Dopamine Imaging in Addiction

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The brain and its transmitter systems

•125 billion neurons (brain cells)
•Every single neuron communicates with approx 10.000 other neurons

Main transmitter systems

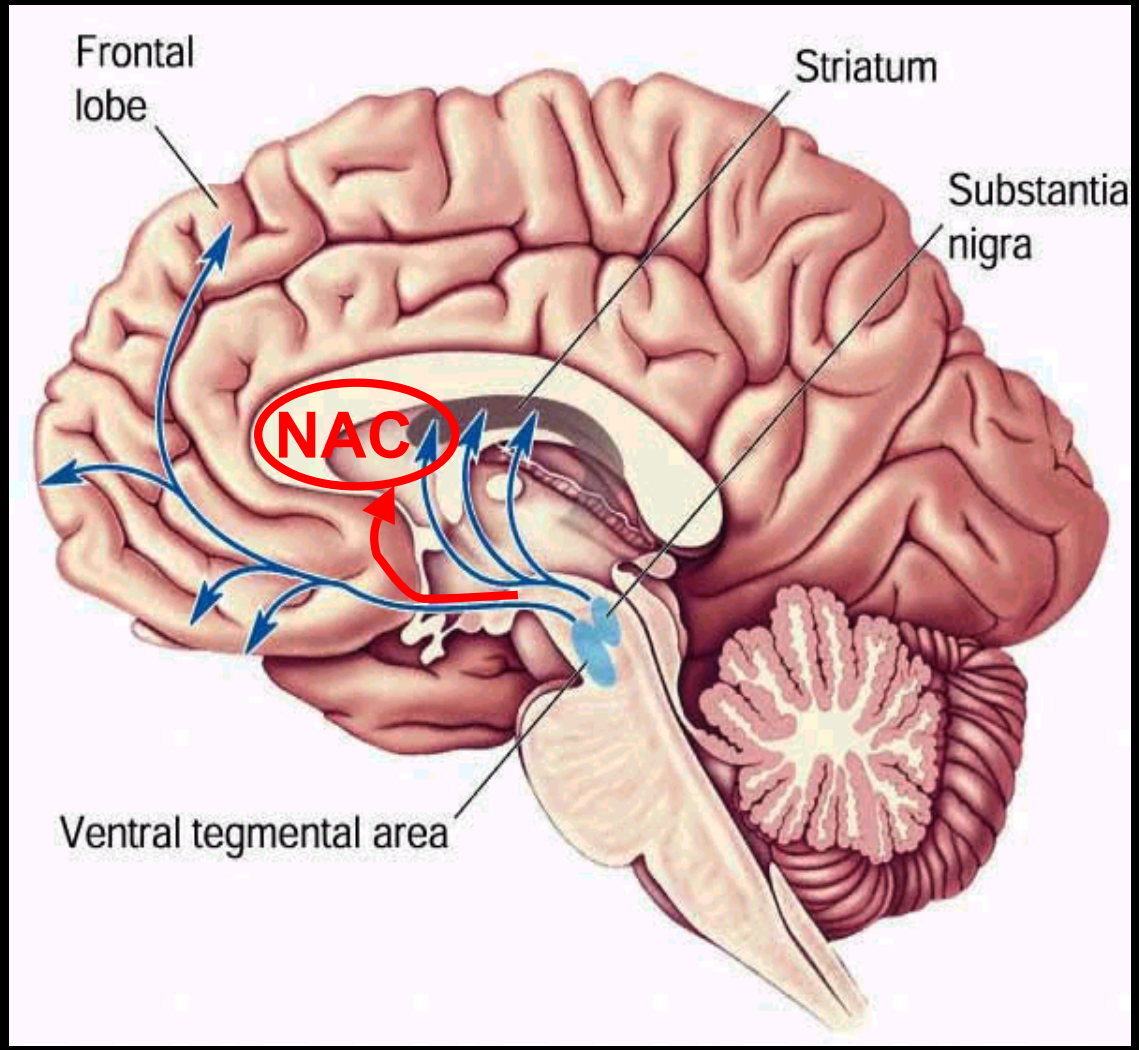
Biogene amines
- •dopamine
- •serotonin (5-HT)
- •noradrenaline
- •adrenaline
- •histamine

Acetylcholine

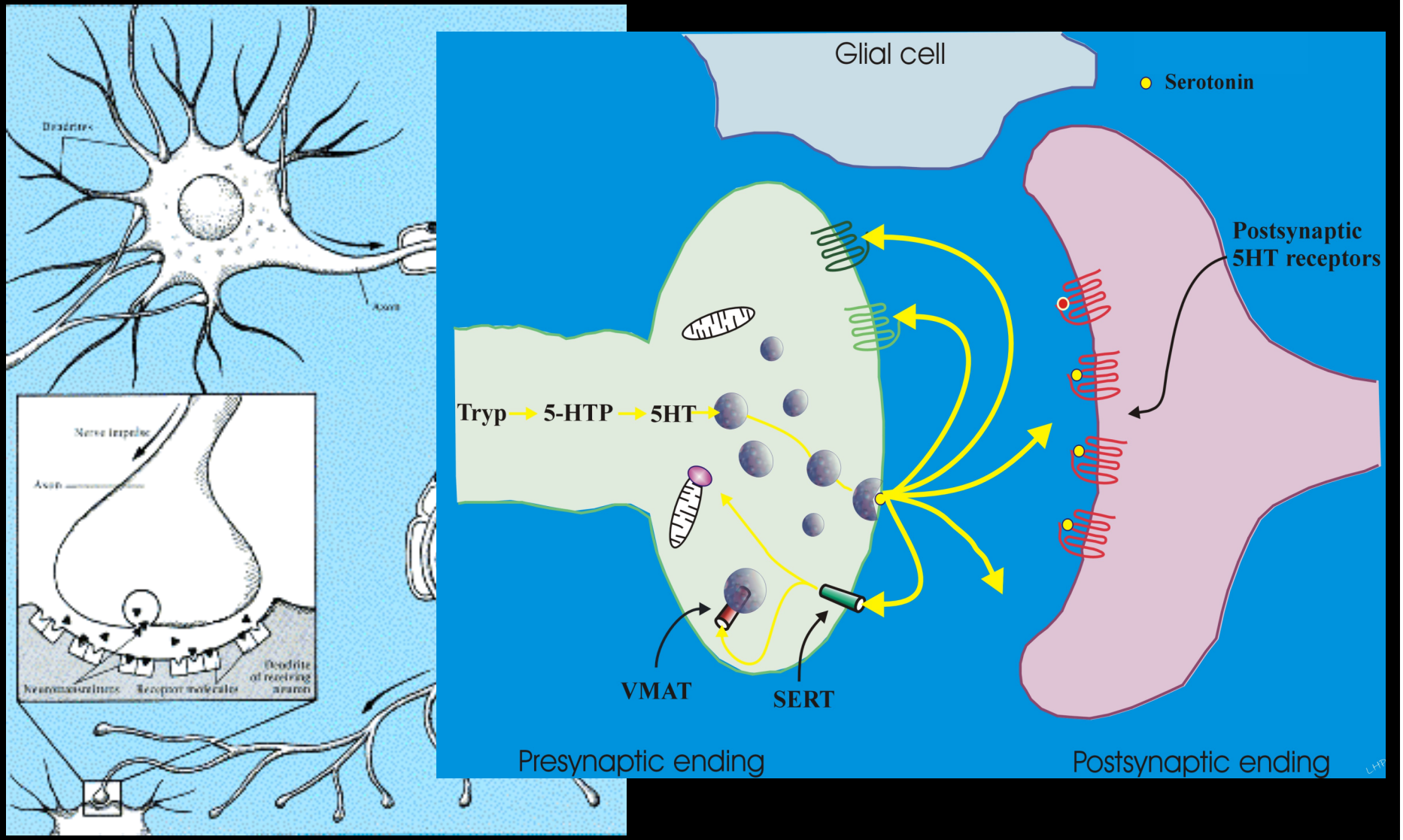
Aminoacids
- •GABA
- •glycine
- •glutamate

