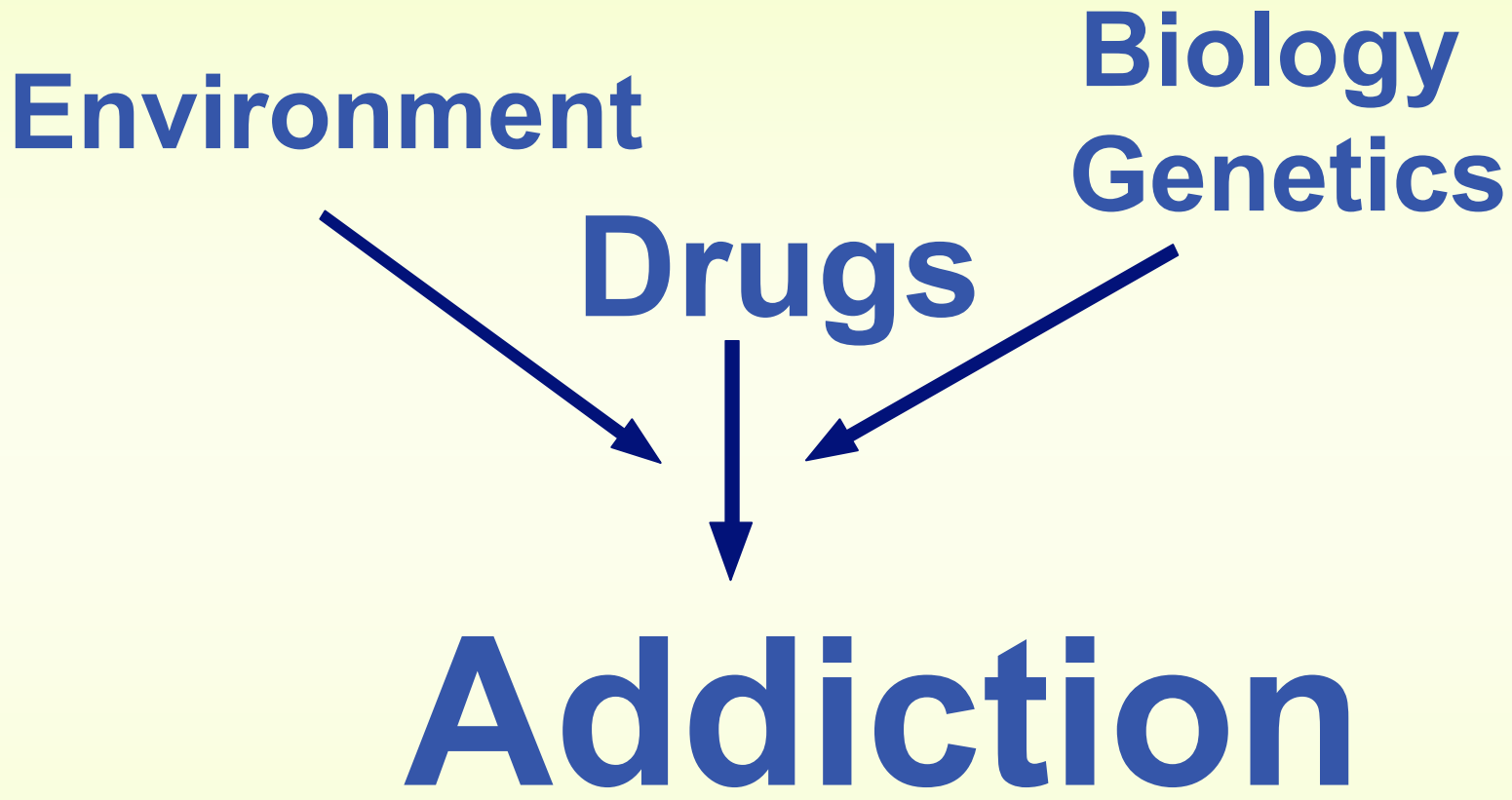
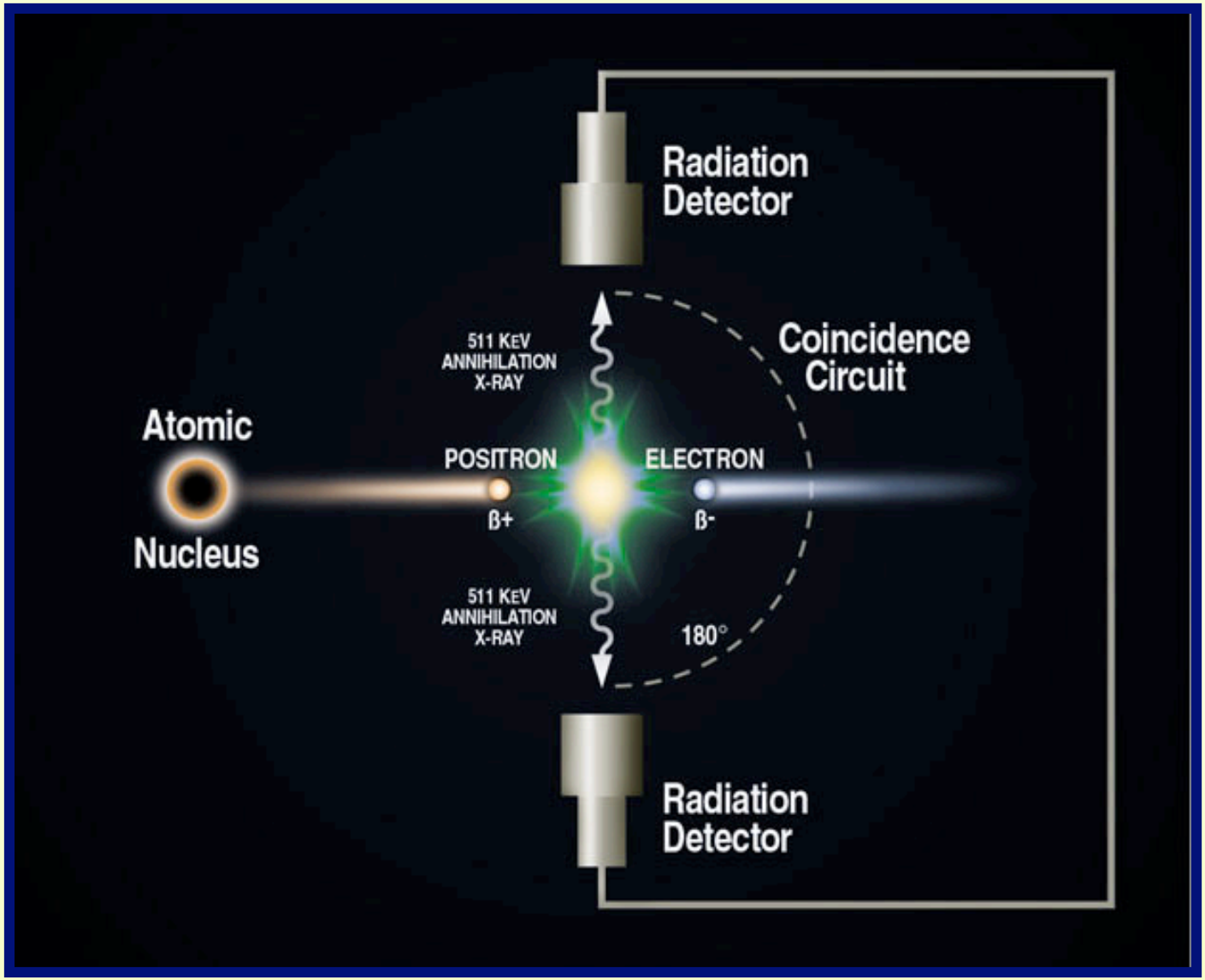

Environment
Biology
Genetics
Drugs
Addiction

PET Scientific Tools

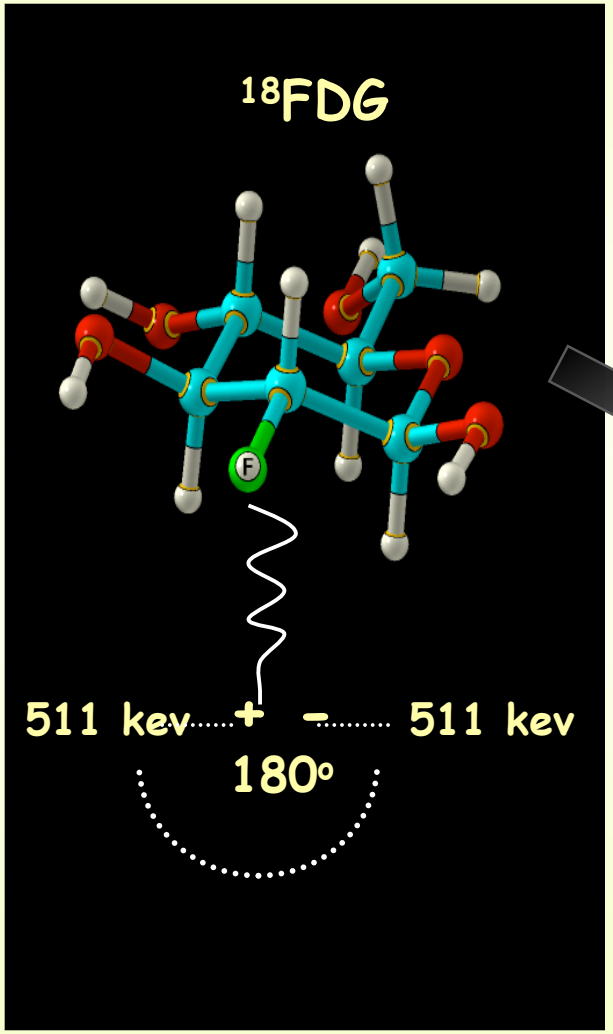
Isotope	half-life
carbon-11	20.4 min
fluorine-18	110 min
nitrogen-13	10 min
oxygen-15	2 min

Requires the development of rapid, microscale synthetic methods

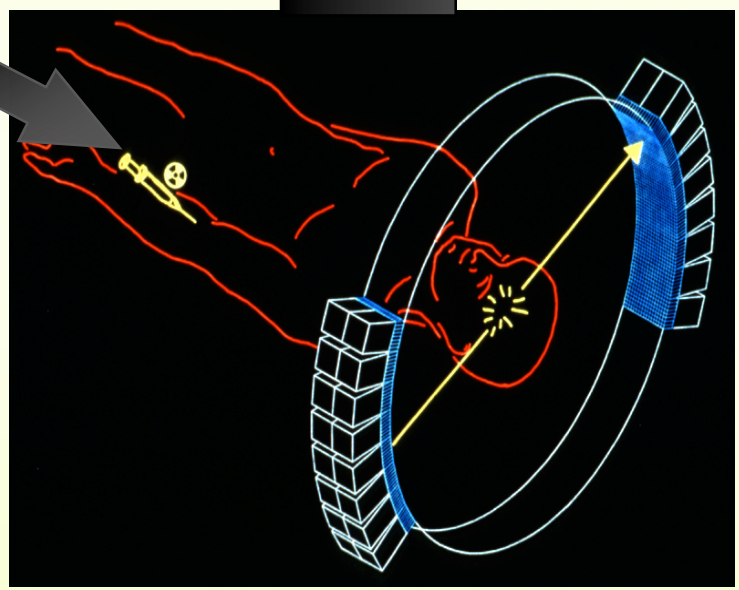
Positron Decay and Coincidence Detection



