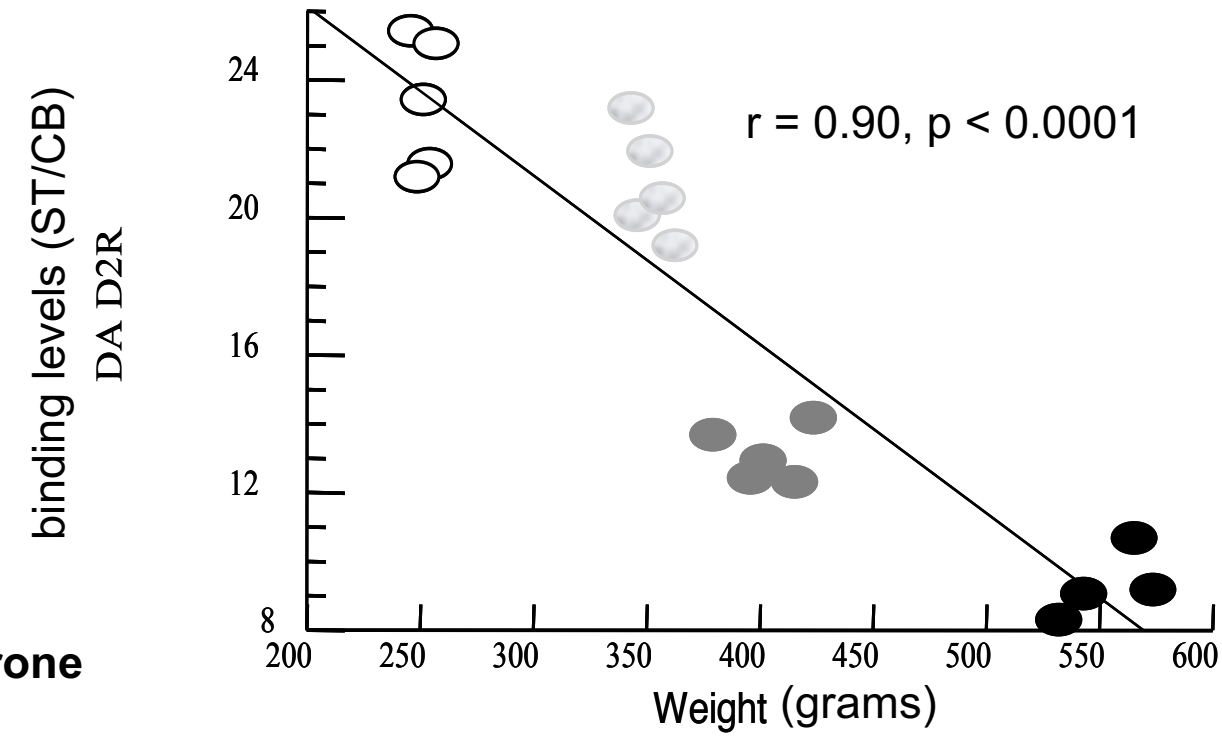
P < 0.008

DA D2 Receptors and BMI in Controls and Obese Subjects

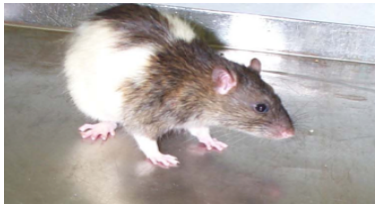


Wang et al, Lancet 2001.