Drugs of abuse increase dopamine concentration in the nucleus accumbens of the mesolimbic system

Dopaminergic projections

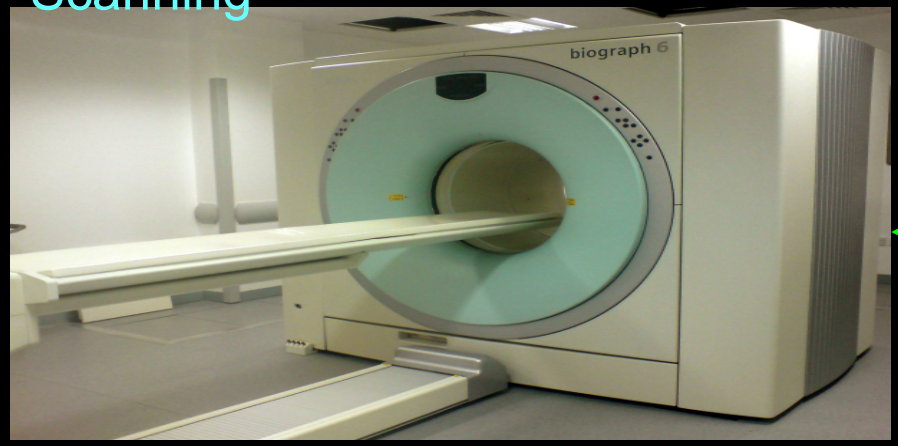


Neurotransmitter systems



In vivo imaging using positron emission tomography (PET)

Scanning



Radio-chemistry

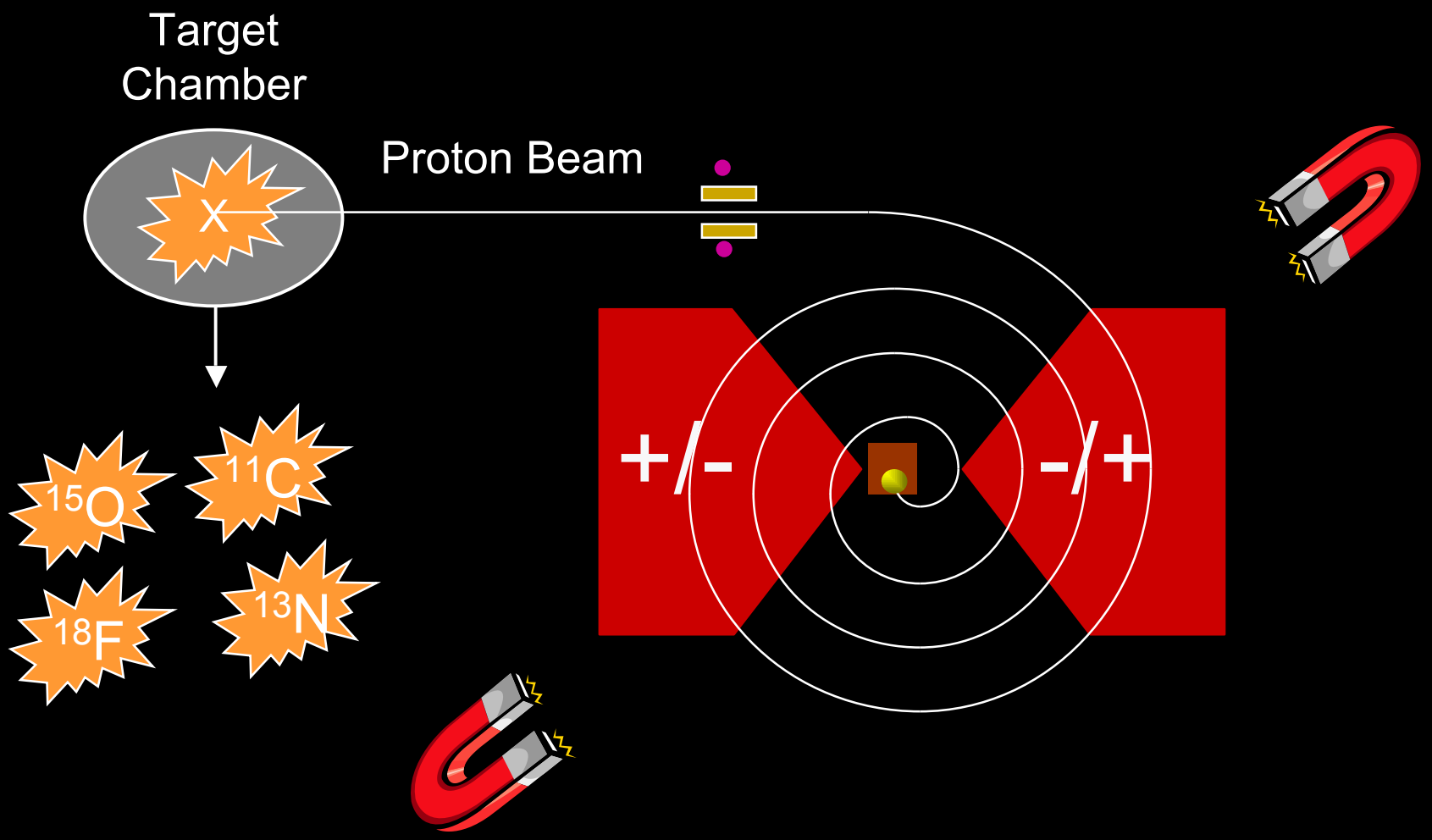
Cyclotron

Clinical area

Blood

Recruiting and Screening

Generating positron emitting radionuclides



In vivo imaging using positron emission tomography (PET)