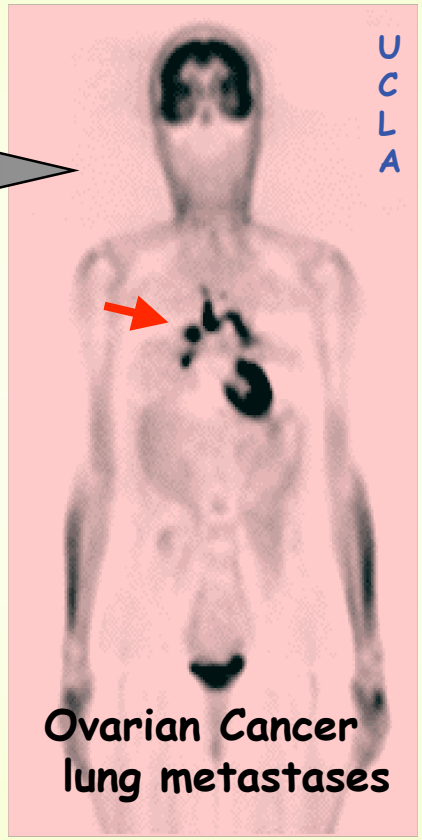
Positron Emission Tomography



Radiotracer

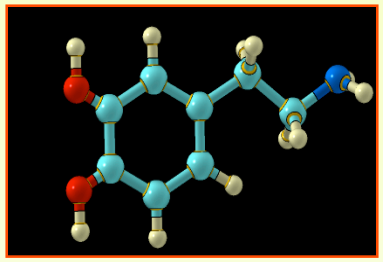


PET Scanner



PET Image

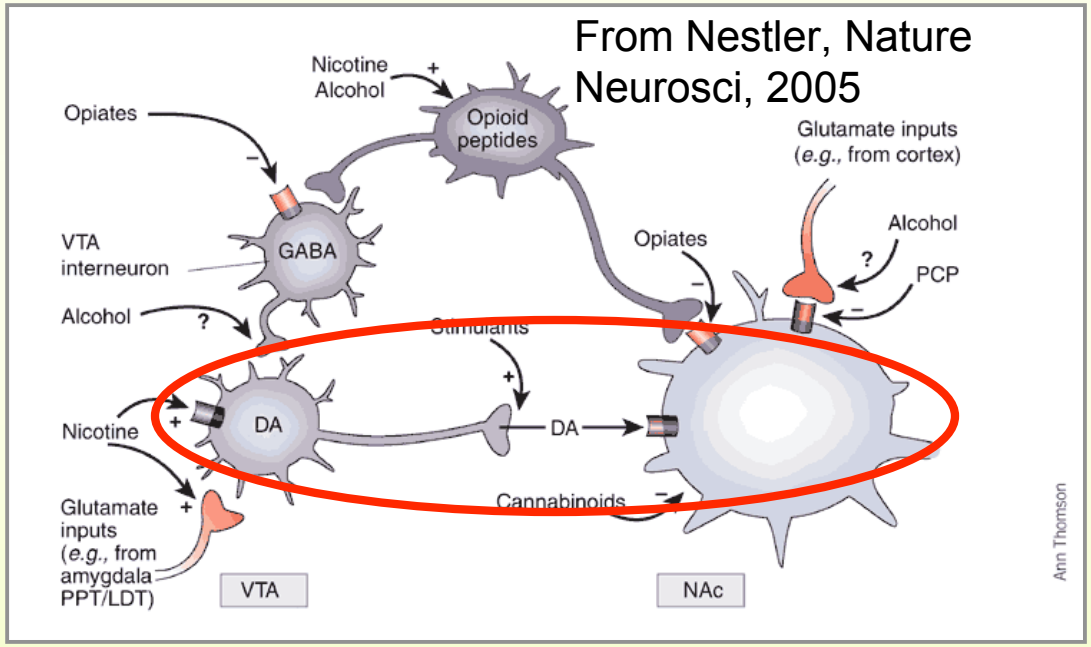
Addiction



dopamine

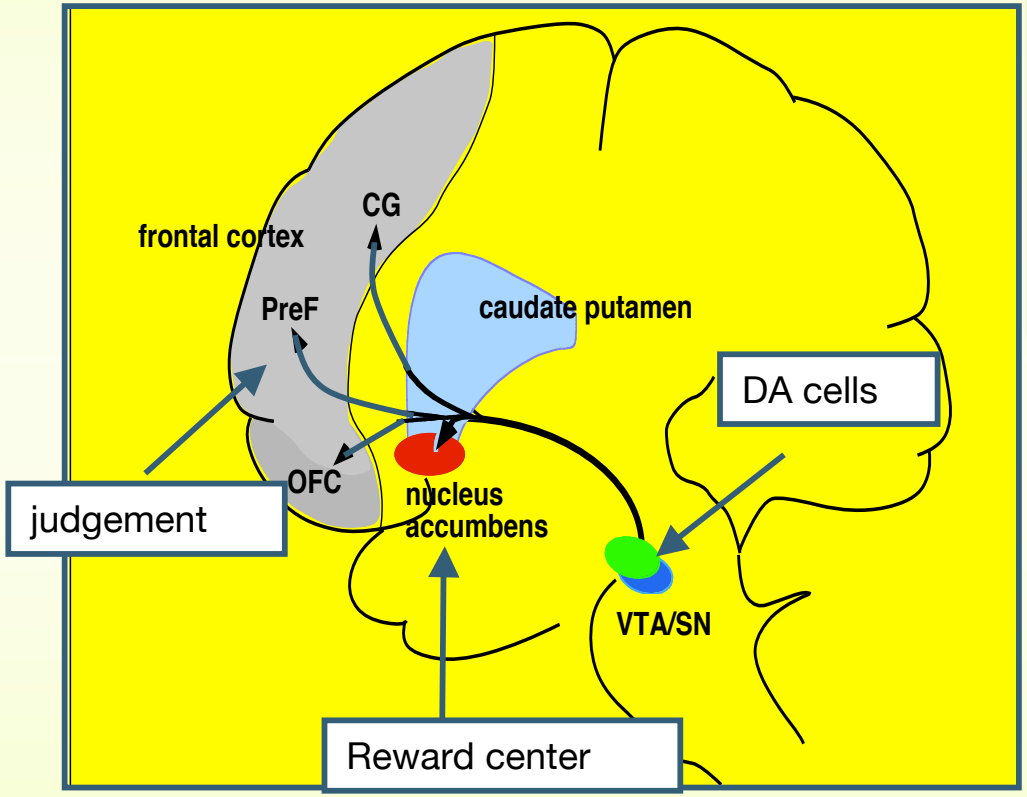
What we know……

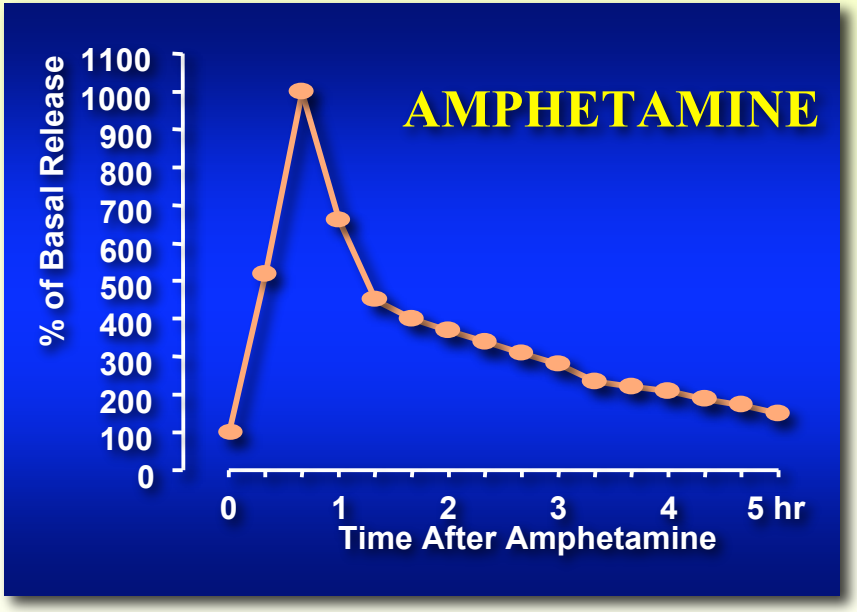
All drugs abused by humans raise brain dopamine levels in the nucleus accumbens

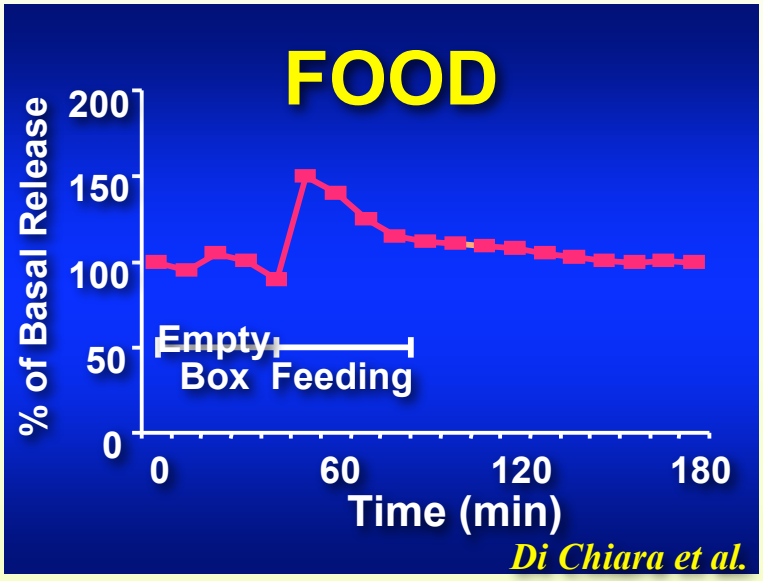


Dopamine is also elevated in feelings of well being and in anticipation of natural reinforcers like highly palatable food.