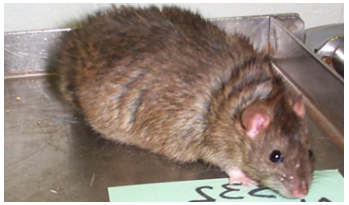
The Effects of Food Restriction to Dopamine D2 Receptor in Lean & Obese Rats at 4 Months Old



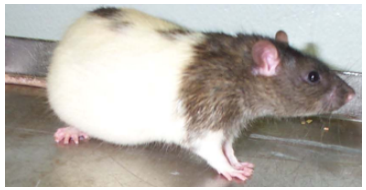
[^{3}H]Spiperone



Ate 80% of averaged diet



Ate 80% of lean rats diet

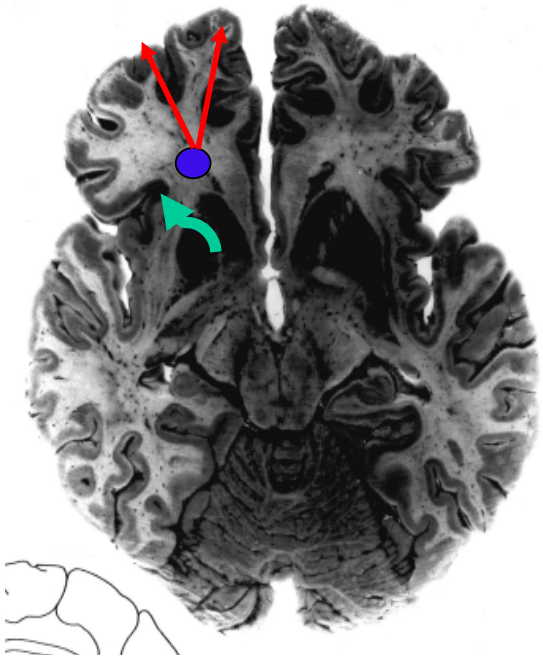


Free access

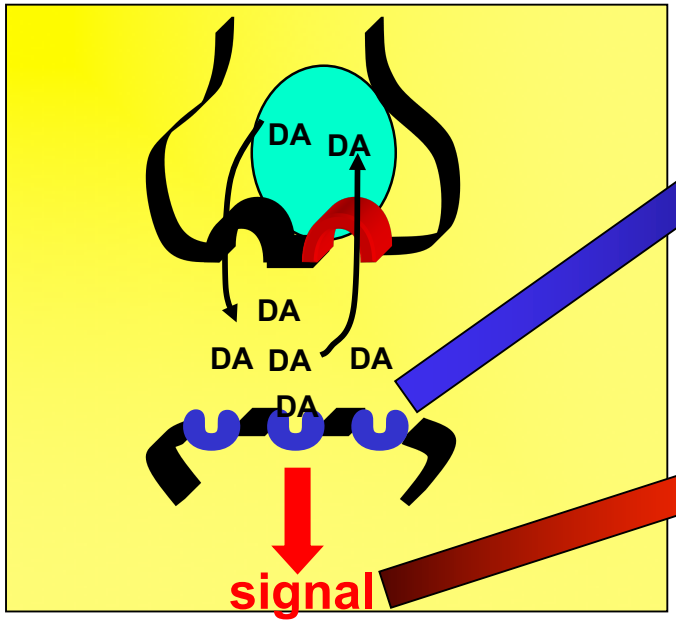
Free access

Thanos PK et al. Synapse; 62:50-61.

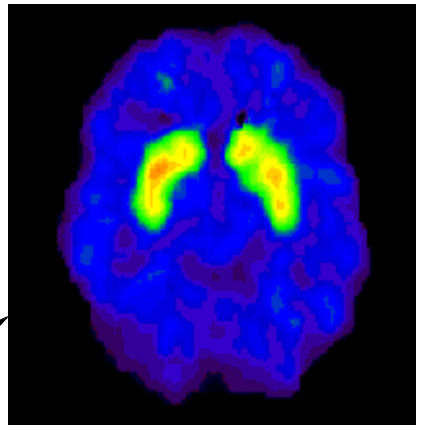
What is the functional significance of low D2-R?