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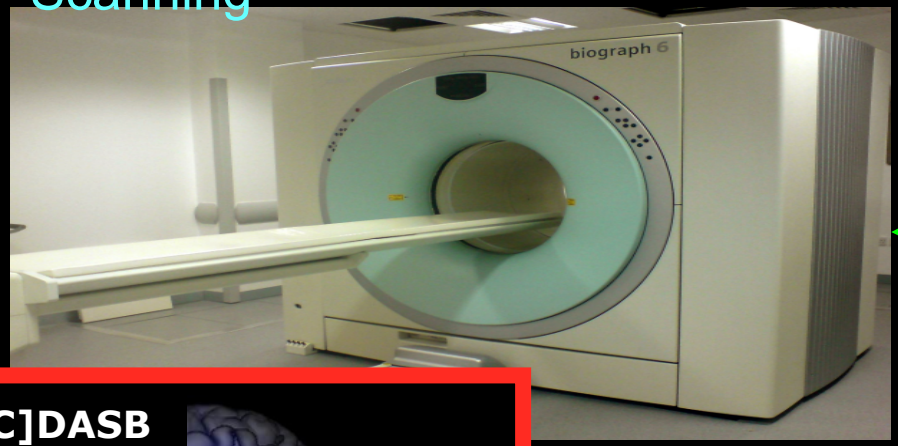
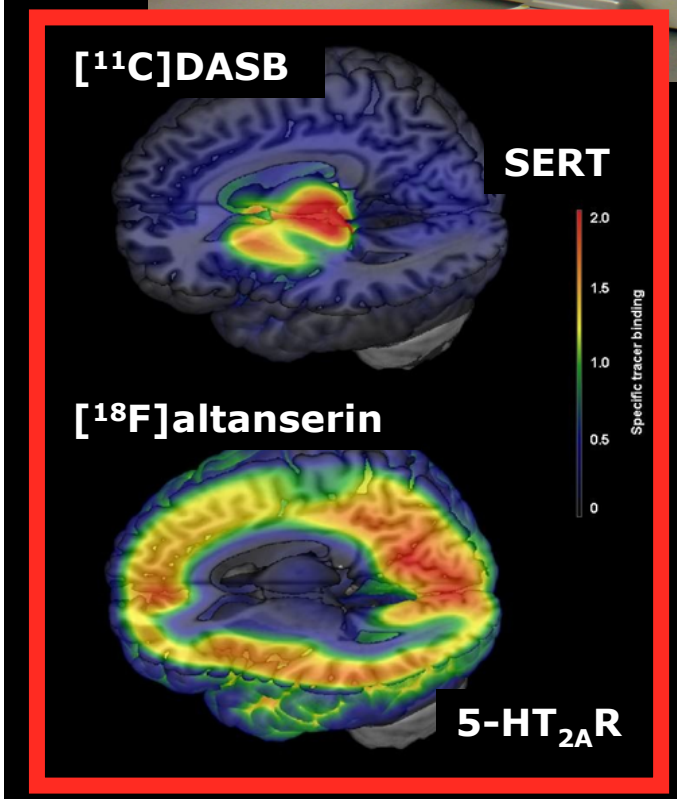


Cyclotron

Radio-chemistry



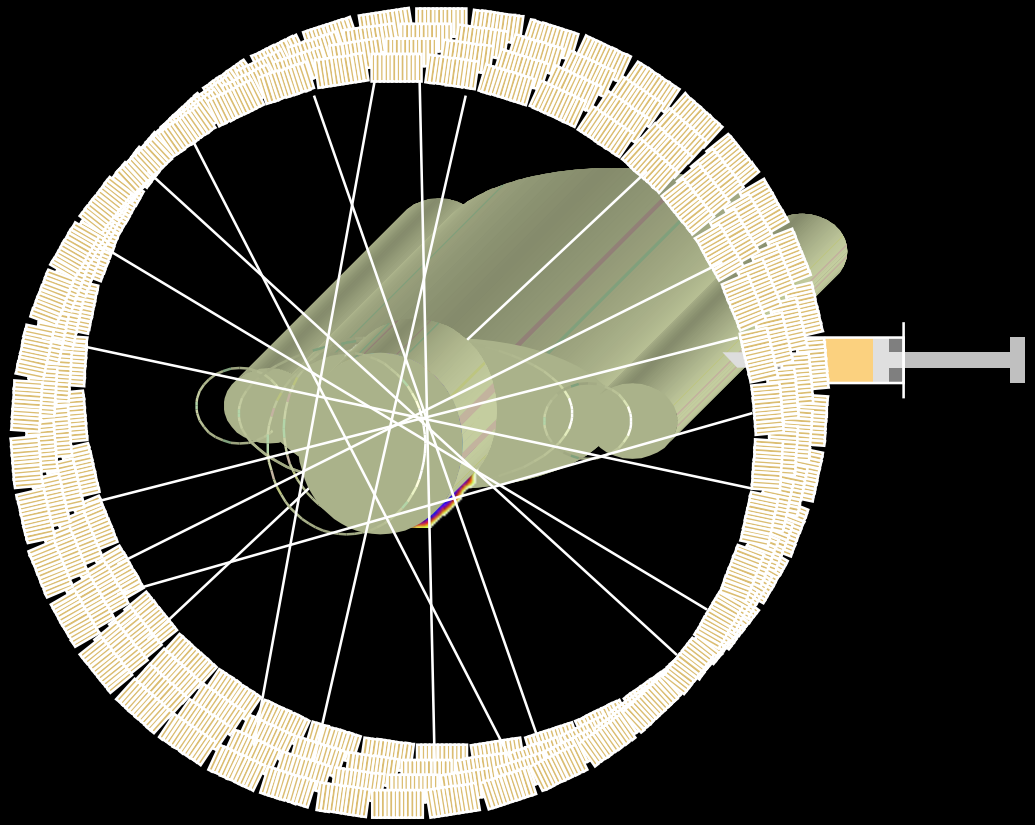
Blood

Clinical area

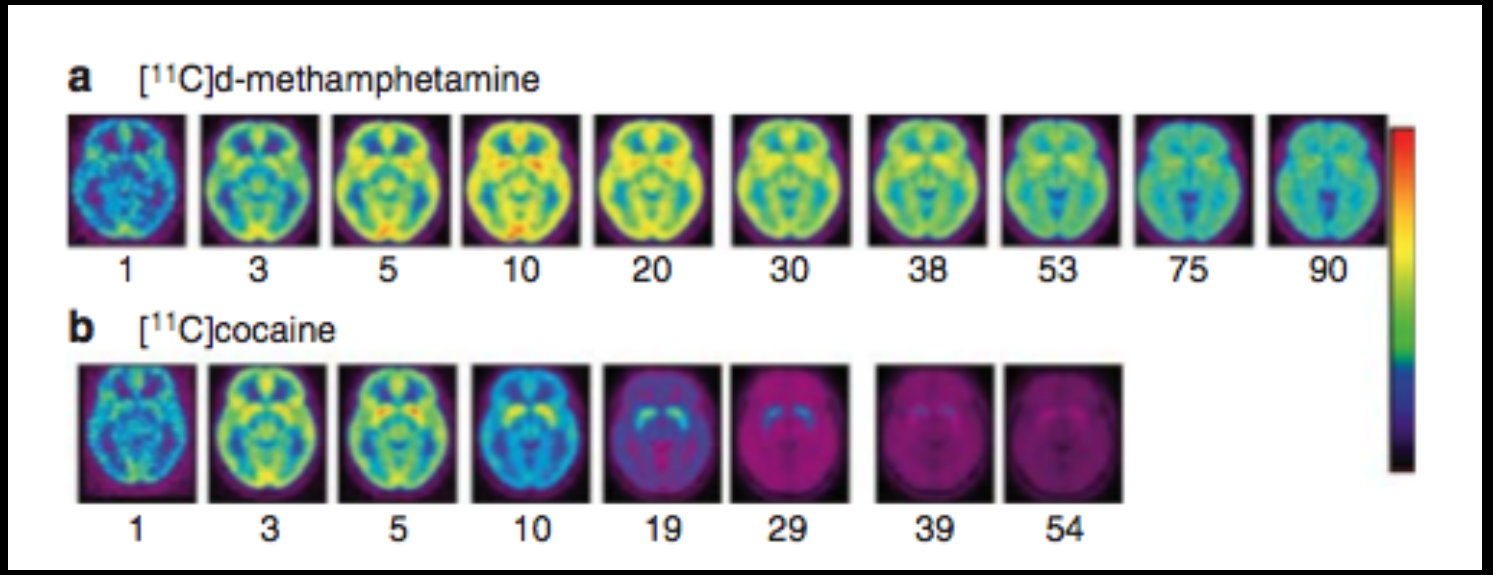
Recruiting and Screening

Detection of γ rays

- Thousands of detectors arranged around patient
- Count many (100s of) millions of coincidences to determine radionuclide distribution