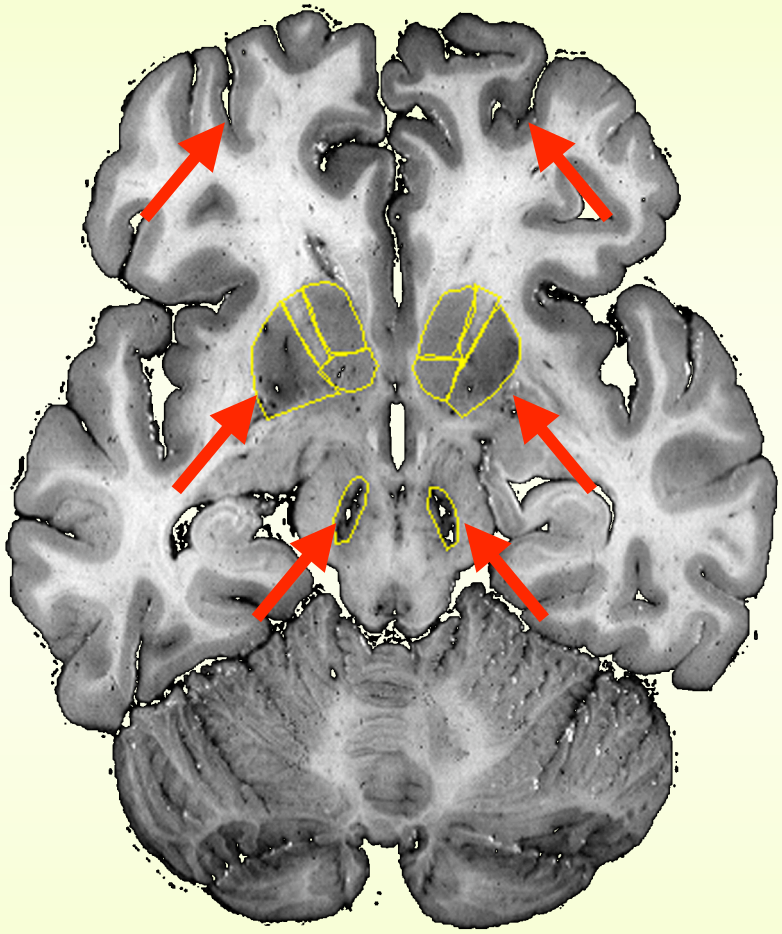
Dopamine Neurotransmission



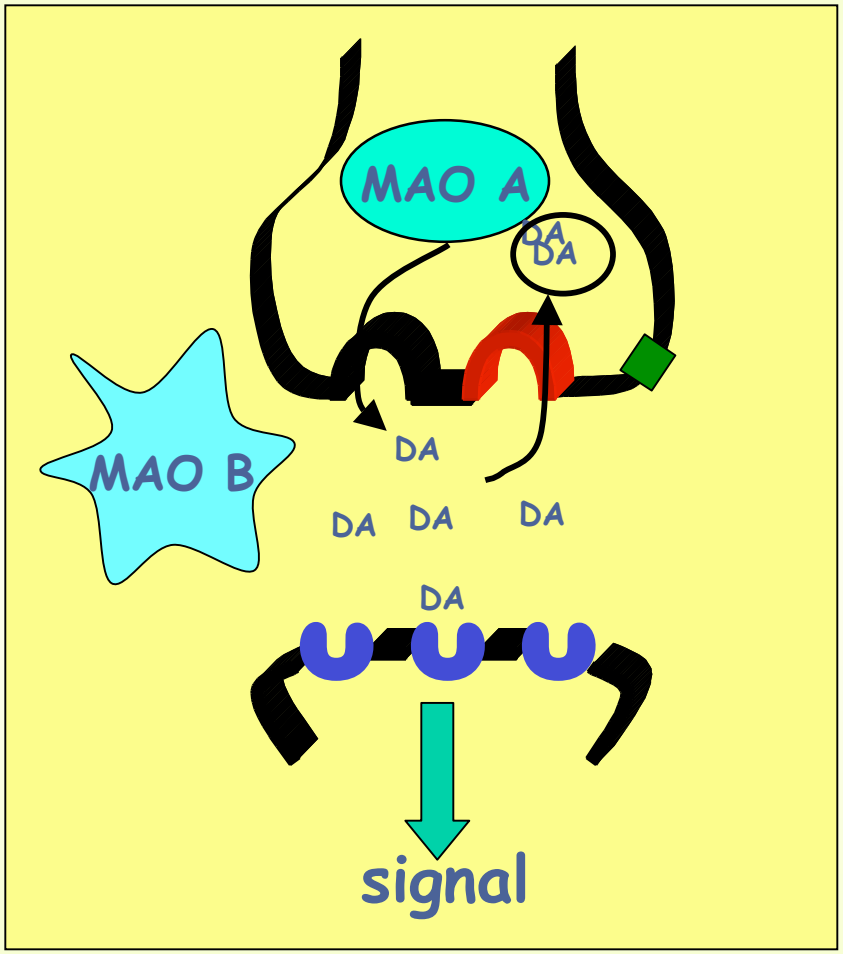




The Brain Dopamine System

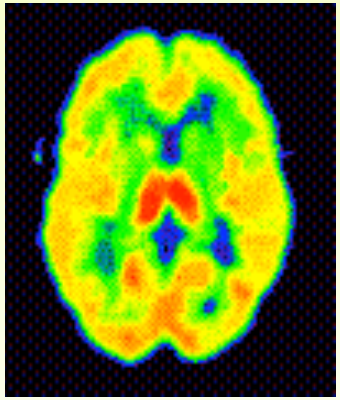


anatomical slice

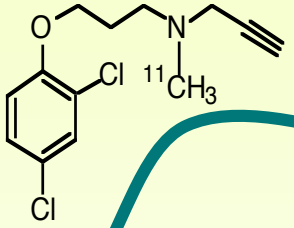


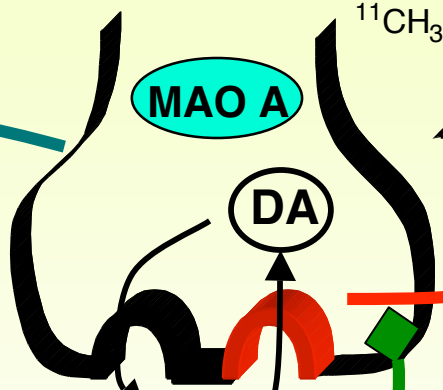
dopamine cell

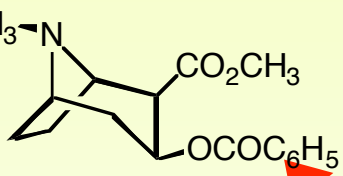
Radiotracers for Brain Studies

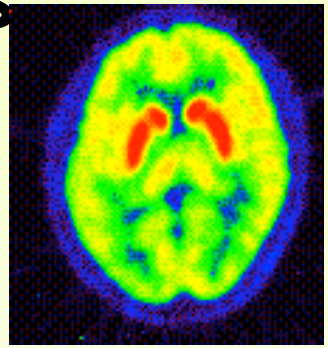


MAO A



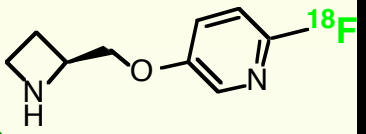


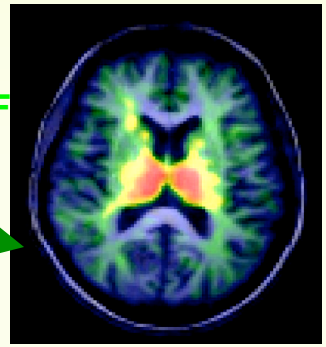




DA transporters

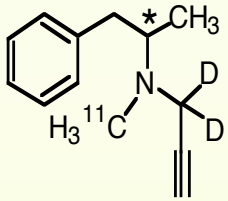
MAO B

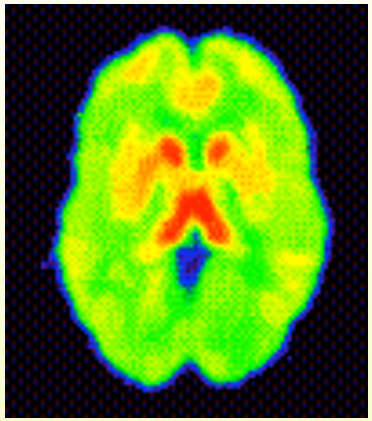


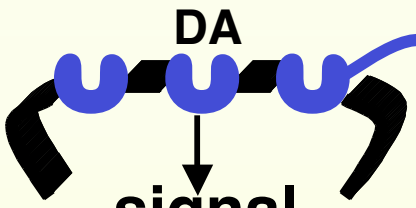


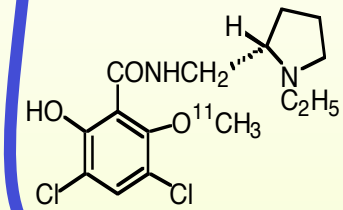
Nicotinic receptors

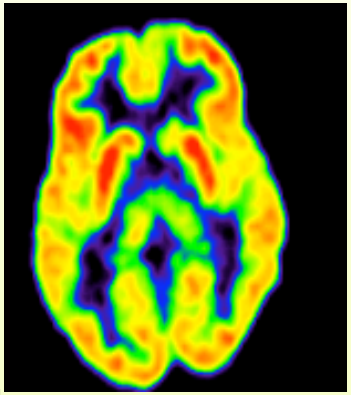
MAO B

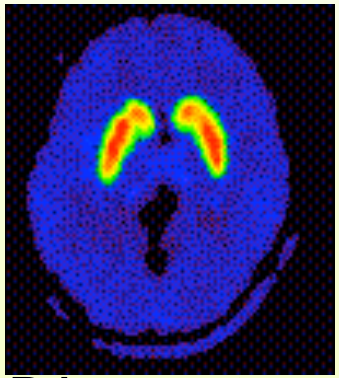




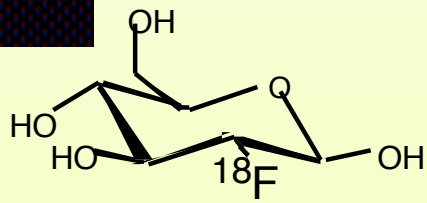




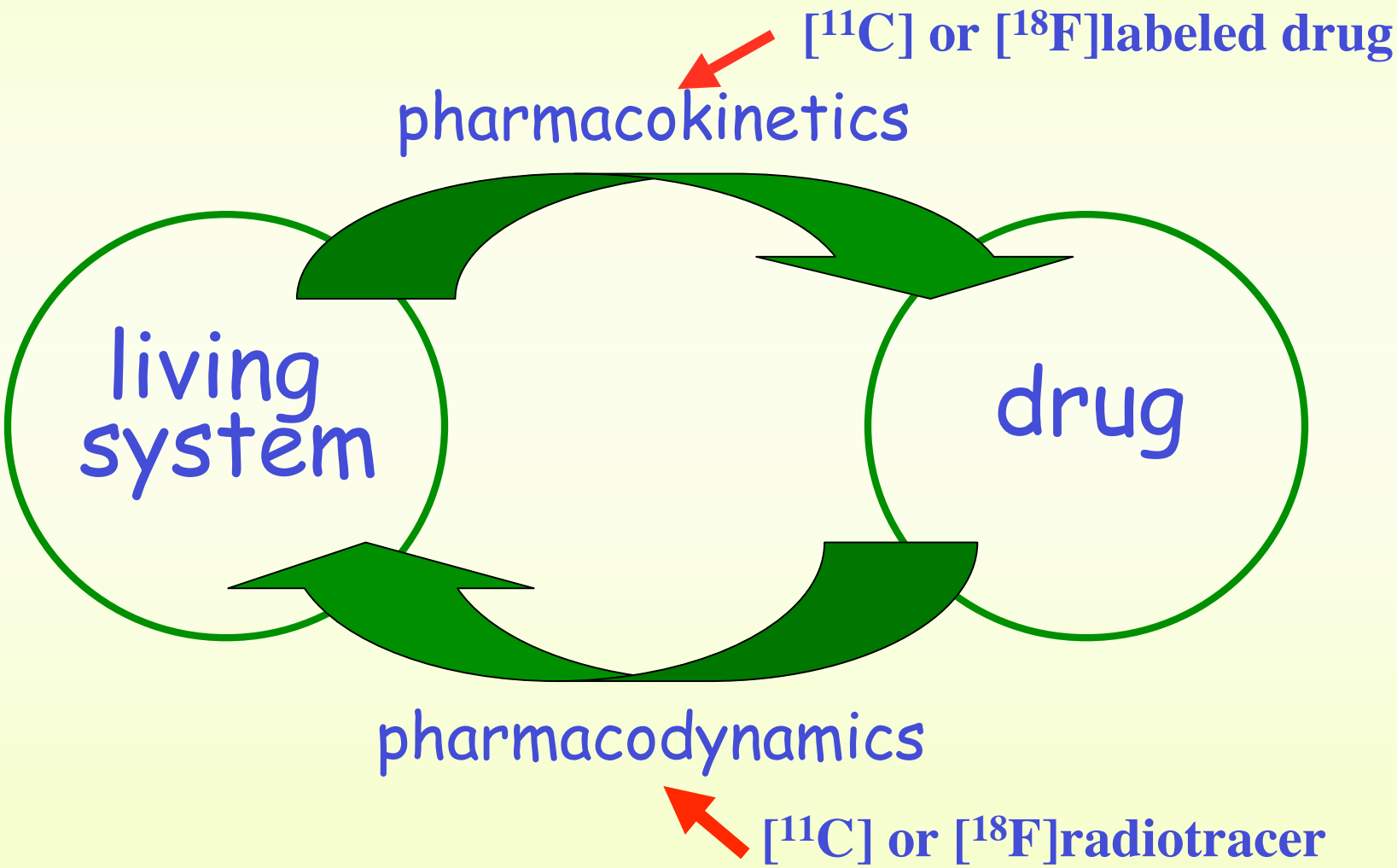




DA receptors



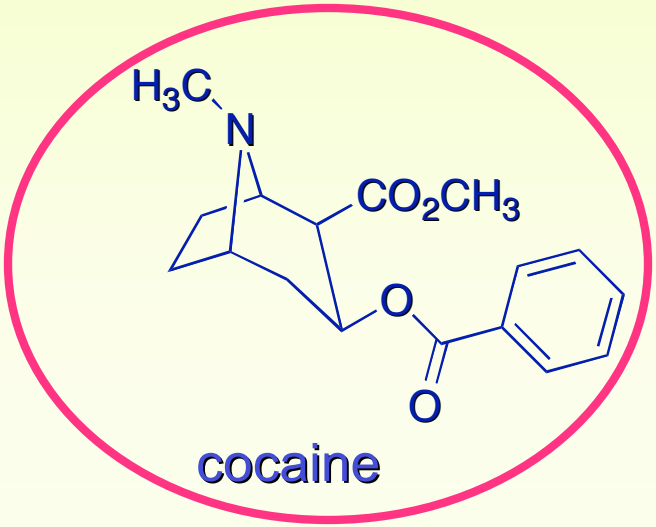
Imaging Drug Action with PET



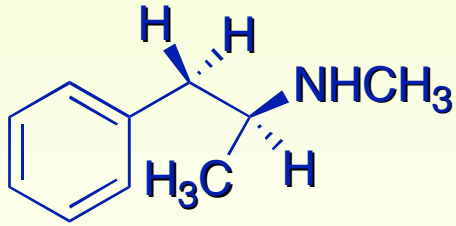
Addiction

Cocaine

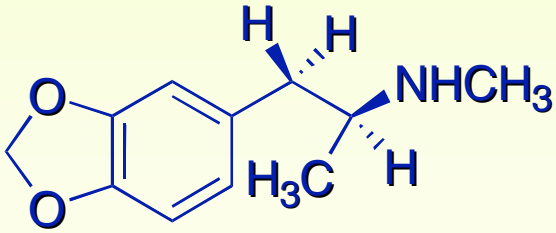
Psychostimulant Drugs



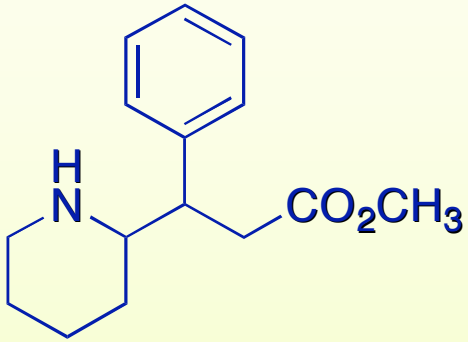
cocaine



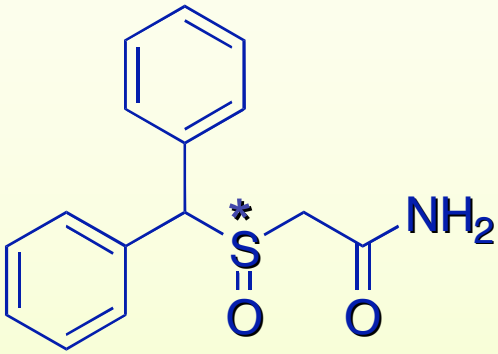
d-methamphetamine



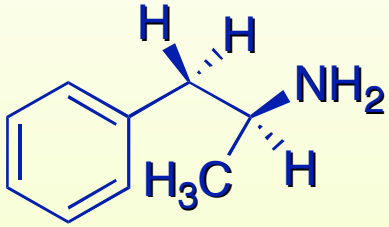
MDMA



methylphenidate

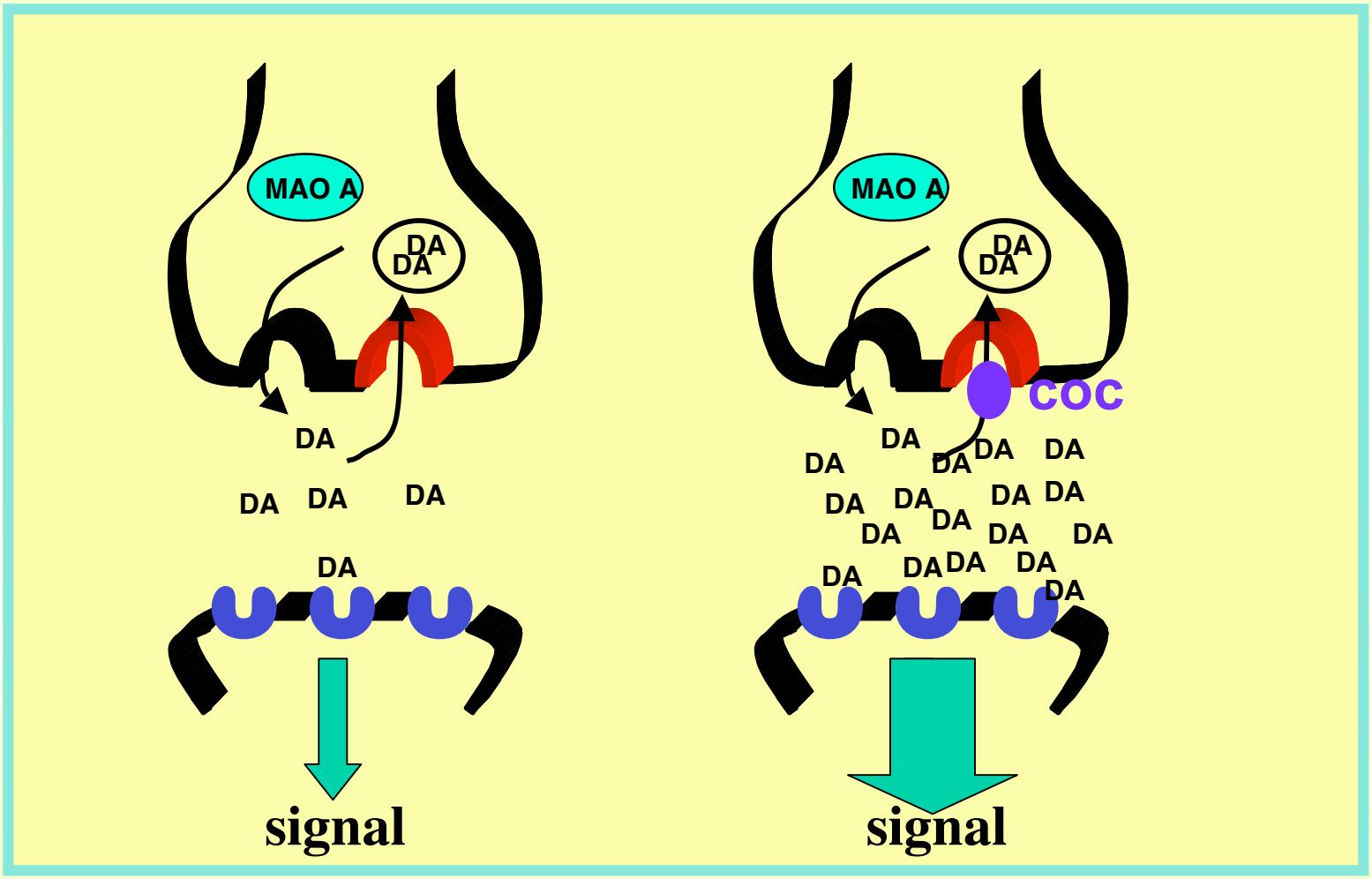


modafinil



amphetamine

Cocaine and Methylphenidate (COC) blocks the Dopamine Transporter



Does the distribution and kinetics and DAT occupancy by cocaine account for its intense behavioral effects?