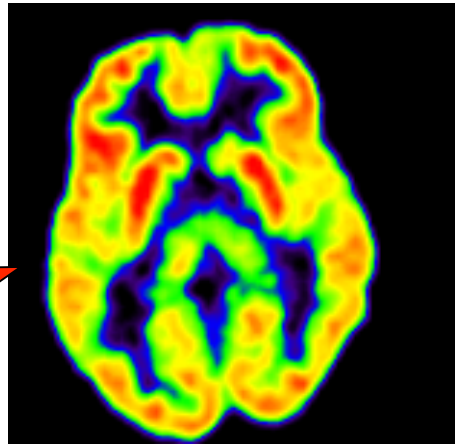
Anatomy



Dopamine Cell

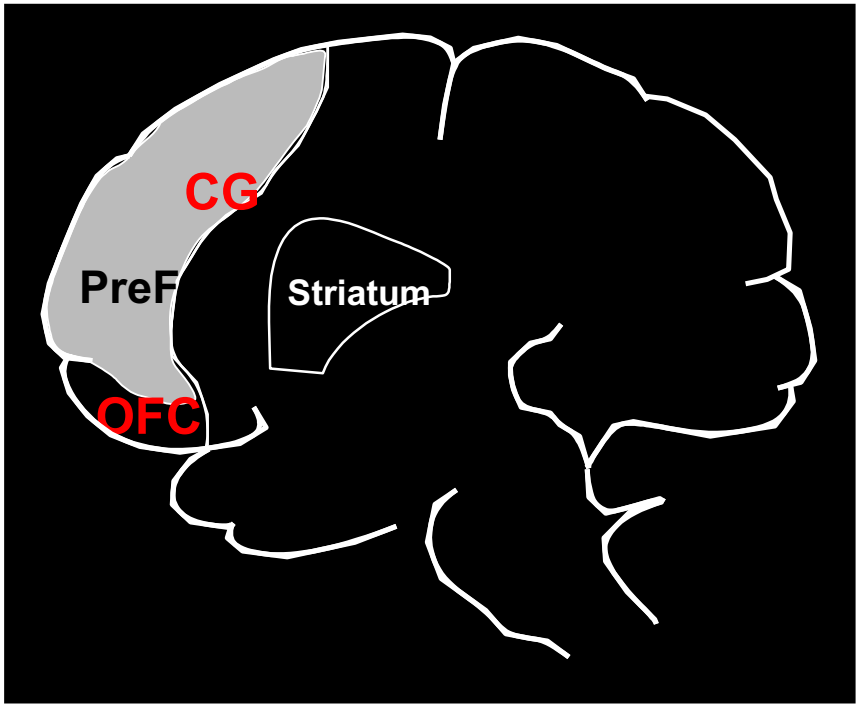


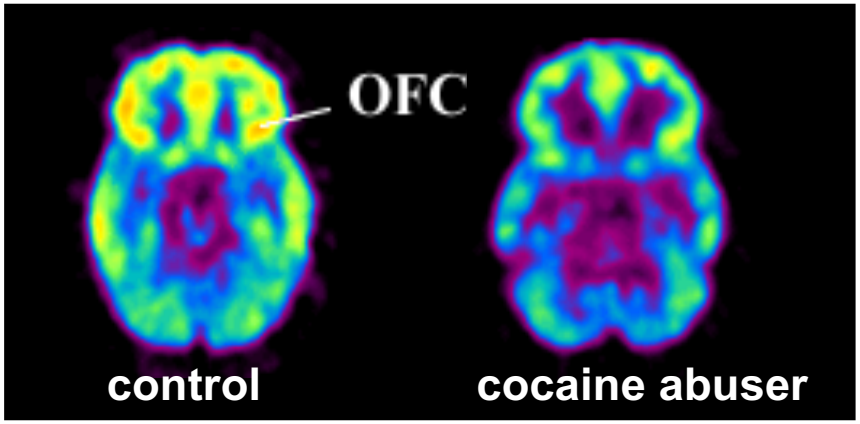