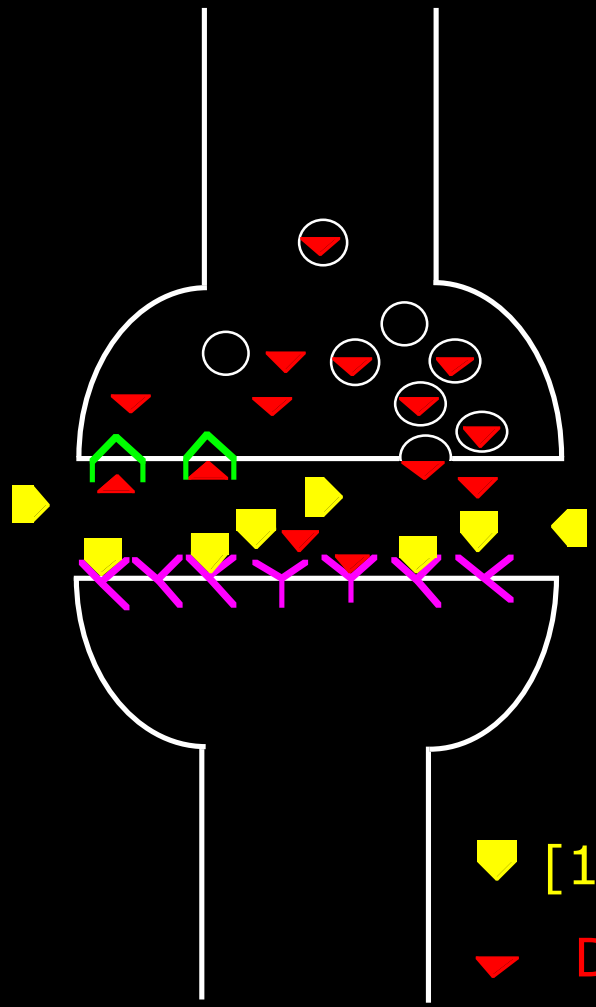
Brain uptake of cocaine and methamphetamine



(Fowler et al, 2008)

Dopaminergic neurotransmission

Baseline



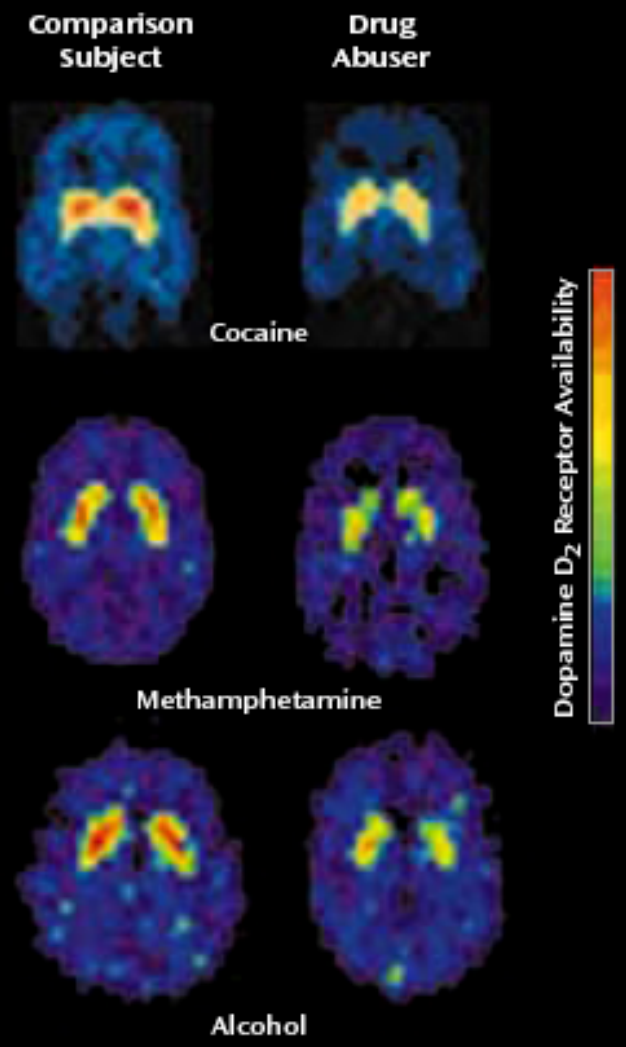
[11C]raclopride

Dopamine

Decreased D2/3 levels in detoxified substance users

Reduced dopamine D2/3 receptor levels have been found in substances of abuse;

Cocaine
Methamphetamine
Alcohol



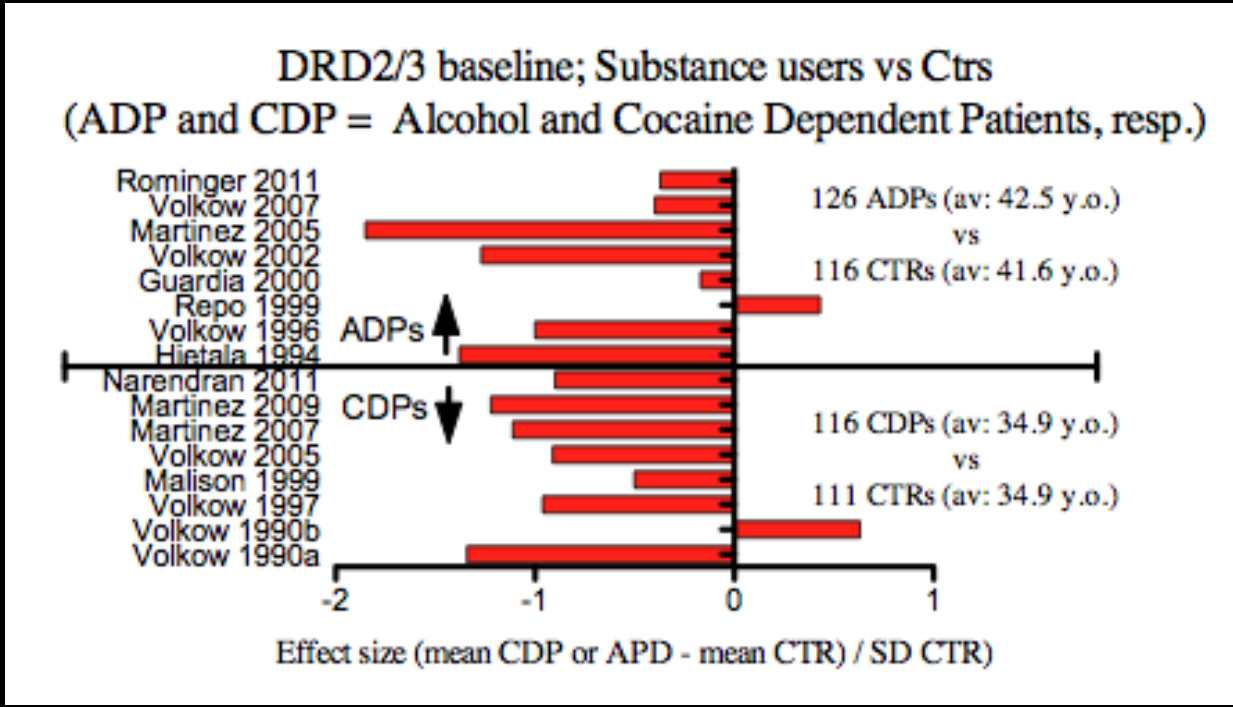
Decreased D2/3 levels in detoxified substance users

Reduced dopamine D2/3 receptor levels have been found in substances of abuse;