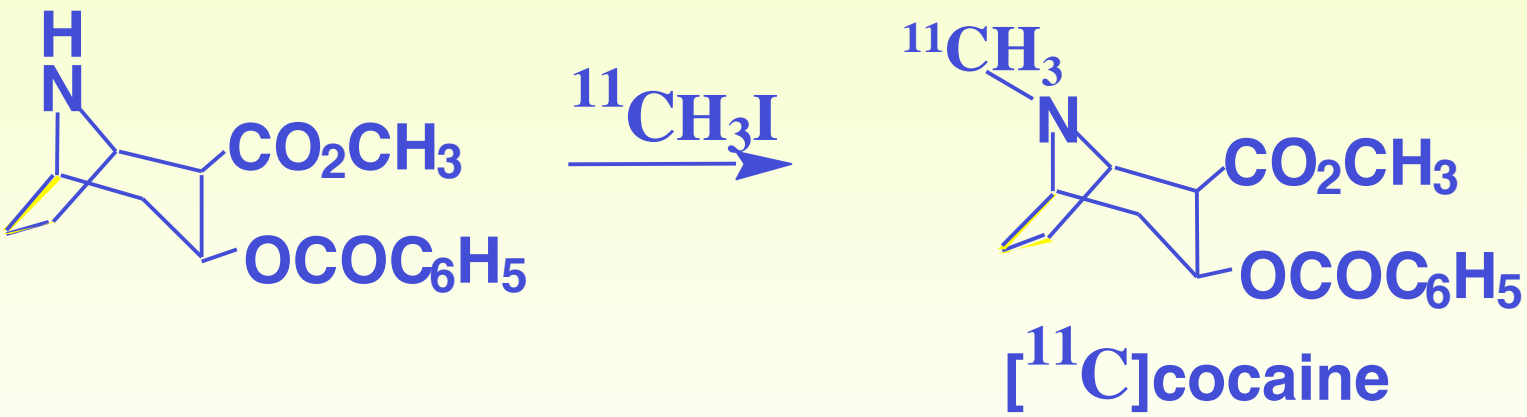
Synthesis of [^{11}C]Cocaine

a

$^{14}N(p,\alpha)^{11}C$

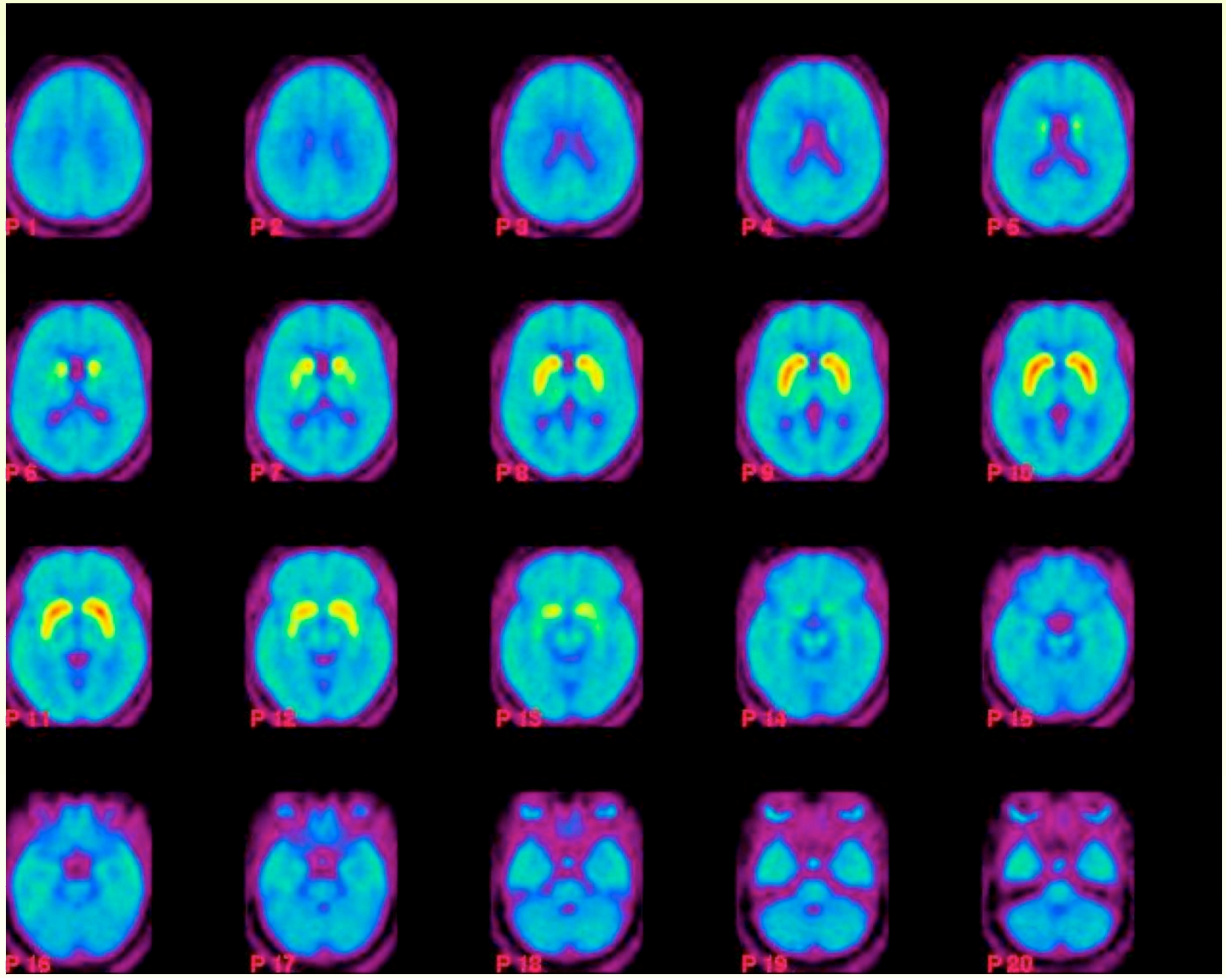
^{11}C is produced as $^{11}CO_2$

$$^{11}CO_2 \longrightarrow {}^{11}CH_3I$$



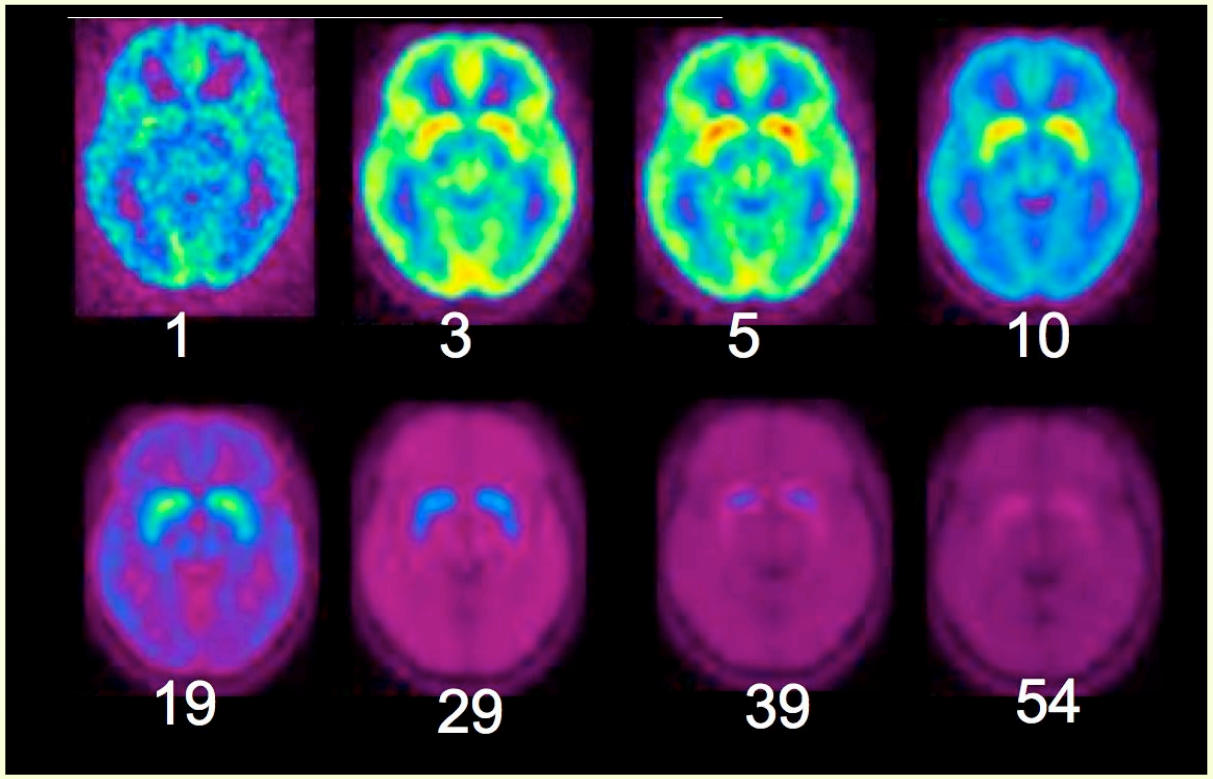
synthesis time: 35 min; < 10 μg

[^{11}C]Cocaine Distribution in Human Brain



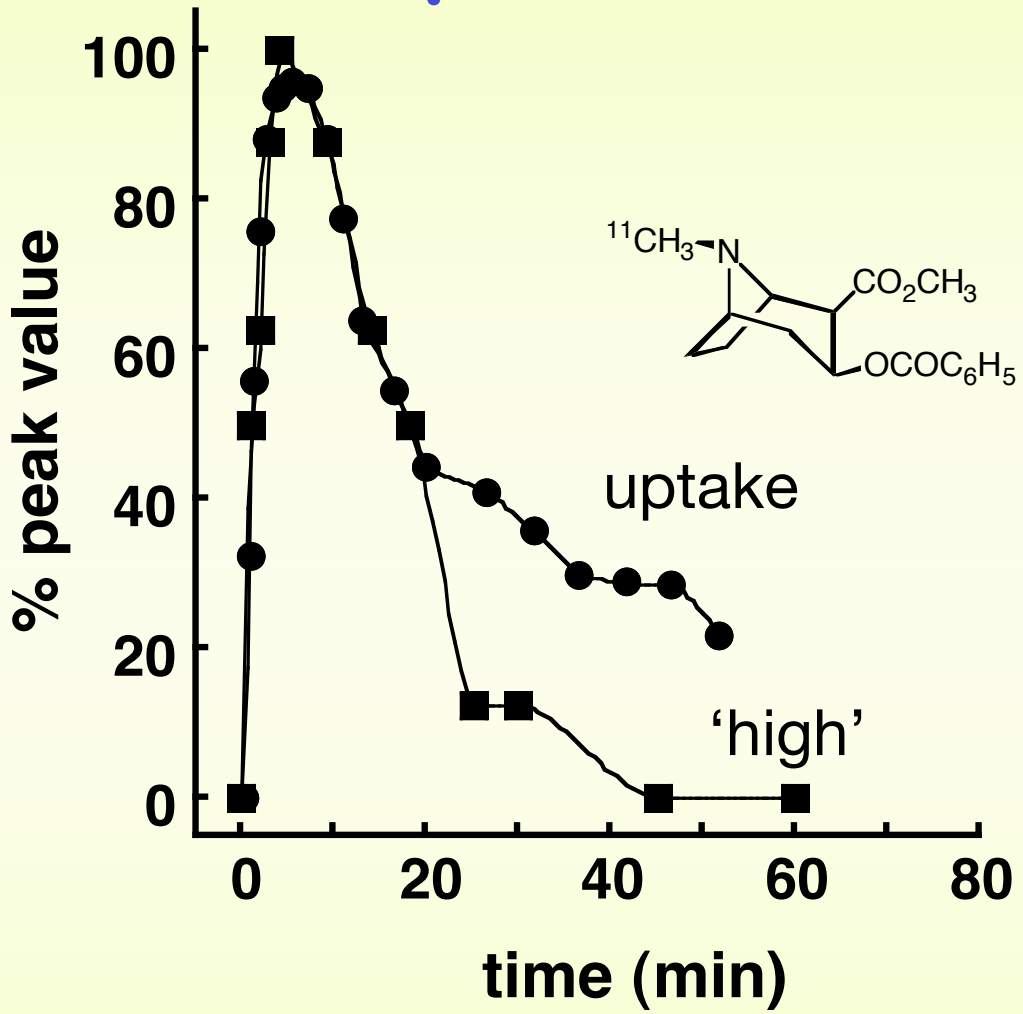
Cocaine concentrates in the basal ganglia which contains the nucleus accumbens (reward center).

Time Course of Cocaine in the Human Brain (iv)



Cocaine's uptake and clearance are rapid

Rate of Uptake vs. "High"

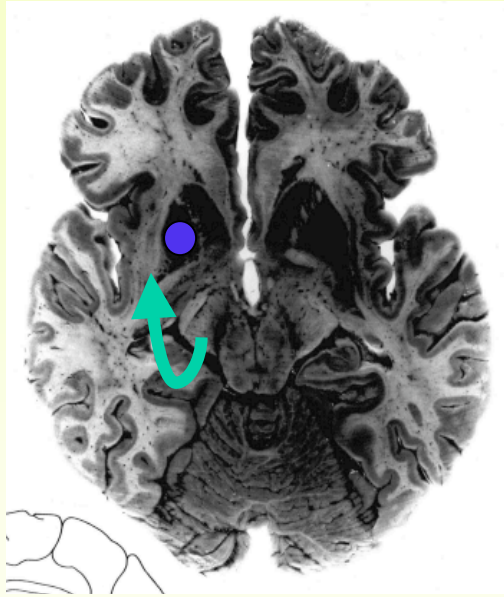


Rapid uptake and clearance are consistent with the highly addictive properties of cocaine and its self-administration in a bingeing pattern.

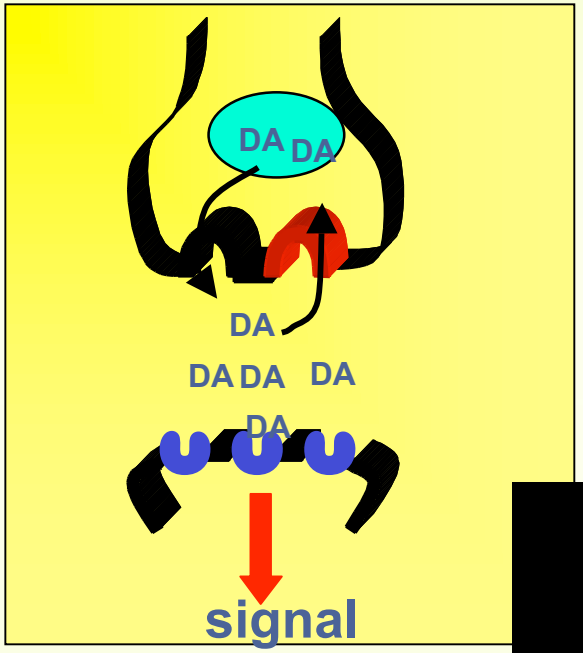
Volkow, Wang et al., 2000

Routes of Administration

- How fast a drug gets to the brain plays a key role in whether it is reinforcing.
- Smoking and iv injection are the most rapid ways to get drugs to the brain.
- Abuse liability is an important issue in the development of therapeutic drugs.

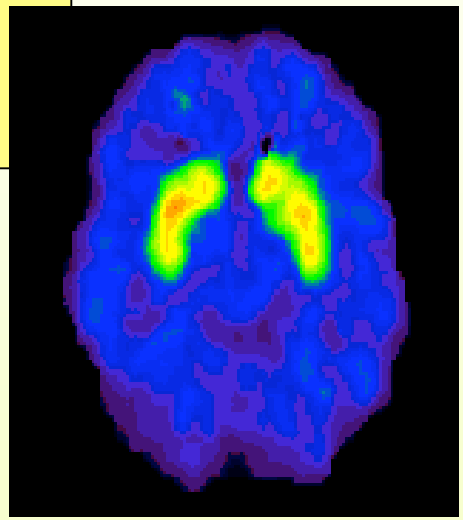


Anatomy



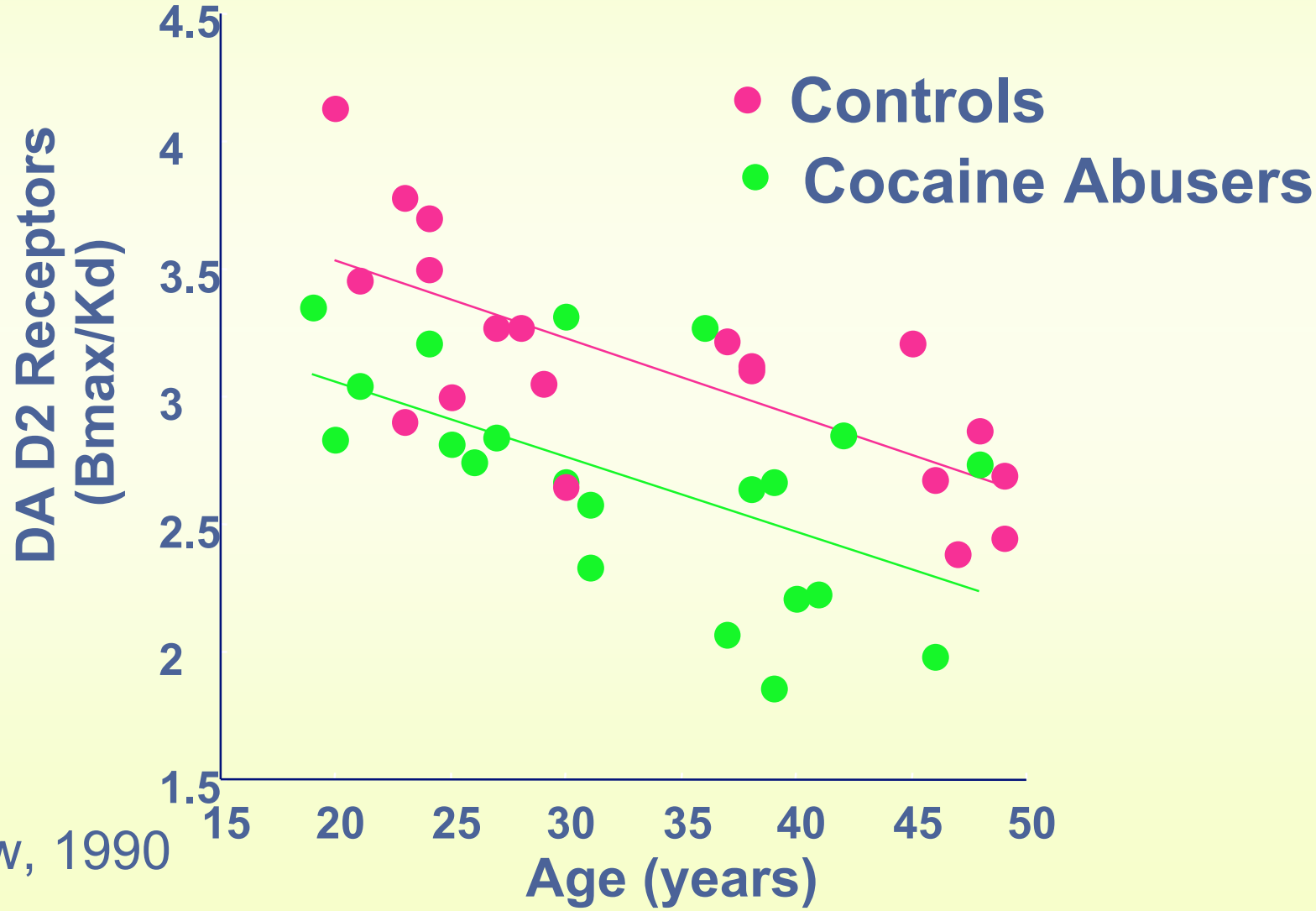
DA Synapse

What is the Role of Dopamine in Drug Addiction?