DA Receptors

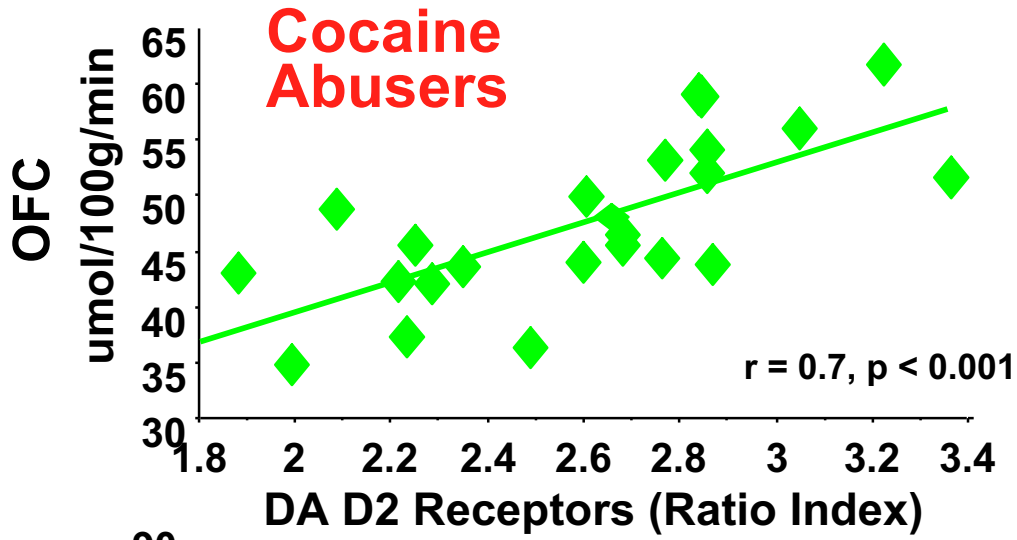


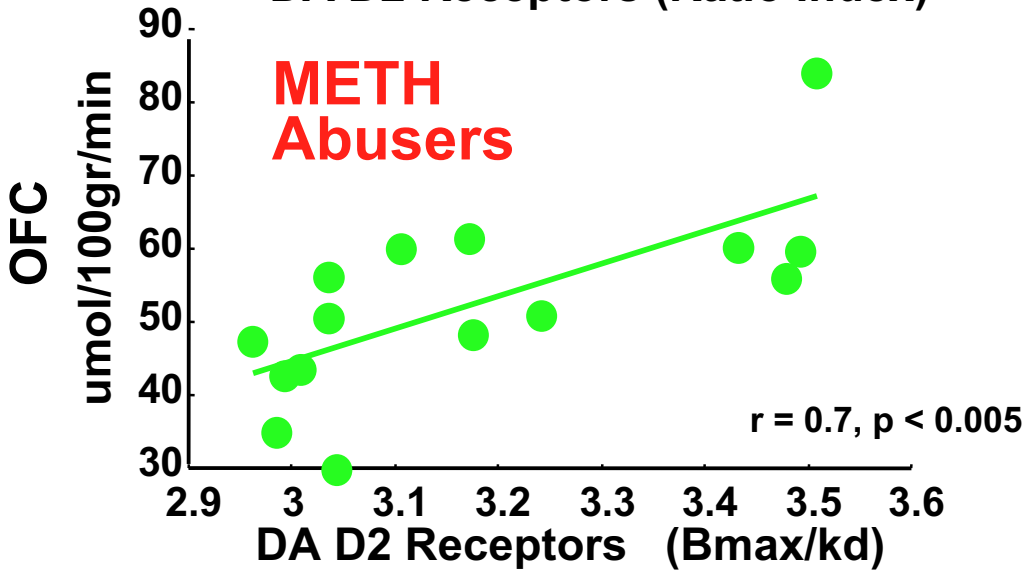
Metabolism

Correlations Between D2 Receptors in Striatum and