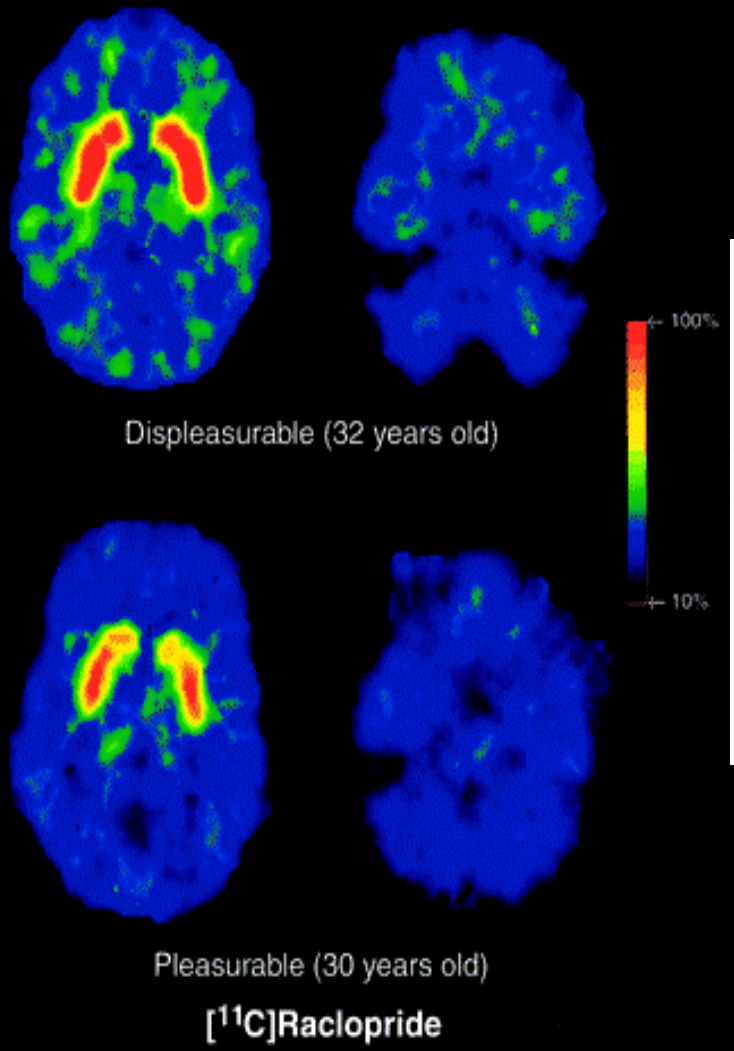
Cocaine
Methamphetamine
Alcohol

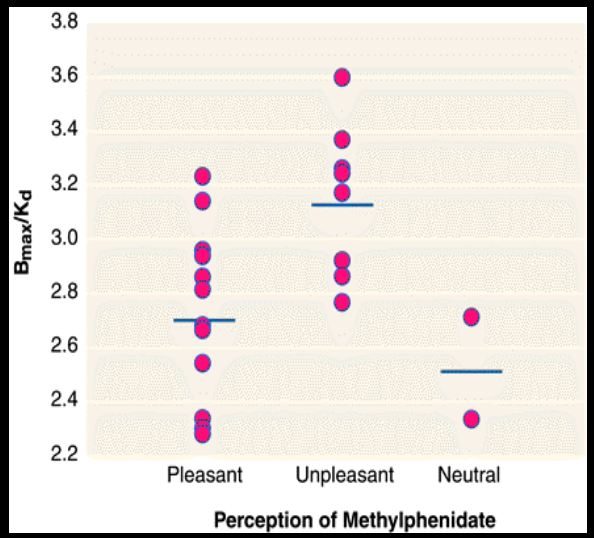
Effect size Alc studies: -0.75 ± 0.75
Effect size Coc studies: -0.79 ± 0.63

Overall reduction: 10% in Alc and 12% in Coc studies, resp.