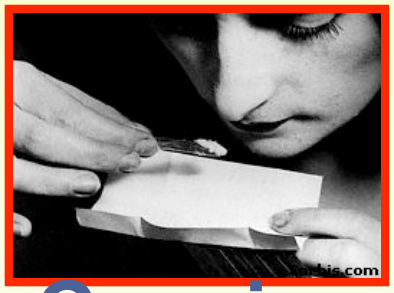
DA D2 Receptors

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



Volkow, 1990

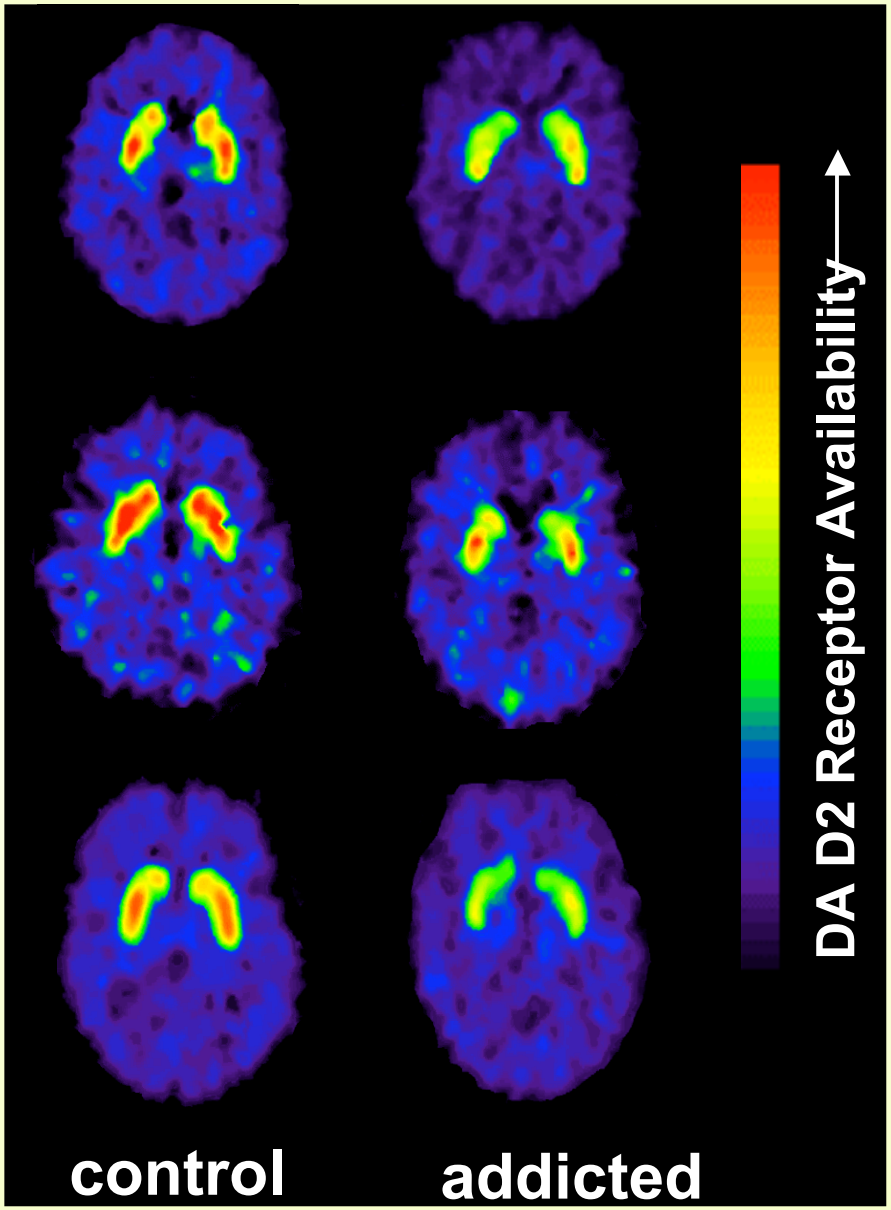
Dopamine D2 Receptors are Lower in Addiction



Cocaine

Alcohol

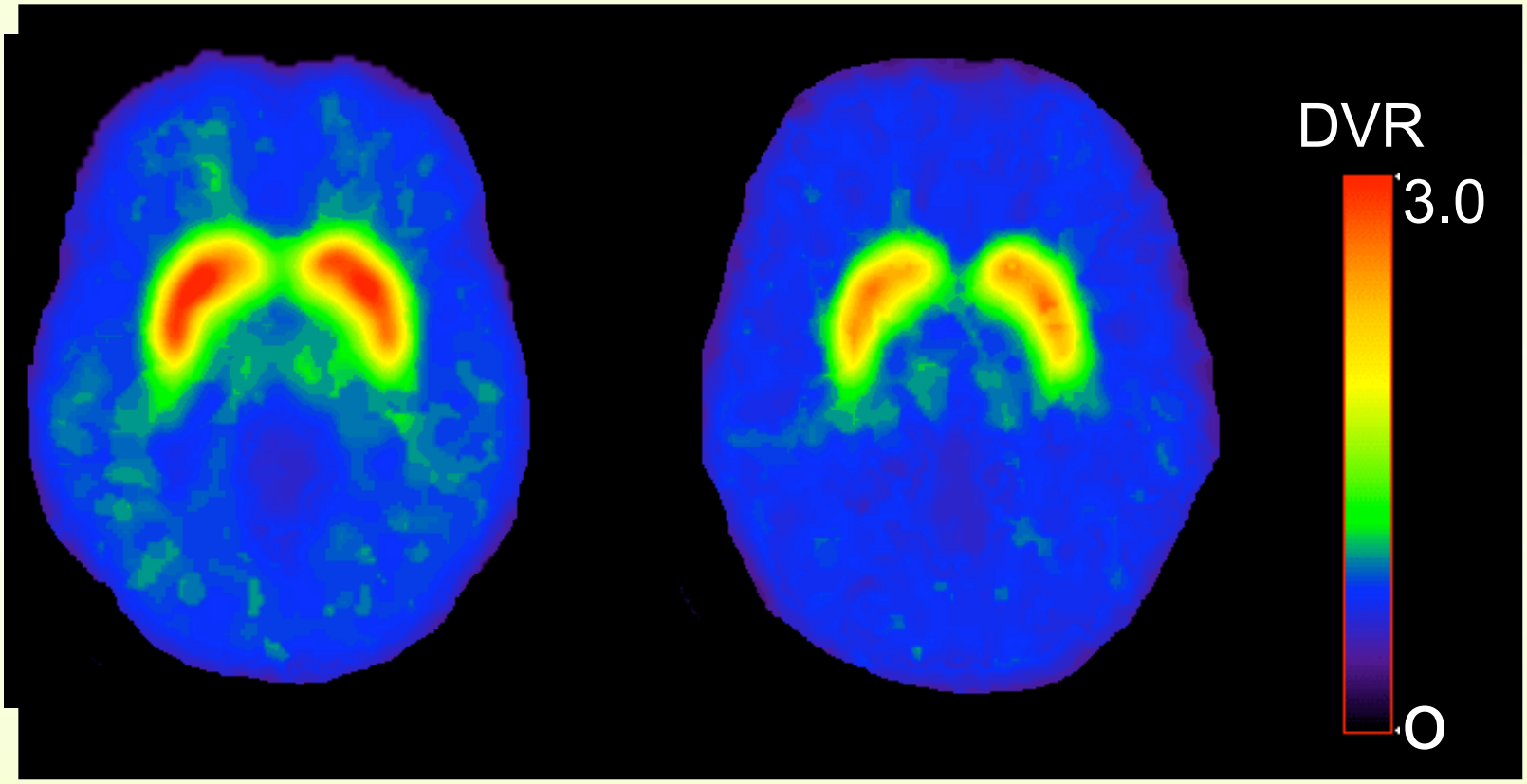
Heroin



Obesity

- Compulsive overeating shares many of the same characteristics as drug addiction
- Drugs that block dopamine cause weight gain and those that raise dopamine are anorexigenic
- Do obese subjects have abnormal dopamine receptors?

Dopamine Receptor Levels are Low in Obese Subjects



Comparison Subject

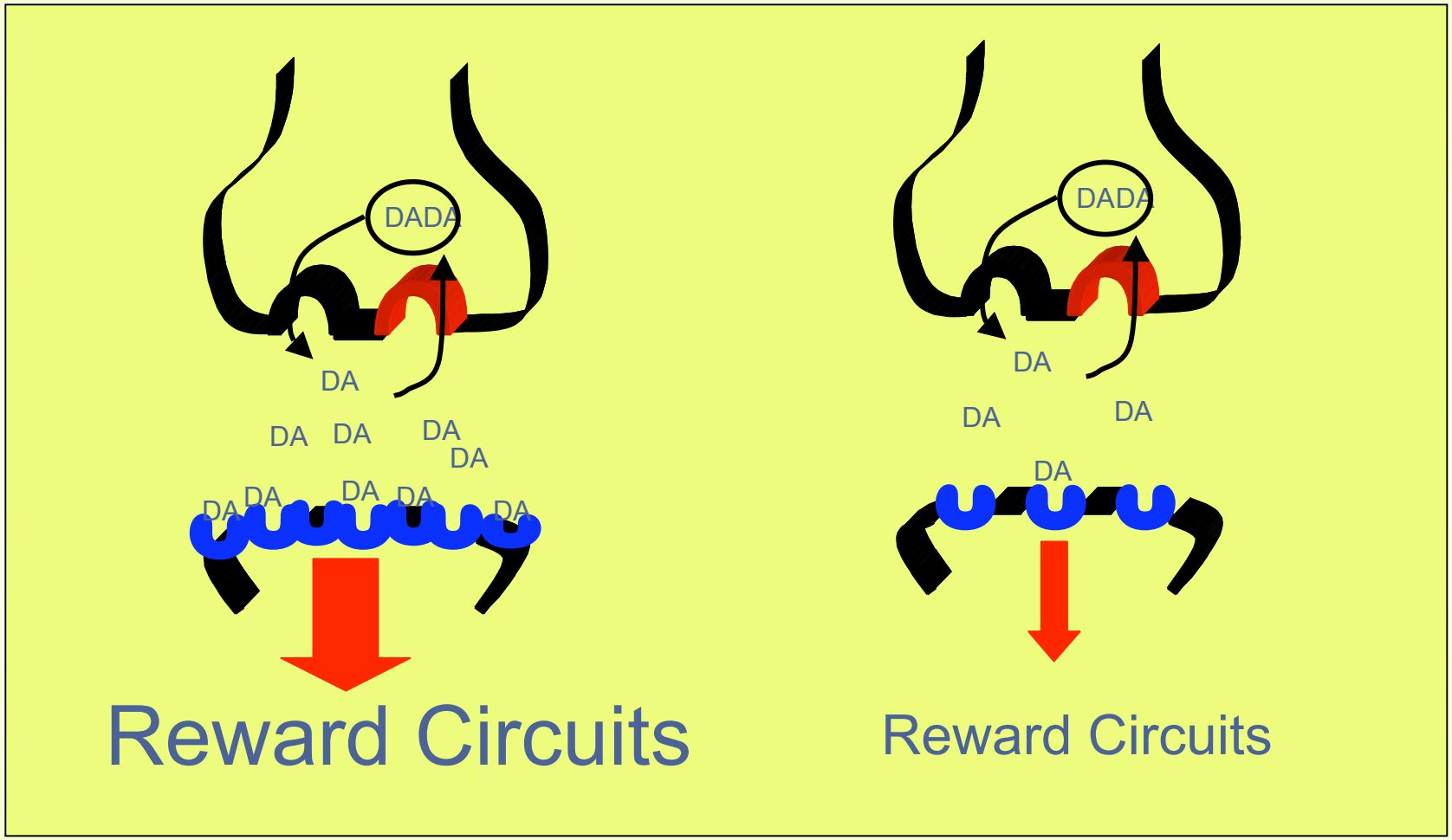
BMI: 23

Obese Subject

BMI: 50

Wang et al., 2000

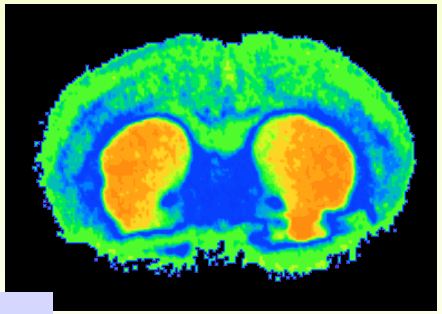
Low Reward Stimulation

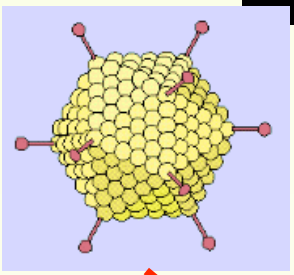


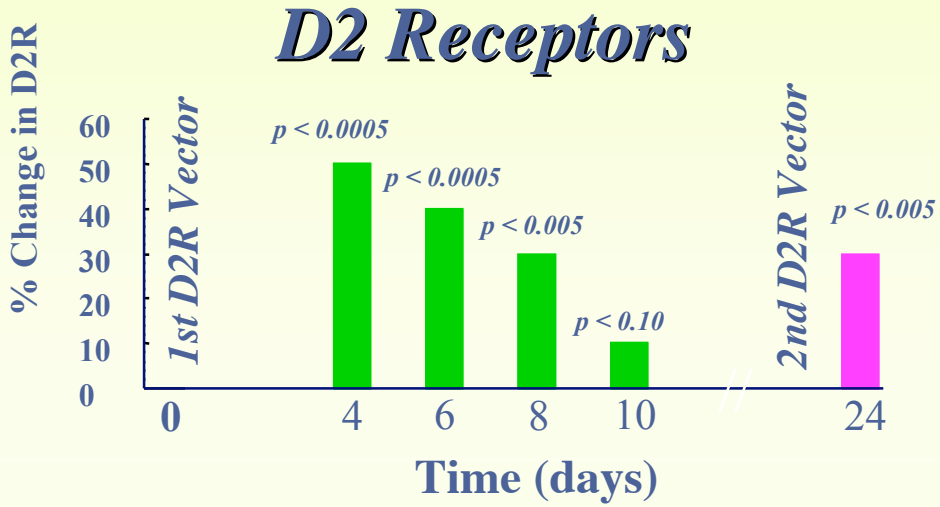
Control *Addicted Subject*

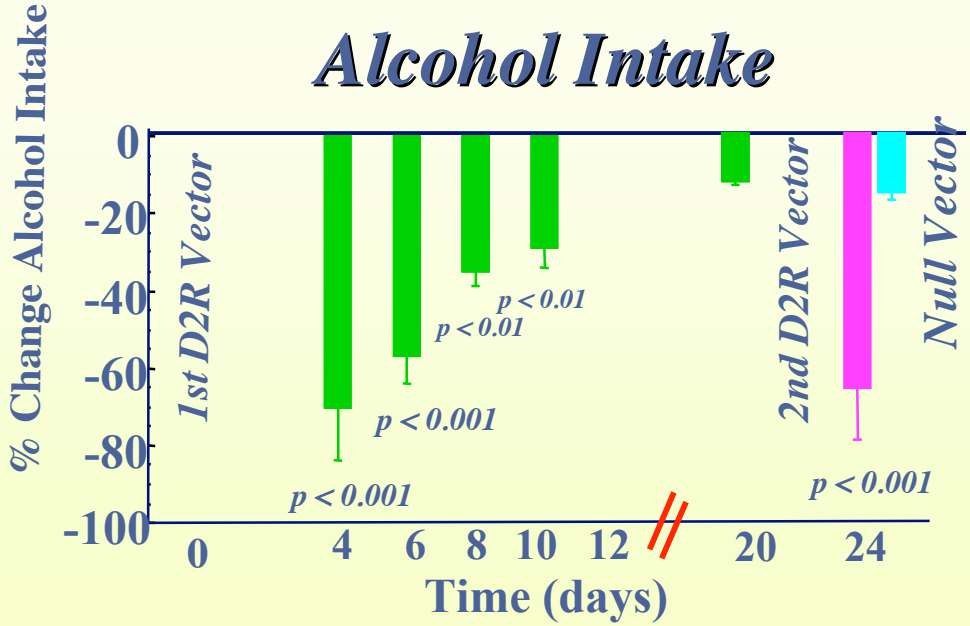
Can increasing dopamine D2 receptors change addictive behavior?