Brain Glucose Metabolism



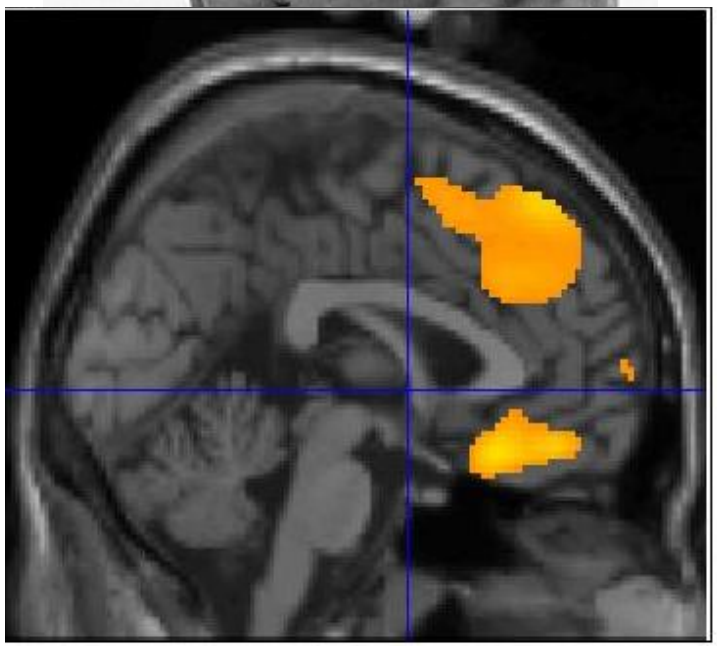




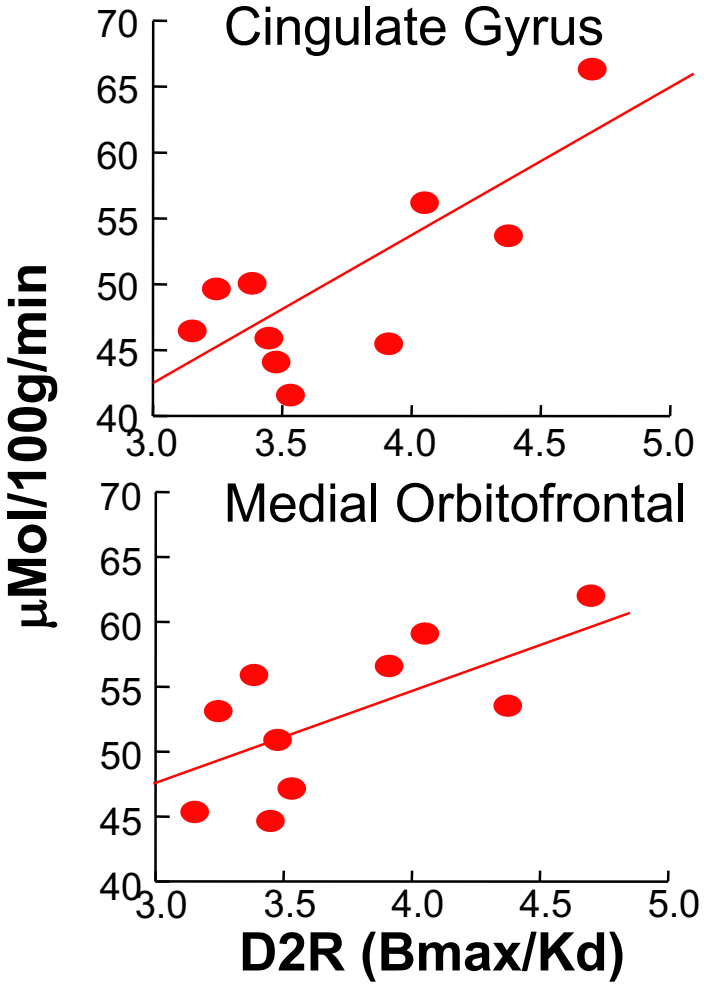


Volkow et al., AJP 158(3):377-382, 2001.