Dopamine D2/3 receptor levels and the reinforcing effect of psychostimulants

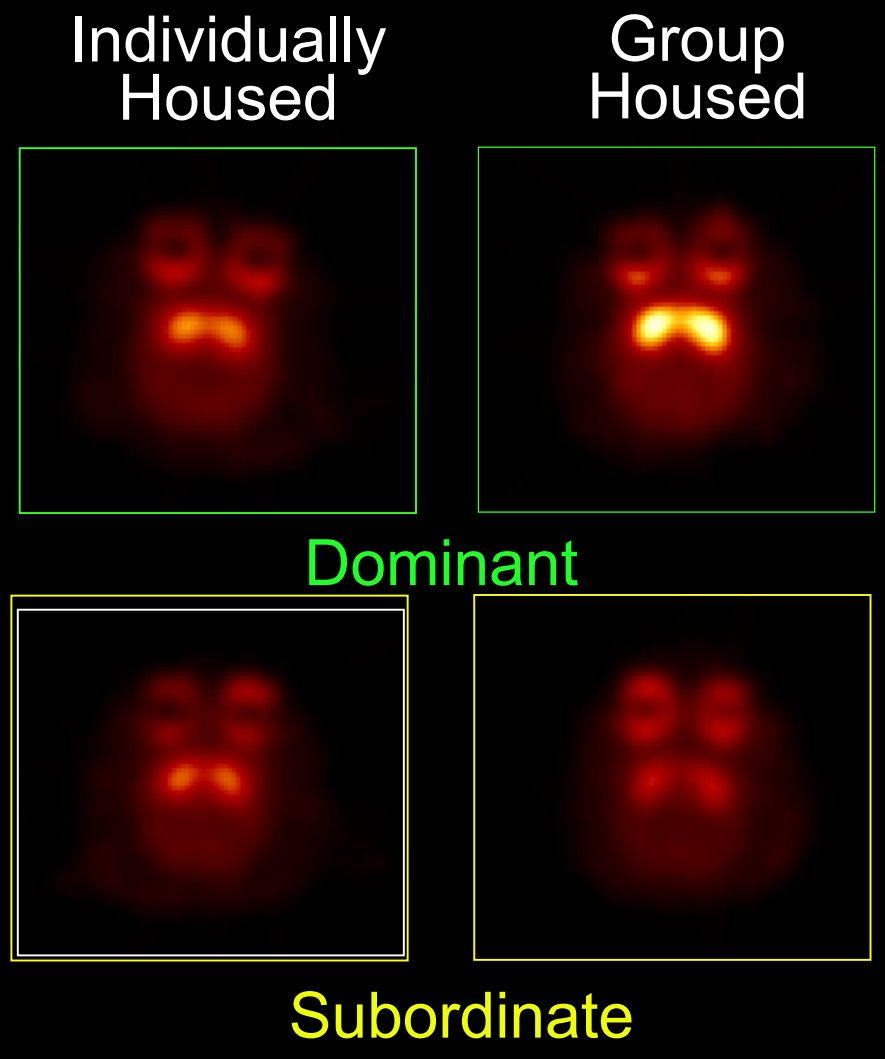


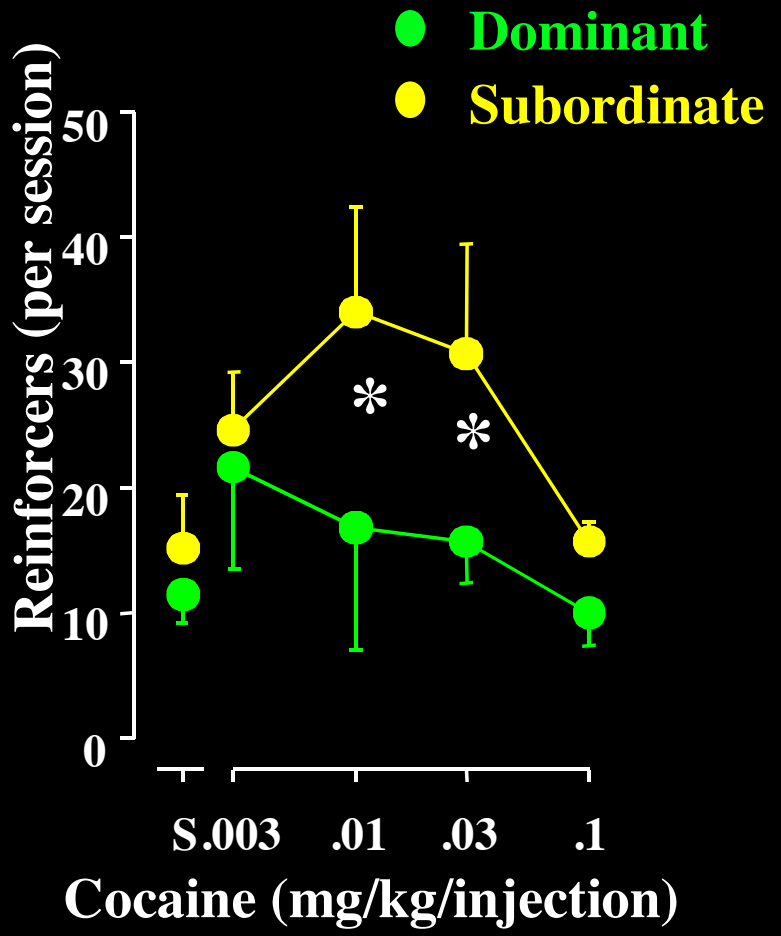


Prediction of reinforcing responses to psychostimulants in humans by brain dopamine D2/3 receptor levels.

Volkow 1999

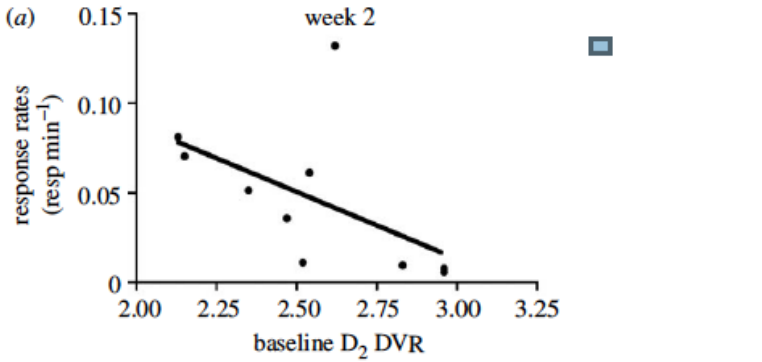
Social dominance in monkeys: Dopamine D2/3 receptors and cocaine self-administration

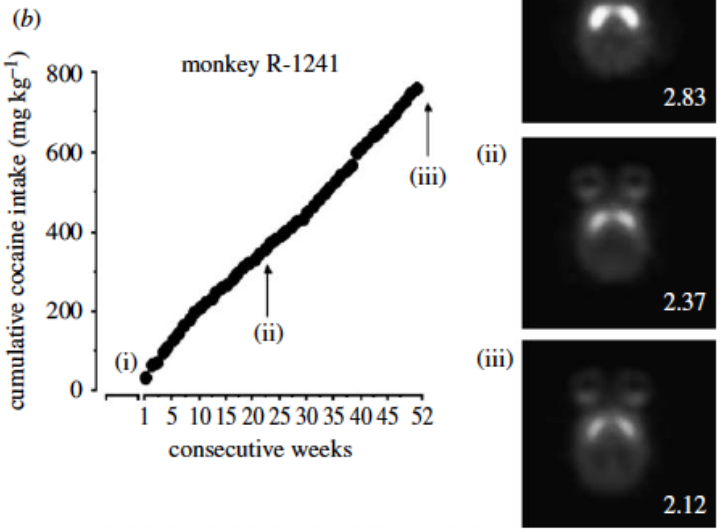




Morgan, et al. 2002.

Dopamine D2/3 receptors and addiction: What is cause and what is effect ?





Nader, et al. 2006.

Figure 1. (*a*) Correlation between baseline D_2 receptor availability and rates of cocaine self-administration in male rhesus monkeys. (*b*) Representative data from one monkey (R-1241) showing cumulative cocaine intake and associated changes in D_2 receptor availability. Adapted from Nader *et al.* (2006).

Dopamine D2/3 receptors and addiction: What is cause and what is effect ?

Is there a relationship between severity of substance use and dopamine D2/3 receptor levels ?

Alcohol studies (n=9):

- Assessed in 5 of these papers.

- Heinz, 2004: Negative relationship btw D2/3 and alcohol craving. (Not found in 2 other studies).

- Martinez, 2005: Negative relationship btw D2/3 and daily alcohol consumption. (Not seen in 3 other studies).

- Rominger, 2011: Negative relationship btw D2/3 and years of abuse. (Not found in 4 other studies).

Dopamine D2/3 receptors and addiction: What is cause and what is effect ?

Is there a relationship between severity of substance use and dopamine D2/3 receptor levels ?

Cocaine studies (n=12):

- Assessed in 5 of these papers.
- No significant relationship between striatal dopamine D2/3 receptor binding and either cocaine craving (Volkow, 1993; Volkow 2006) or dependence severity (Martinez, 2004; Martinez 2007; Volkow 2006) was reported was described in most of these studies.
- Volkow, 1993: Negative correlation btw D2/3 receptor binding and years of cocaine use.
- Martinez, 2009:Positive association btw D2/3 receptor binding and amount of cocaine used.

Dopamine D2/3 receptors and addiction:
Is the reduced D2/3 reversible over time?

- Assessed in only one of the Alcohol papers (n=9) and in two of the Cocaine papers (n=12).

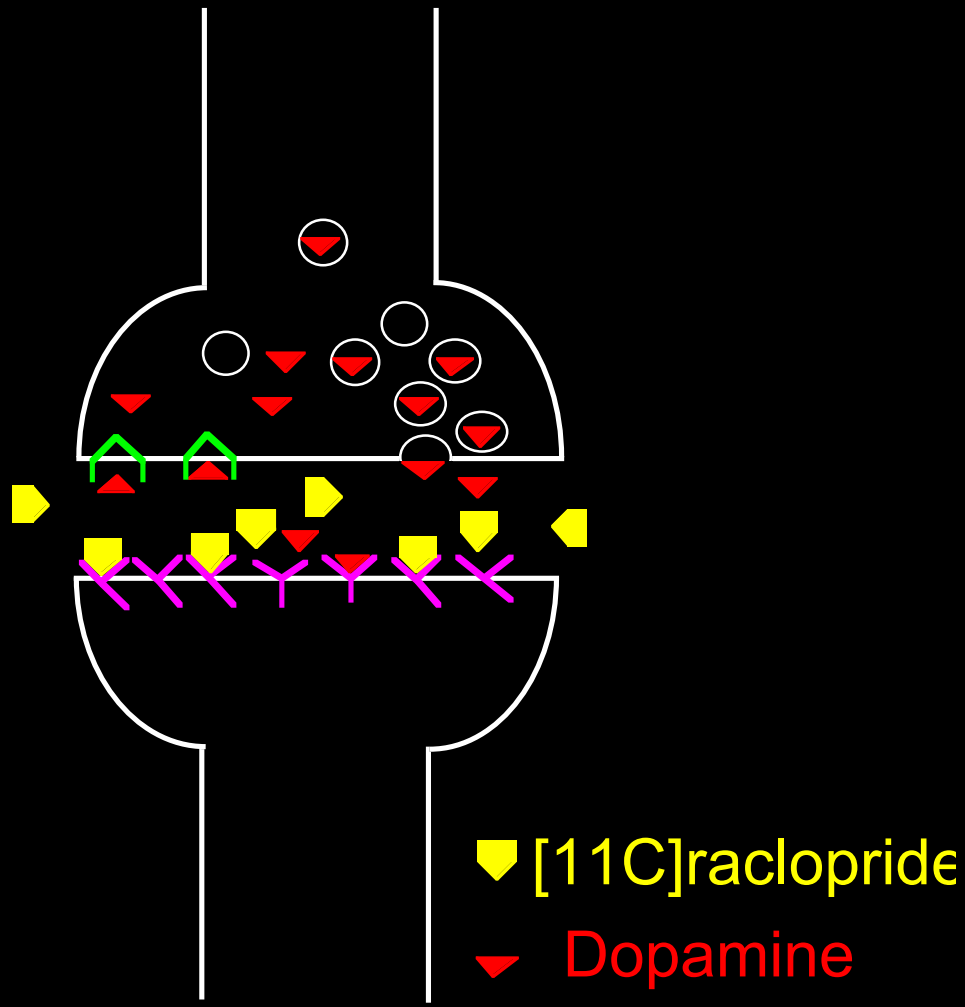
- Volkow, 1993: Still decreased D2/3 density after 3 months of sustained cocaine abstinence in 7 re-scanned CDPs.
No recovery?