Effects of Increasing Brain DA D2 Receptors in Alcohol Drinking Behavior (Thanos e al., 2001)

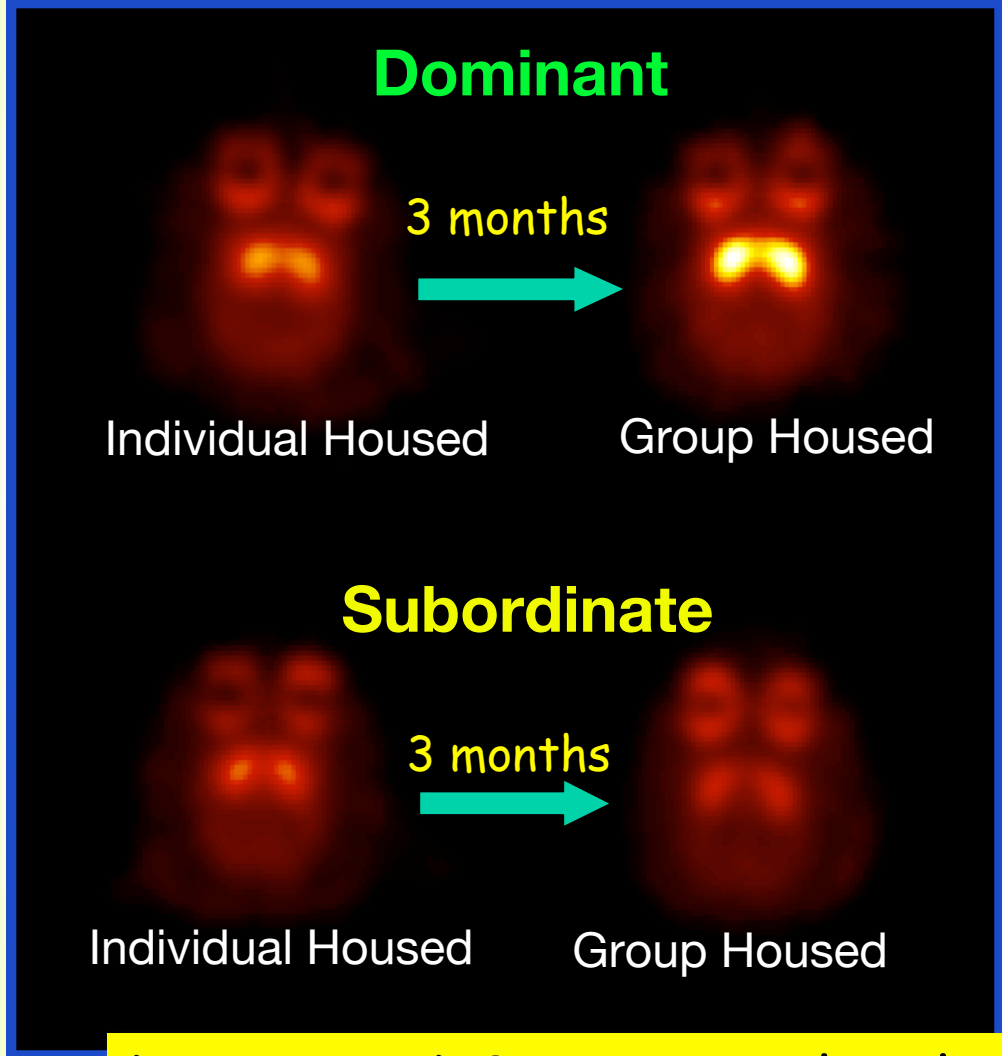


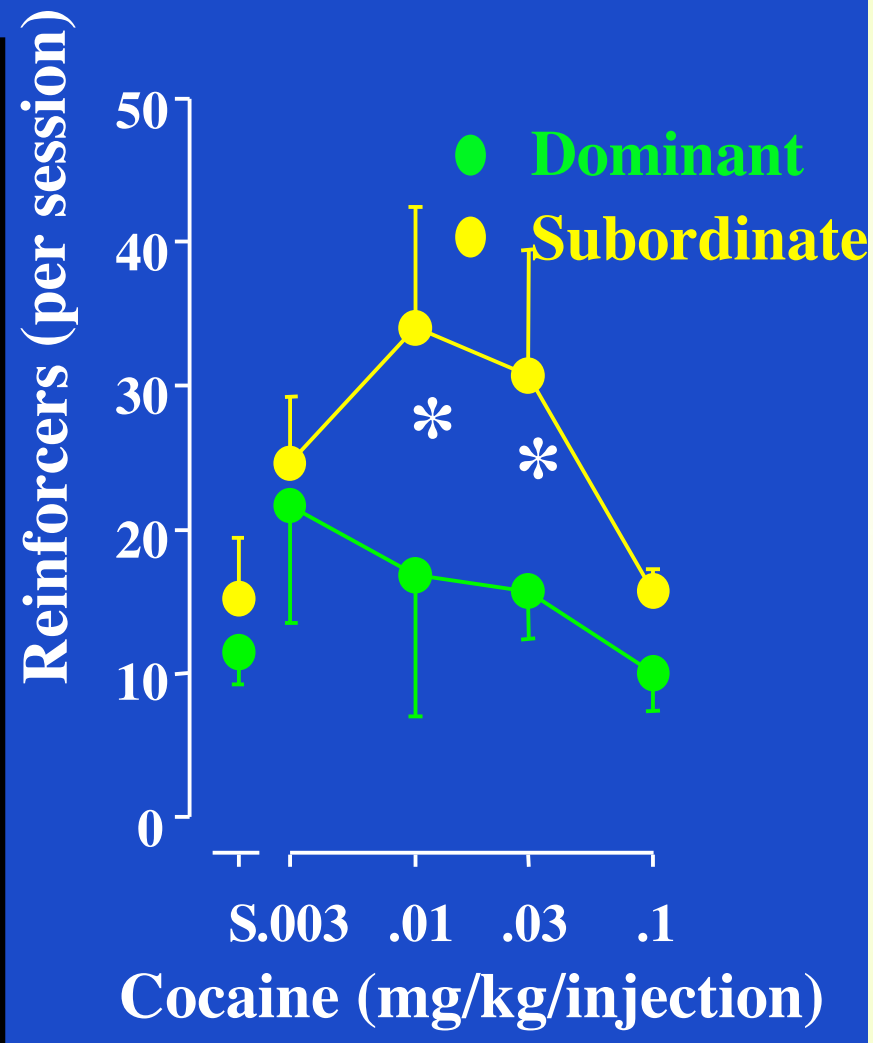






Social Rank and Vulnerability to Drug Abuse



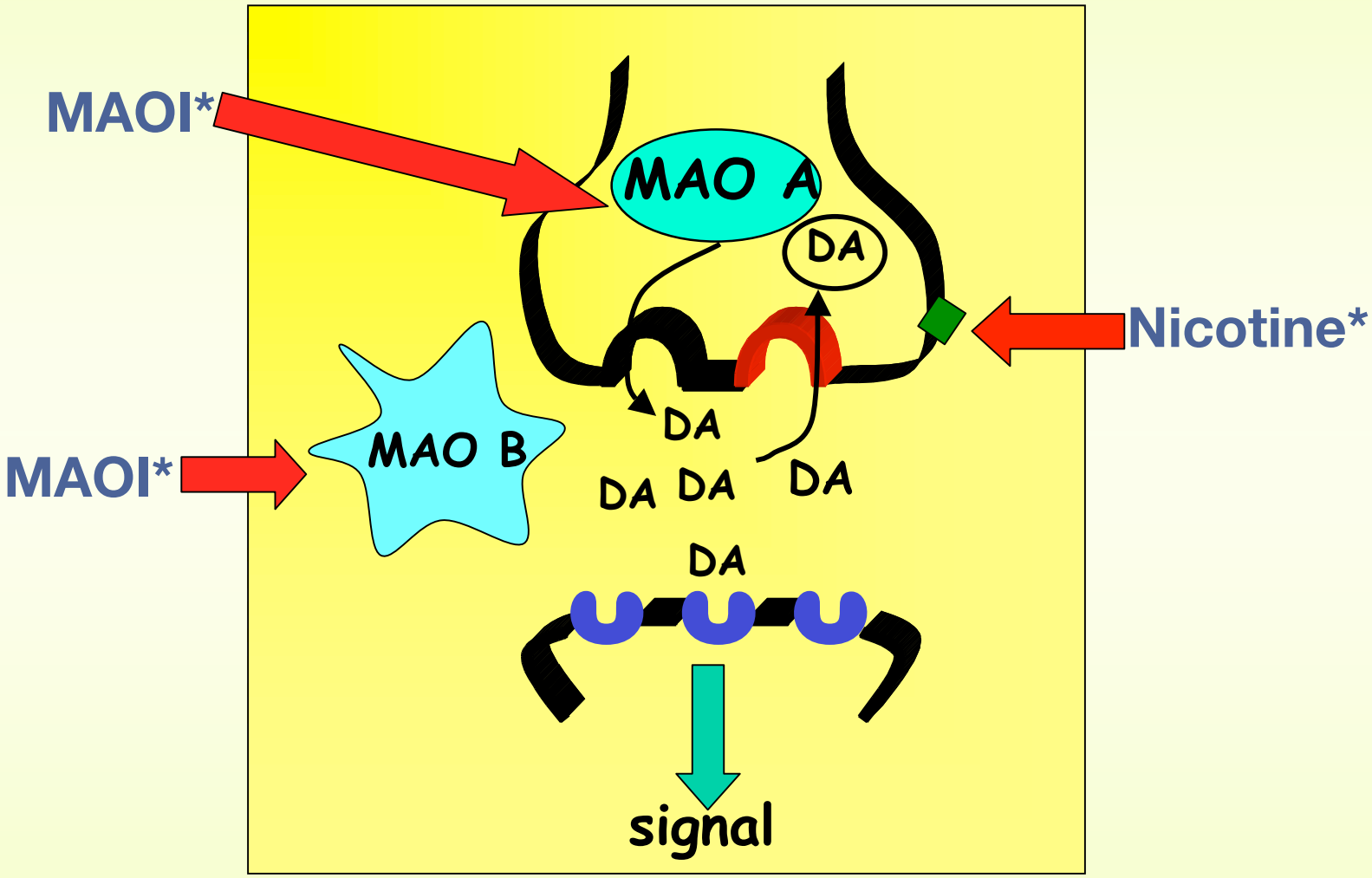


Dopamine D2 receptor level can change within the time frame of normal social activities (Morgan et al., 2002)

Addiction

Tobacco Smoke

Sites of Action for Tobacco Smoke



*components of tobacco smoke

Monoamine Oxidase

$$RCH_2NH_2 + O_2 + H_2O \xrightarrow{MAO} RCHO + NH_3 + H_2O_2$$

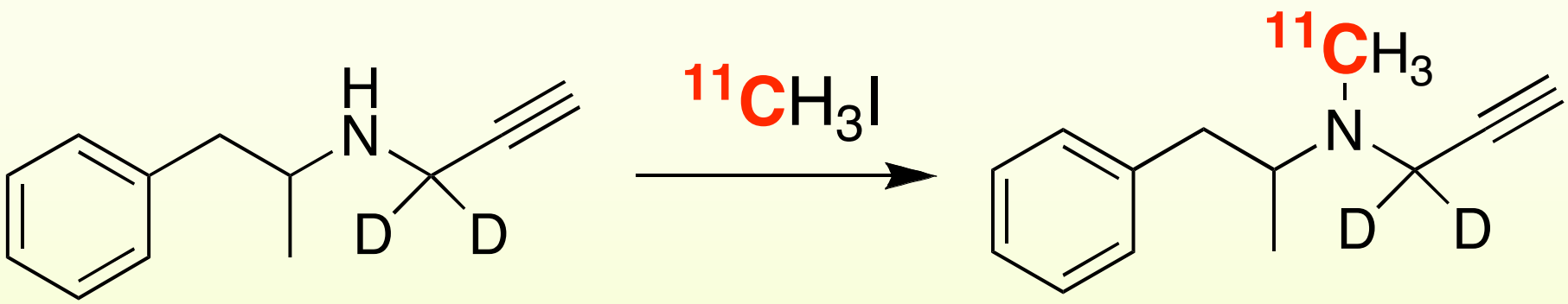
- Oxidizes neurotransmitters
- Produces hydrogen peroxide
- Two subtypes: MAO A (NE, 5HT, DA) and MAO B (PEA, DA)

MAO inhibitor drugs are used to treat depression and Parkinson's disease.

Rapid Organic Synthesis

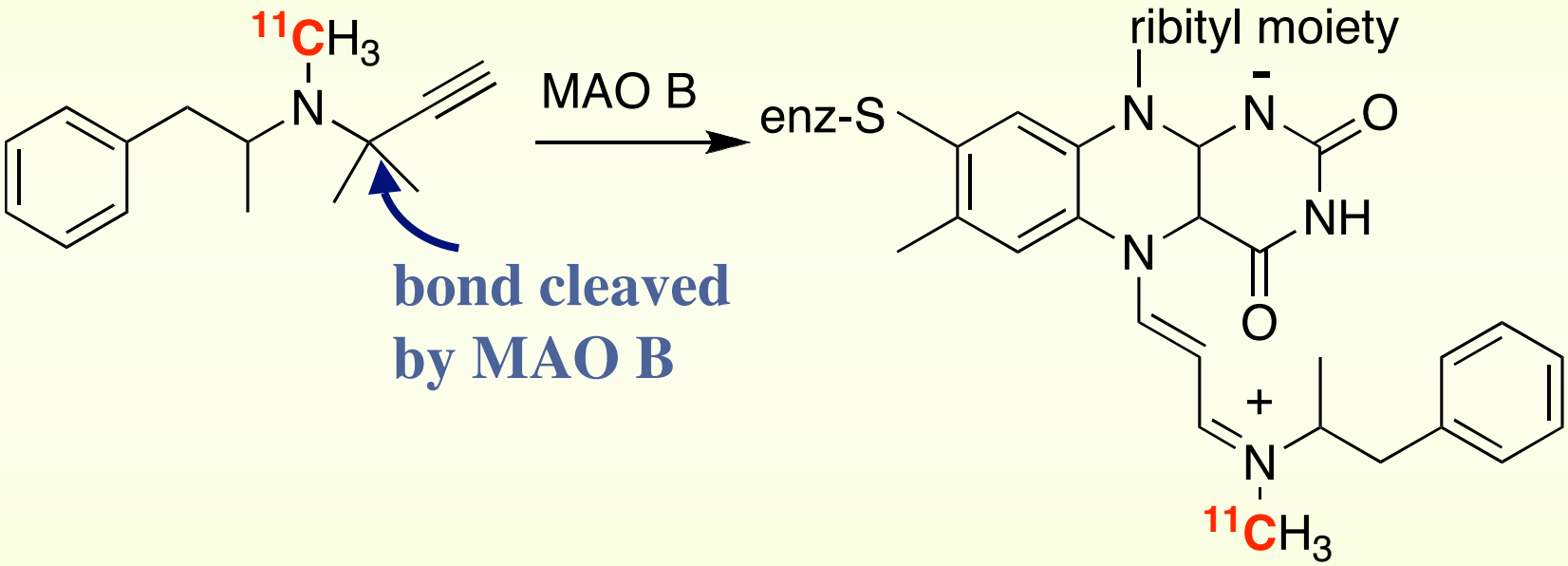
$^{14}N\ (p,\alpha)\ ^{11}C$ (as $^{11}CO_2$)

$$^{11}CO_2 \longrightarrow {}^{11}CH_4 \longrightarrow {}^{11}CH_3I$$



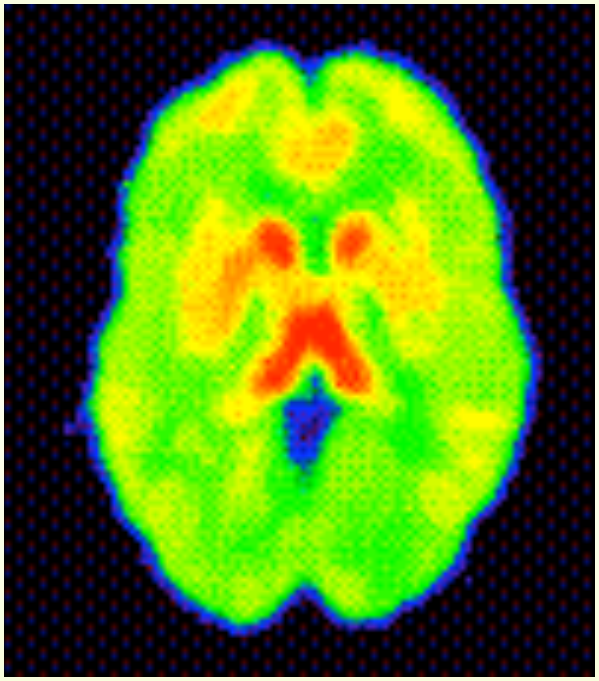
synthesis time: 35 minutes
yield: 5 micrograms