Relationship Between DA D2 Receptors (D2R) and Brain Metabolism in Obese Subjects

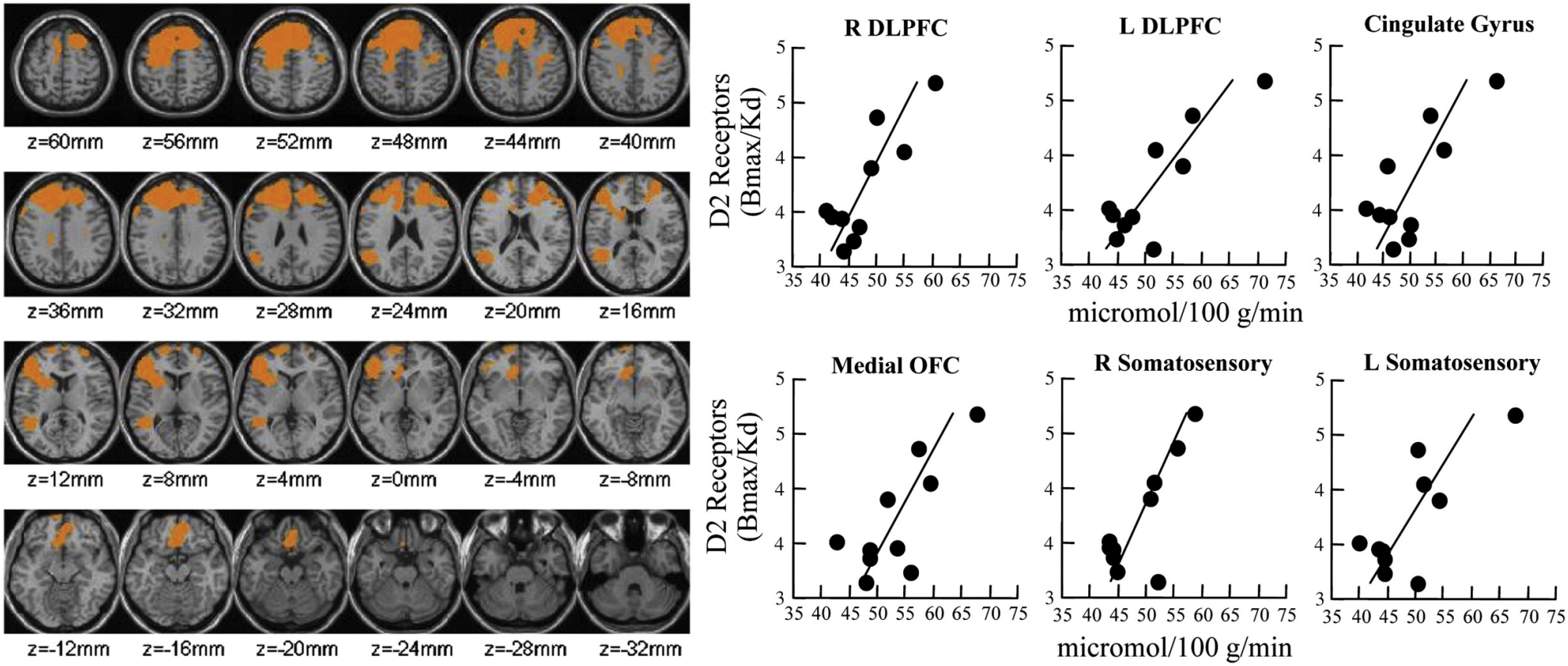


p < 0.005