- Rominger, 2011: Four ADPs re-scanned after 1 year of abstinence/sign. decrease in use.
➡ 29% increase in D2/3 from baseline.
- Volkow, 1990: Seven CDPs up to one week of abstinent **but not** 3 CDPs with longer abstinence (4 weeks) had reduced DRD2/3 binding when compared to matched CTRs.
Recovery?

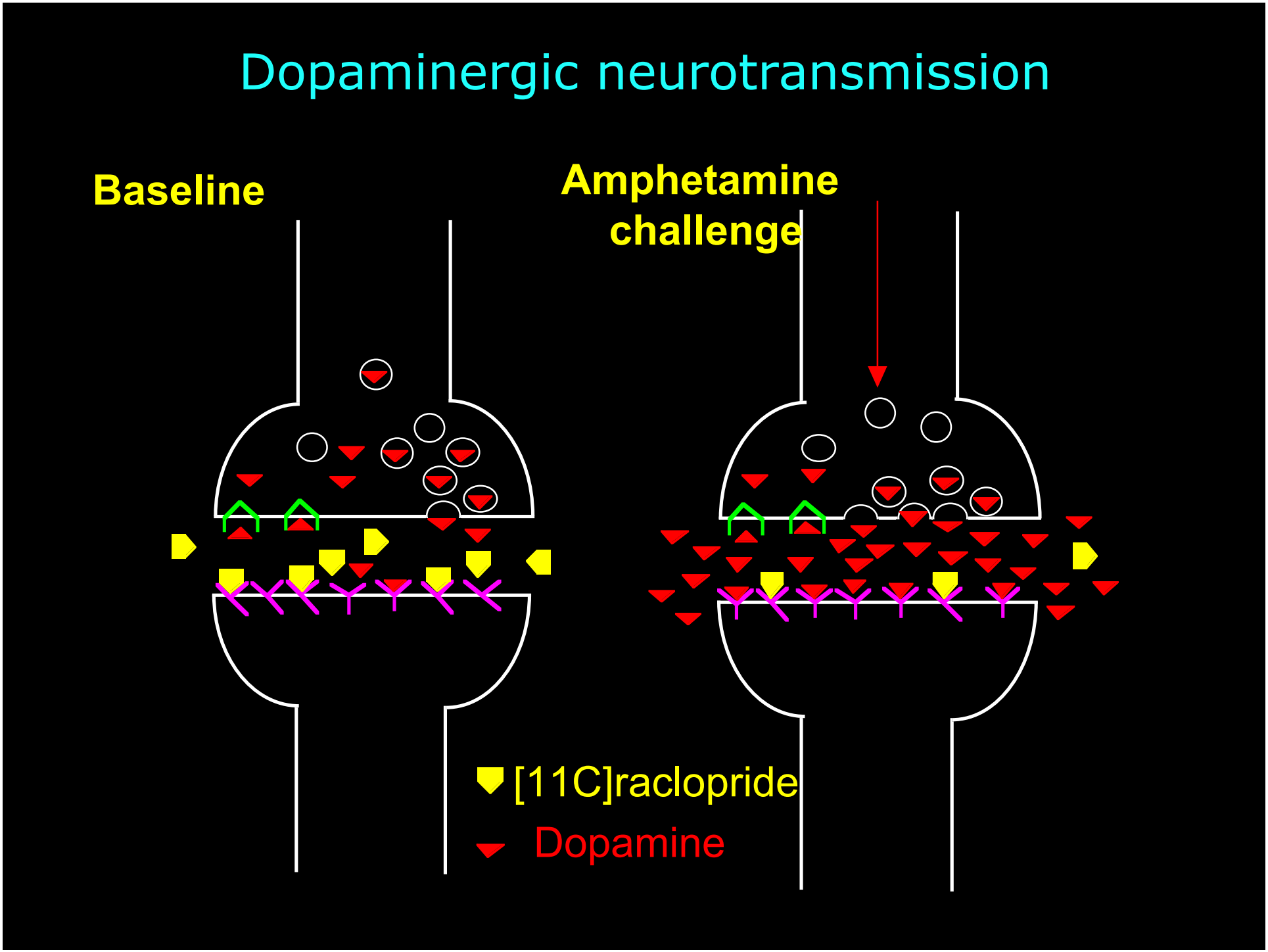
(CDP and ADP= Cocaine and Alcohol Dependent Patients, respectively).

Dopaminergic neurotransmission

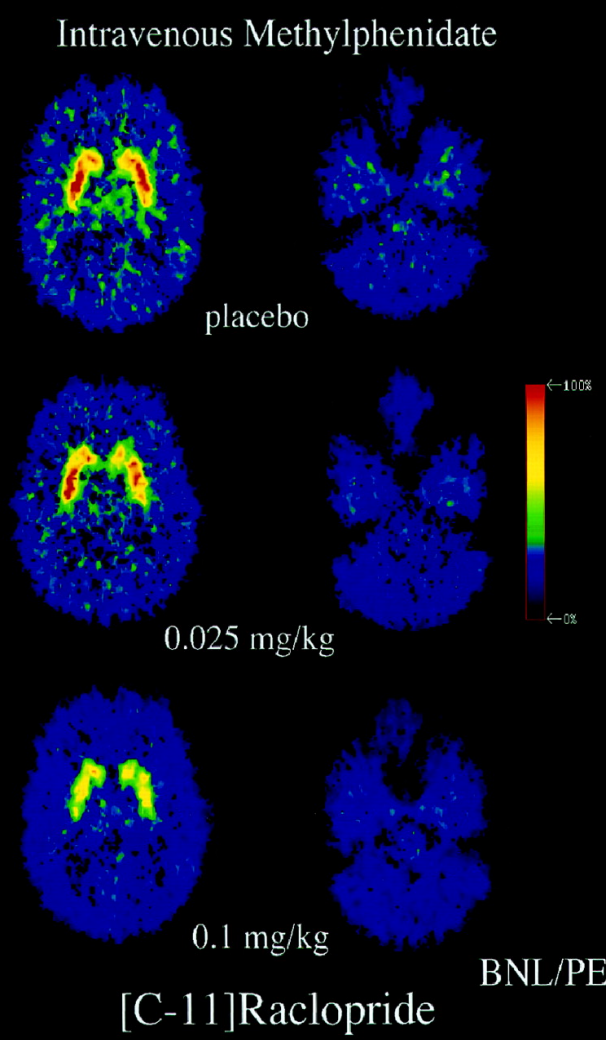
Baseline



Dopaminergic neurotransmission



Dopamine release measured with 11C-raclopride



Volkow 1999

Dopamine :