Labeling MAO B *in vivo*



[^{11}C]MAO B

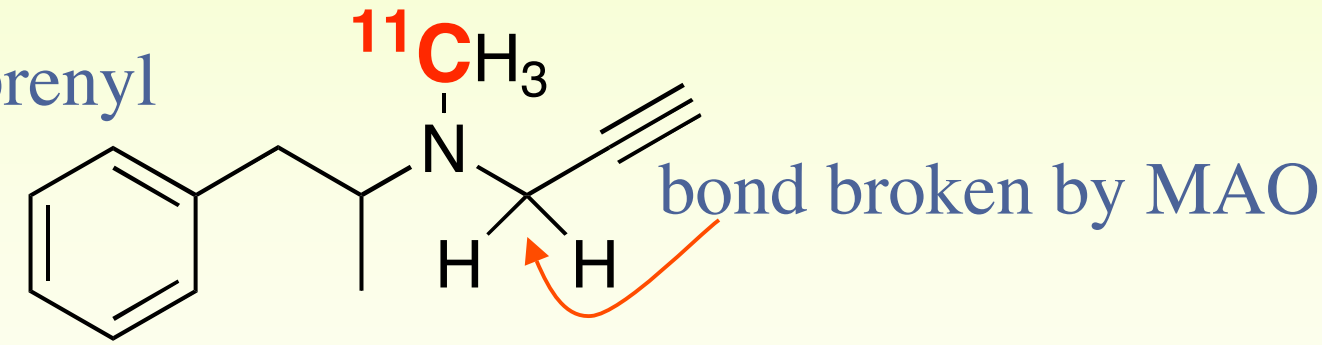
PET Image of [^{11}C]L-Deprenyl in human brain



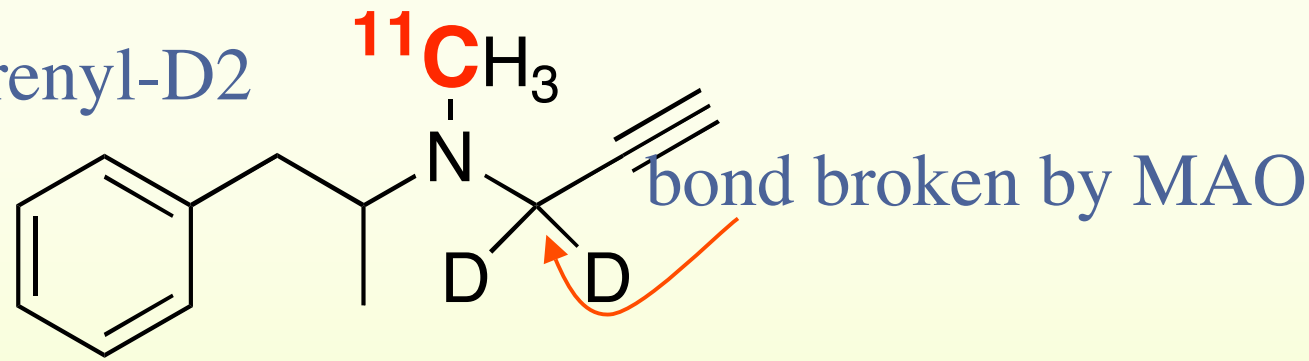
Does the image represent MAO?

MECHANISMS: Deuterium Substitution

[^{11}C]L-Deprenyl

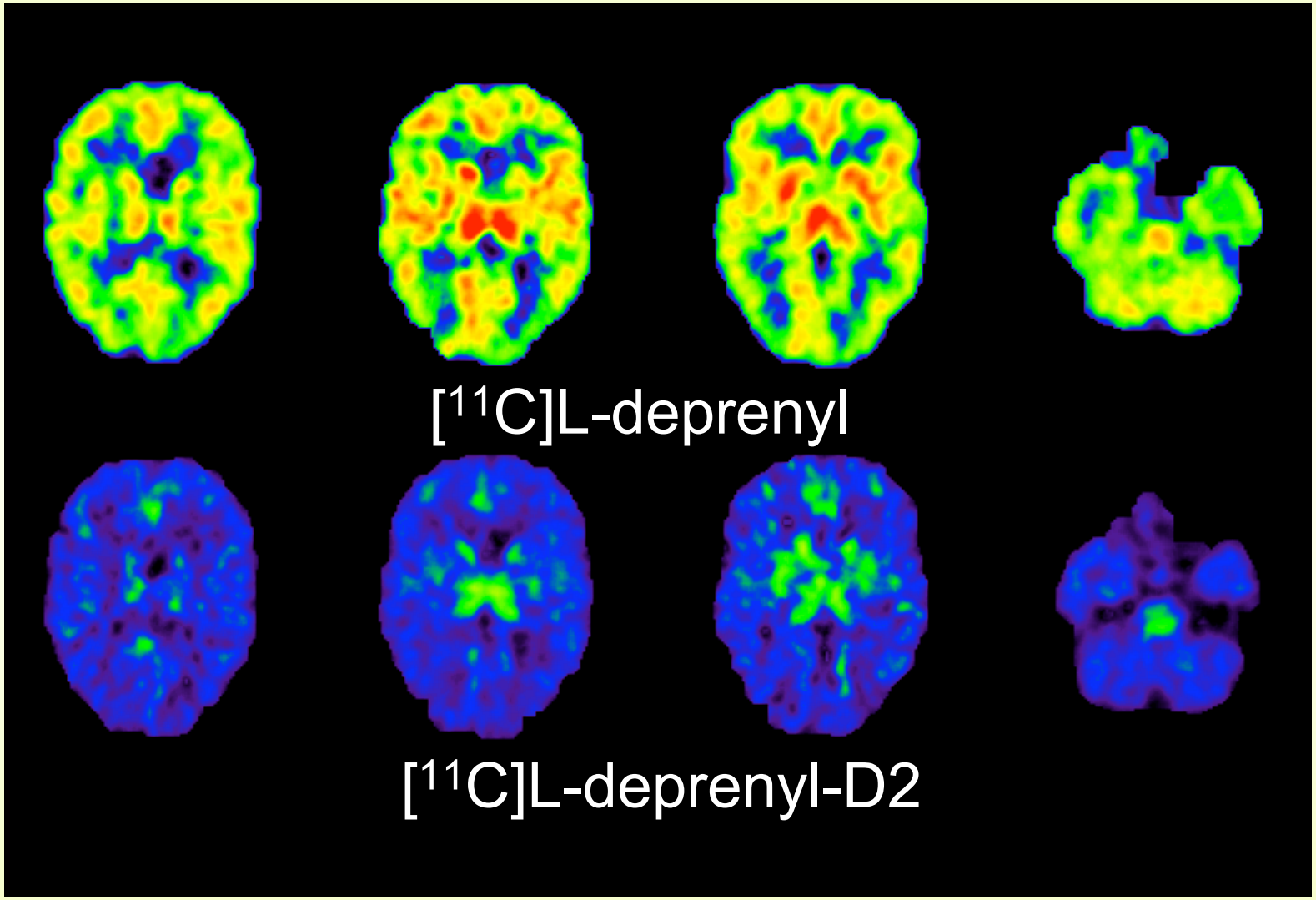


[^{11}C]L-Deprenyl-D2



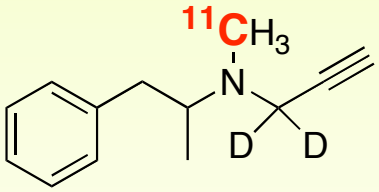
A C-D bond is more difficult to cleave than a C-H bond. Deuterium substitution reduces the rate of trapping and improves radiotracer sensitivity

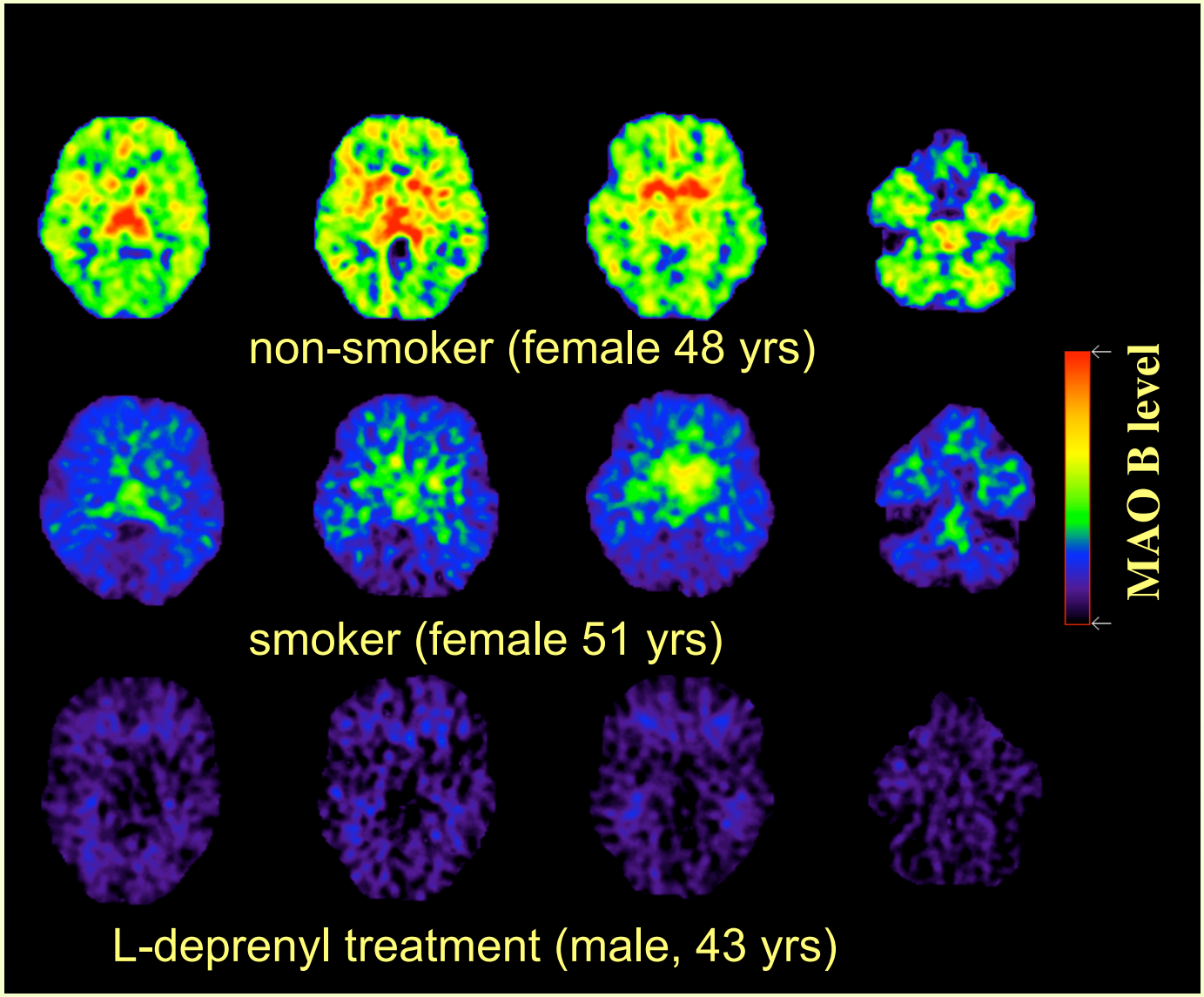
Deuterium Isotope Effects



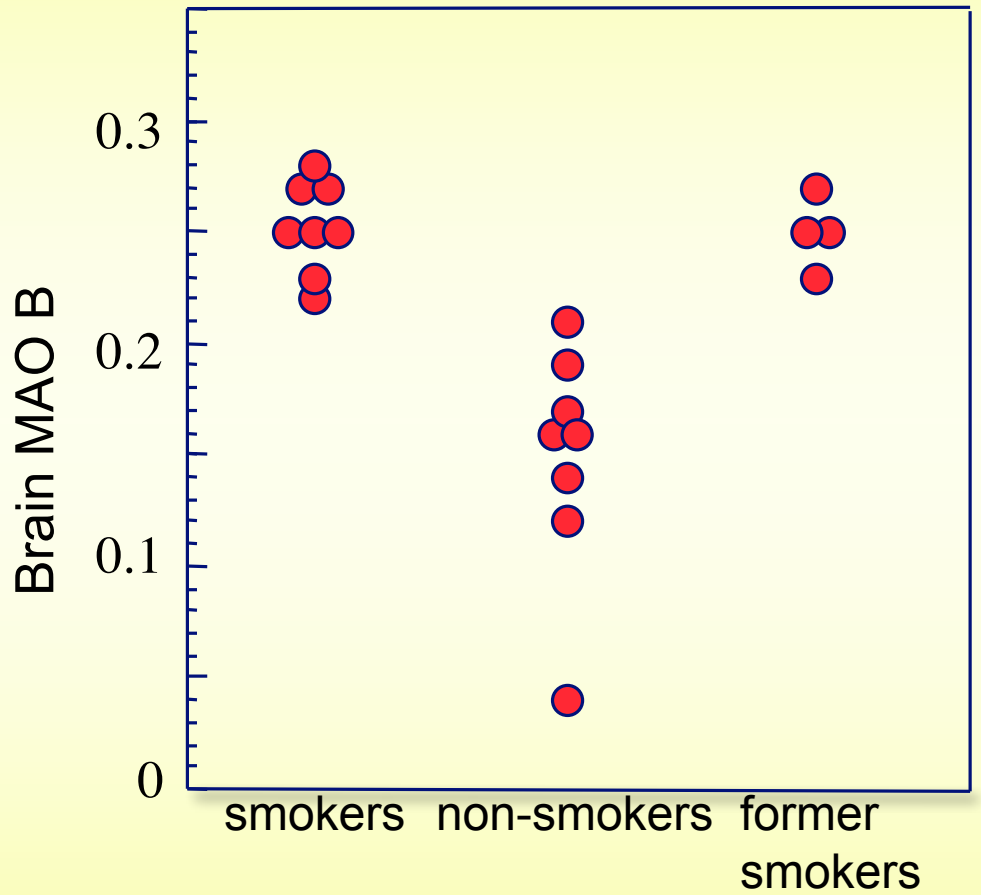
Fowler et al., 1995

Smoking inhibits MAO B in the human brain





Former Smokers Have Normal MAO B Levels



Low brain MAO in smokers is caused by the tobacco smoke and not by biology or genetics

Does MAO inhibition by smoke contribute to the behavioral and epidemiological features of smoking?

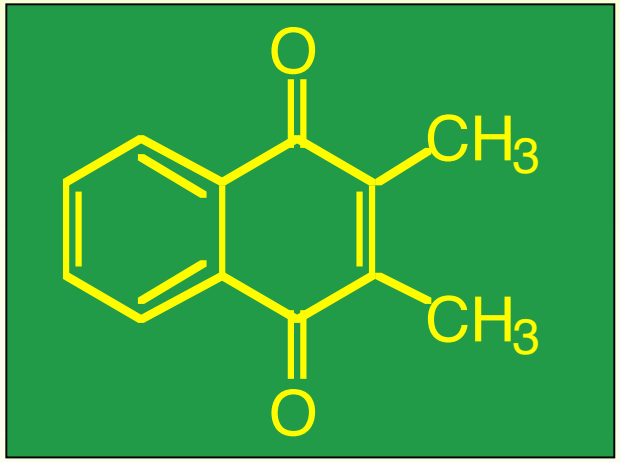
Smoking Epidemiology

Smokers have a *decreased* risk of Parkinson's disease (Morens et al, 1995)

Is tobacco smoke neuroprotective?