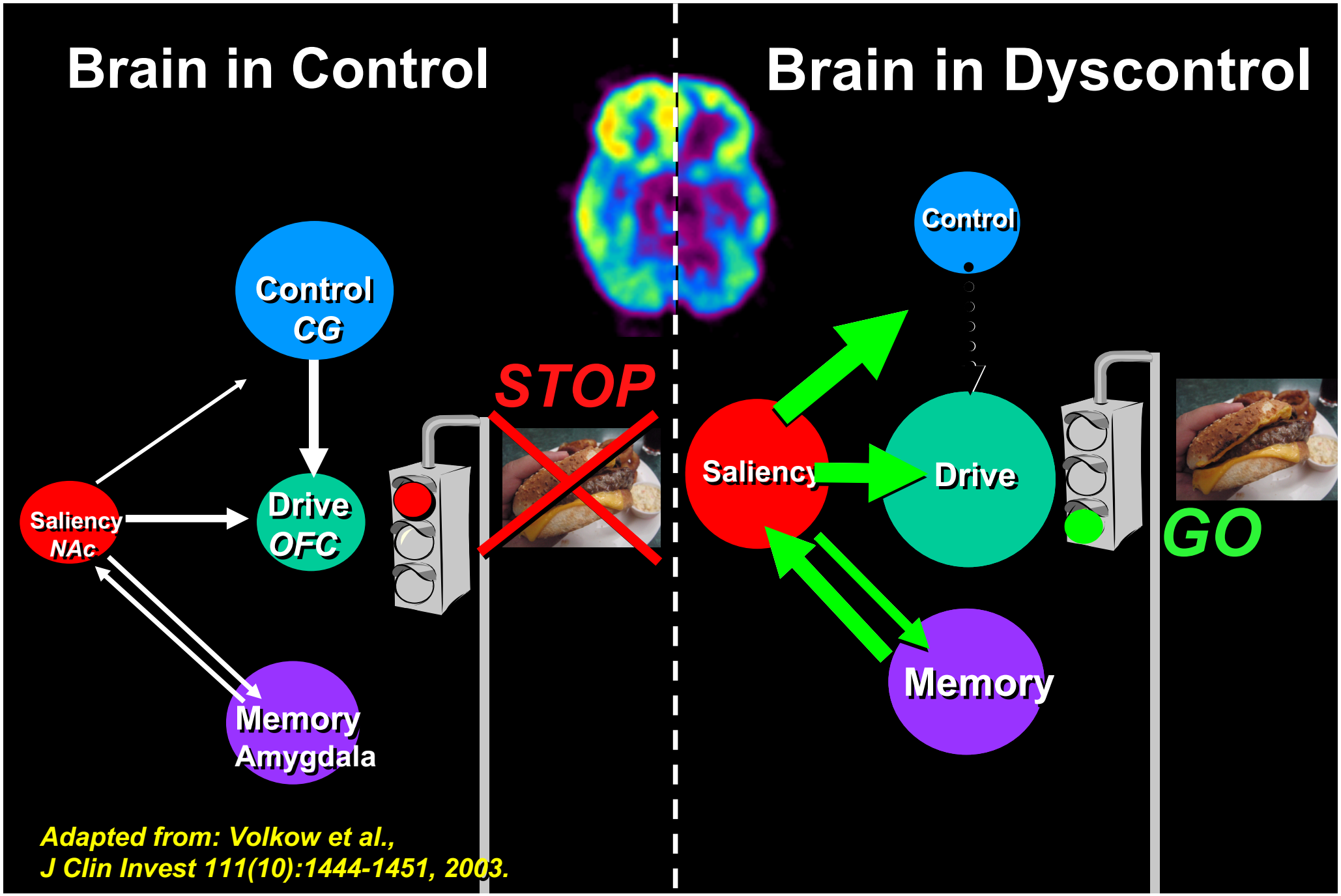


Low D2R in obese subjects is associated in with reduced metabolism in cingulate gyrus and medial orbitofrontal cortex

Low Dopamine Striatal D2 Receptors Are Associated with Prefrontal Metabolism in Obese Subjects

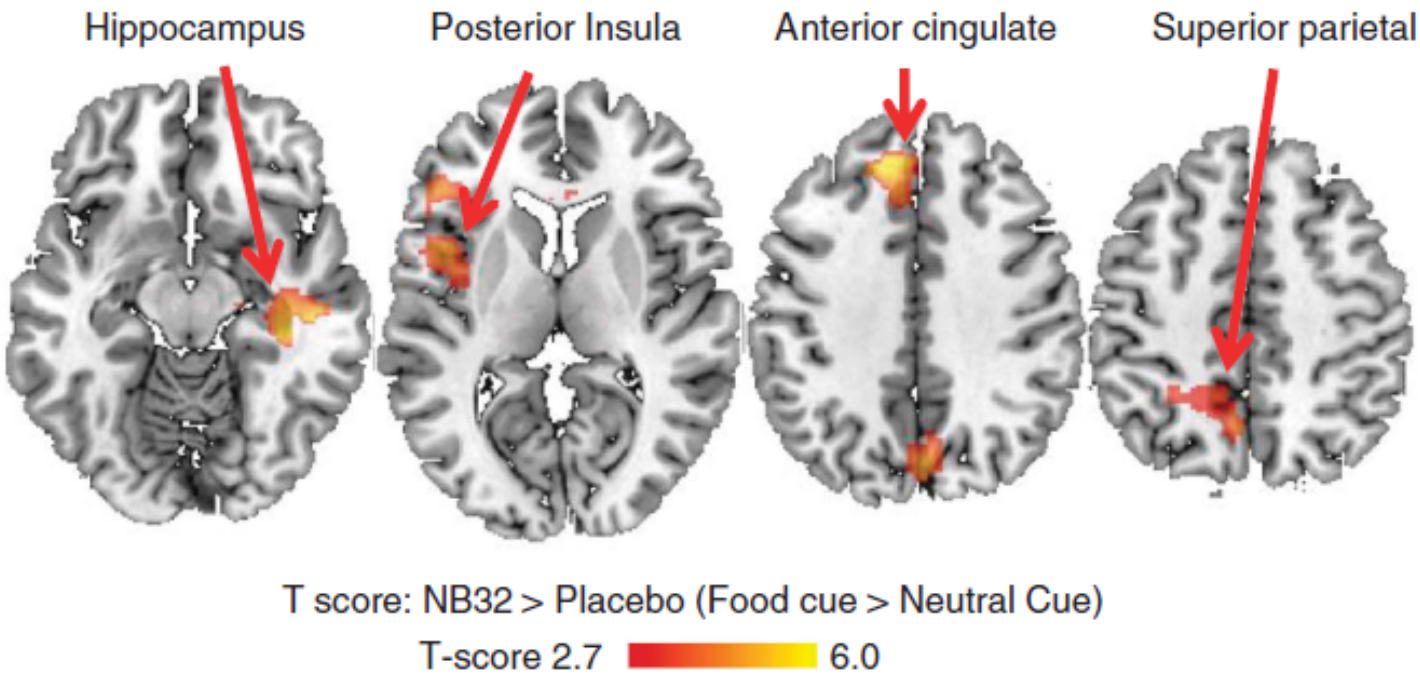


Volkow ND et al., NeuroImage 2008; 42: 1537-1543.


Brain in Control
Brain in Dyscontrol
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.

The Greater Effect of NB32* As Compared With Placebo In Response to Visual Food Cues

In a fasted condition, the NB32 group, following exposure to food cues, had decreased activation in the hypothalamus and enhanced activation in brain regions involved in inhibitory control, internal awareness, memory/conditioning & somatosensory processing.



***(Combination naltrexone-sustained release (SR) 32mg and bupropion SR 360mg)**

Wang G-J et al., Int J Obesity 2014; 38:682-688.