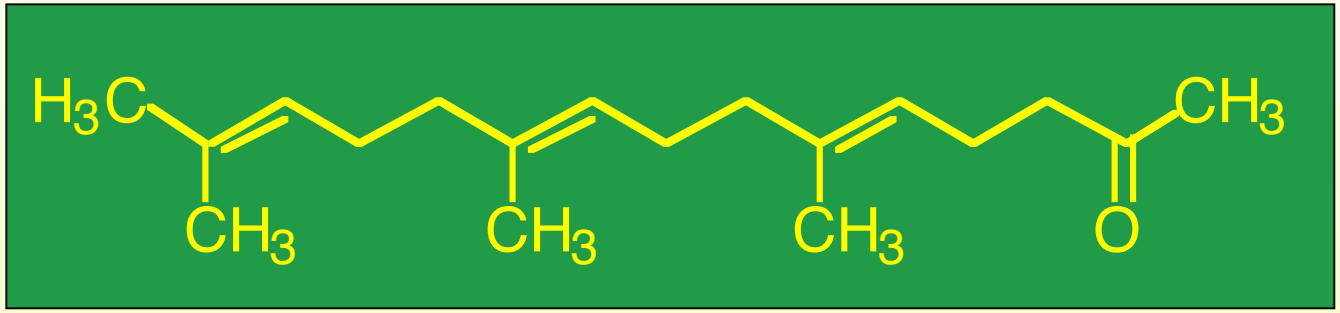
$$RCH_2NH_2 + O_2 + H_2O \xrightarrow{\text{MAO}} RCHO + NH_3 + H_2O_2$$

Isolation of MAO Inhibitors from Tobacco Leaves



2,3,6-trimethyl-1,4-naphthoquinone

(Ki 3-6 μM (human liver, non-selective; protective against MPTP neurotoxicity in mice (Castagnoli et al., 2000, 2001))



Farnesyl acetone

(Ki 0.8 μM (human liver, MAO B selective) (Khalil, Davies and Castagnoli, 2006)

Who is at higher risk for smoking? Co-morbidity with Mental Illness

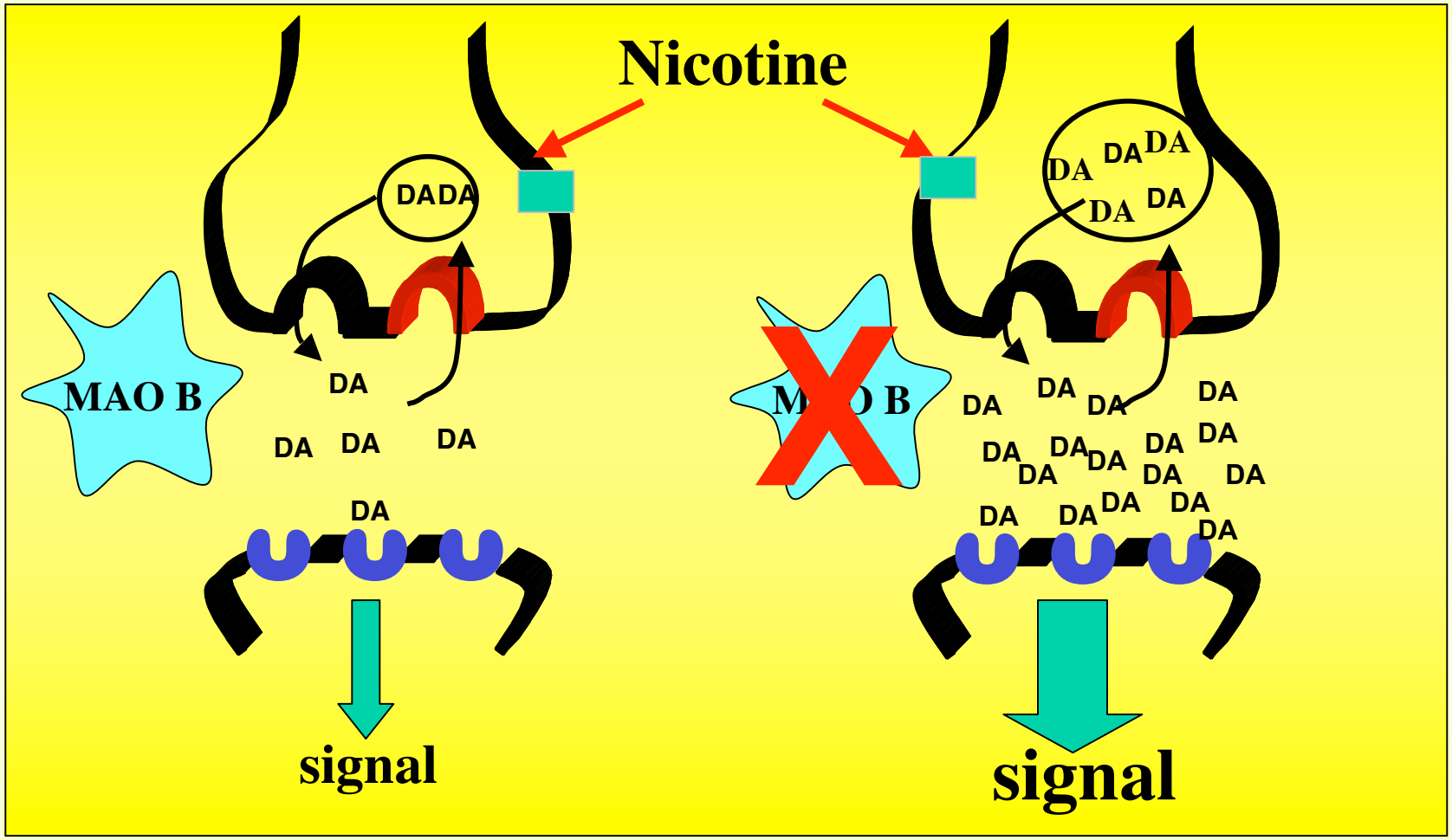
- 44% of all cigarettes consumed in the US are by individuals with a current psychiatric disorder
- $256 Billion spent on cigarettes
- 75% of patients in addiction and mental health treatment programs smoke cigarettes

Smoking Epidemiology

normal population:	23% (US)
	67(4) (China)
	64(44) (Turkey)
alcoholism:	90%+
other addictions:	90%+
schizophrenia:	85%
depression:	80%

Are smokers self-medicating?

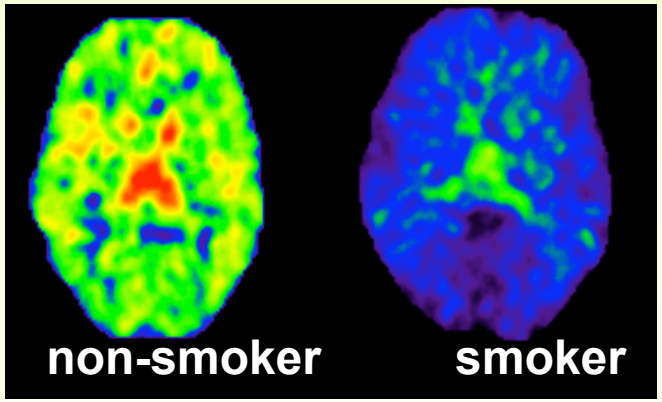
MAO Inhibition by Tobacco Smoke



Non Smoker

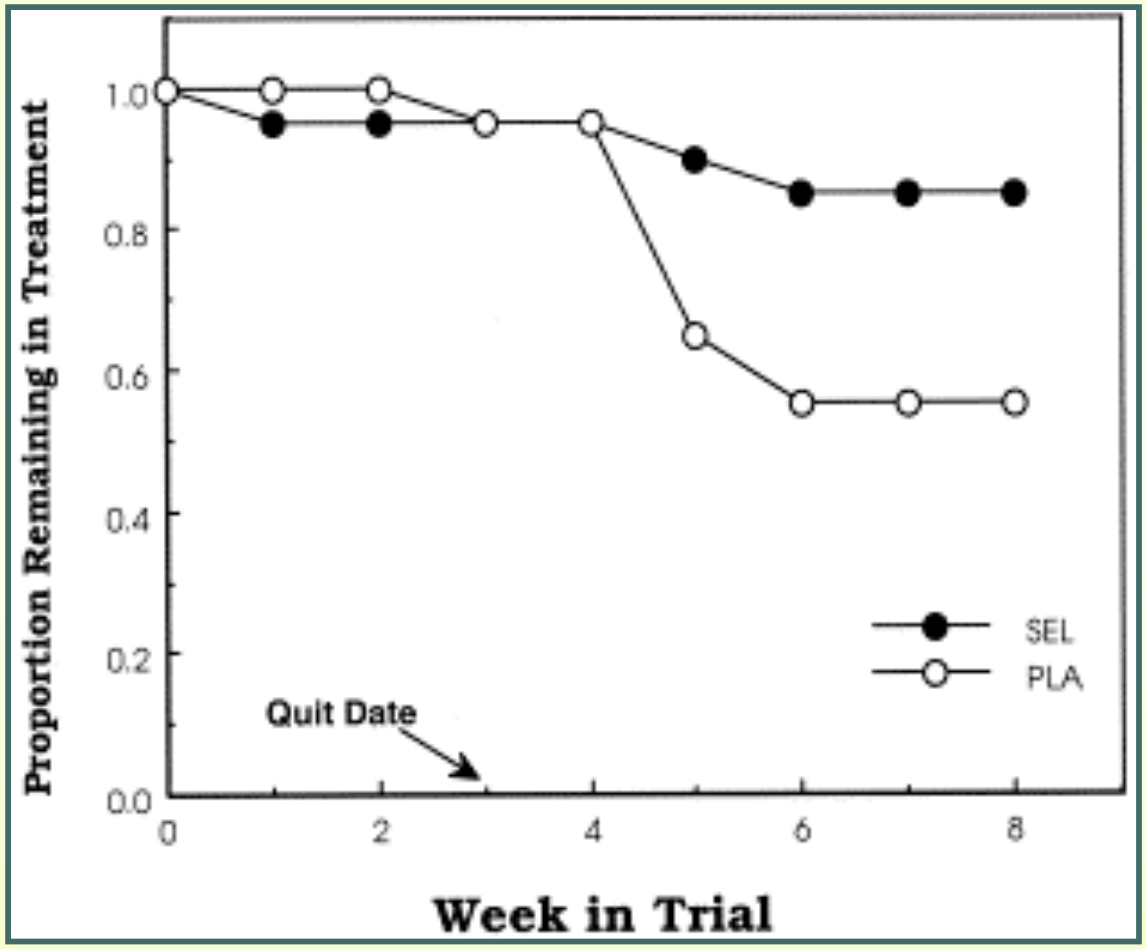
Smoker

MAO B Inhibition to Treat Smoking Addiction



Could MAO B inhibition account for some of the psychoactive properties of tobacco?

Can MAO B inhibition help the smoker who wants to quit?



George et al., Biological Psychiatry 53: 136-143, 2003

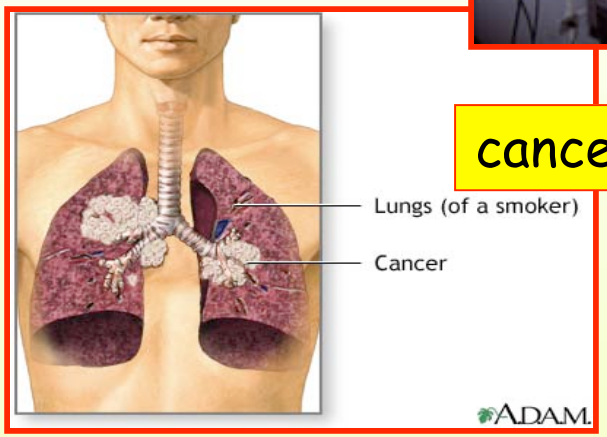
Addiction and Public Health

heart disease

accidents

AIDS

obesity



cancer

violence

PET and Drug Development

In vivo efficacy at target

Degree of occupancy/inhibtion

Duration of drug action

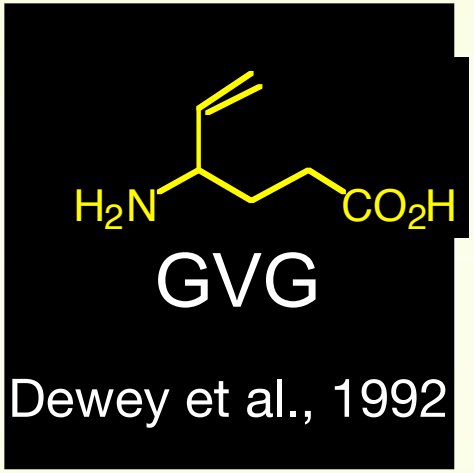
Minimum effective dose

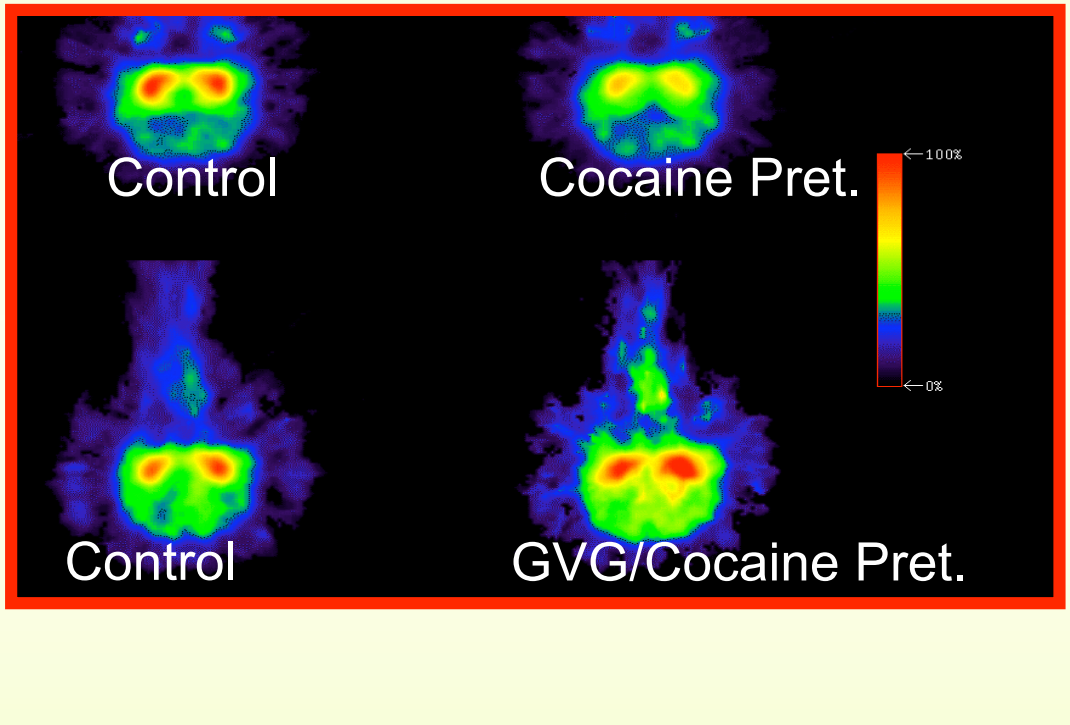
Drug pharmacokinetics

Pharmacological profile and toxicity

This knowledge facilitates the introduction of new drugs into the practice of medicine

Addiction Treatment





First successful clinical trials in cocaine and METH abusers (Dewey, Brodie et al., 2004, 2005, 2007).

Brookhaven Center for Translational Neuroimaging

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