In healthy volunteers

Psychostimulants [methylphenidate, amphetamine]

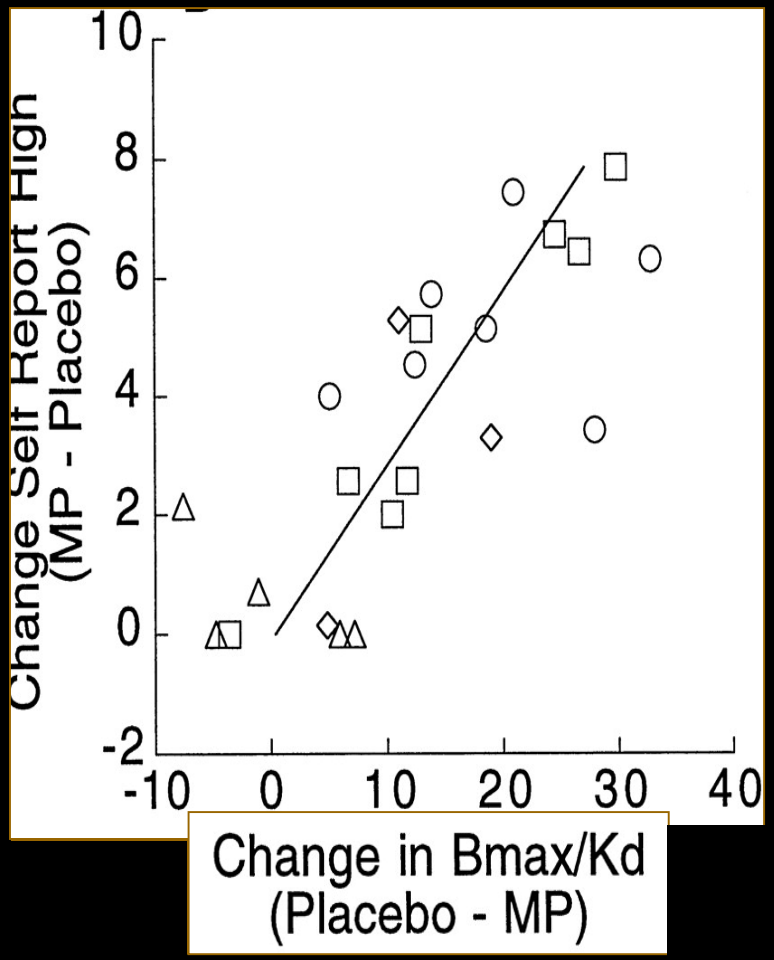
Volkow, Laruelle, Brier, Drevets, Leyton (oral, 'drug wanting' not euphoria)

Alcohol

- *Boileau et al (oral); Yoder et al (iv; no); Salonen et al (oral;no)*

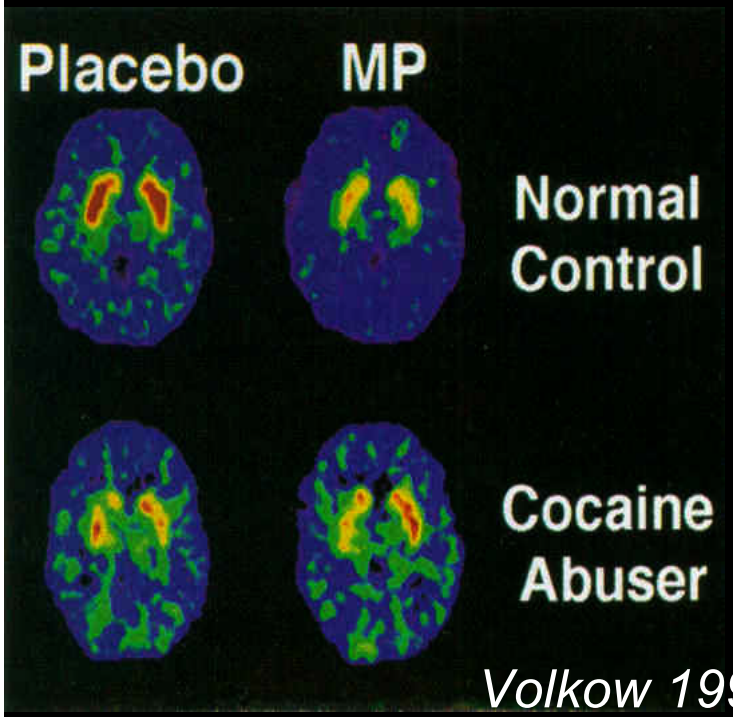
Dopamine (DA) release; relation to subjective drug effects

Increases in brain dopamine are associated with reinforcing effects of psychostimulants in humans.



Volkow 1999

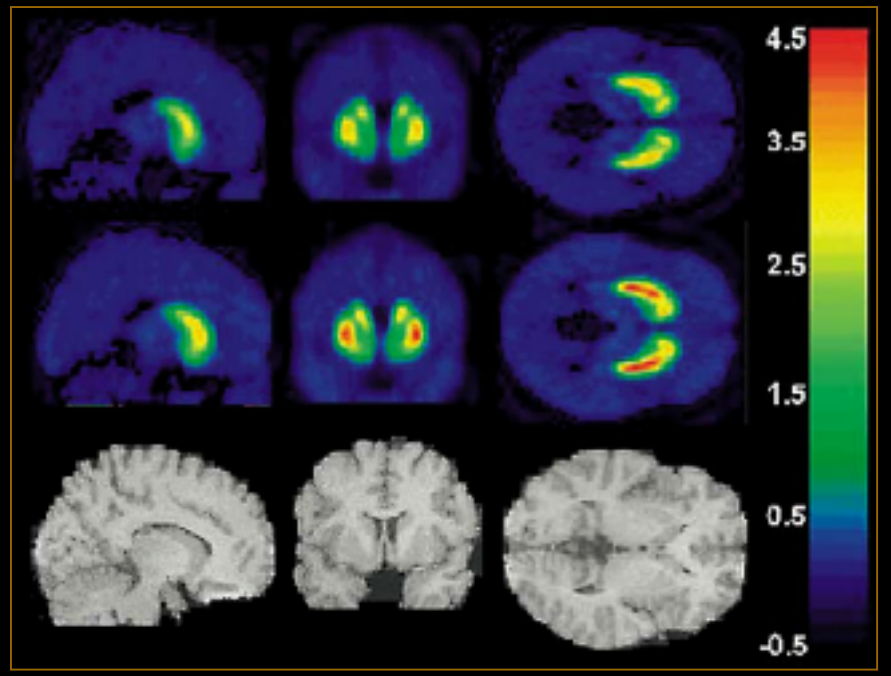
Decreased striatal dopaminergic responsiveness in detoxified alcohol and cocaine users



Volkow 1997

Alc

Ctr



Martinez 2007

Alcohol Dependence Is Associated with Blunted Dopamine Transmission in the Ventral Striatum

Diana Martinez, Roberto Gil, Mark Slifstein, Dah-Ren Hwang, Yiyun Huang, Audrey Perez, Lawrence Kegeles, Peter Talbot, Suzette Evans, John Krystal, Marc Laruelle, and Anissa Abi-Dargham

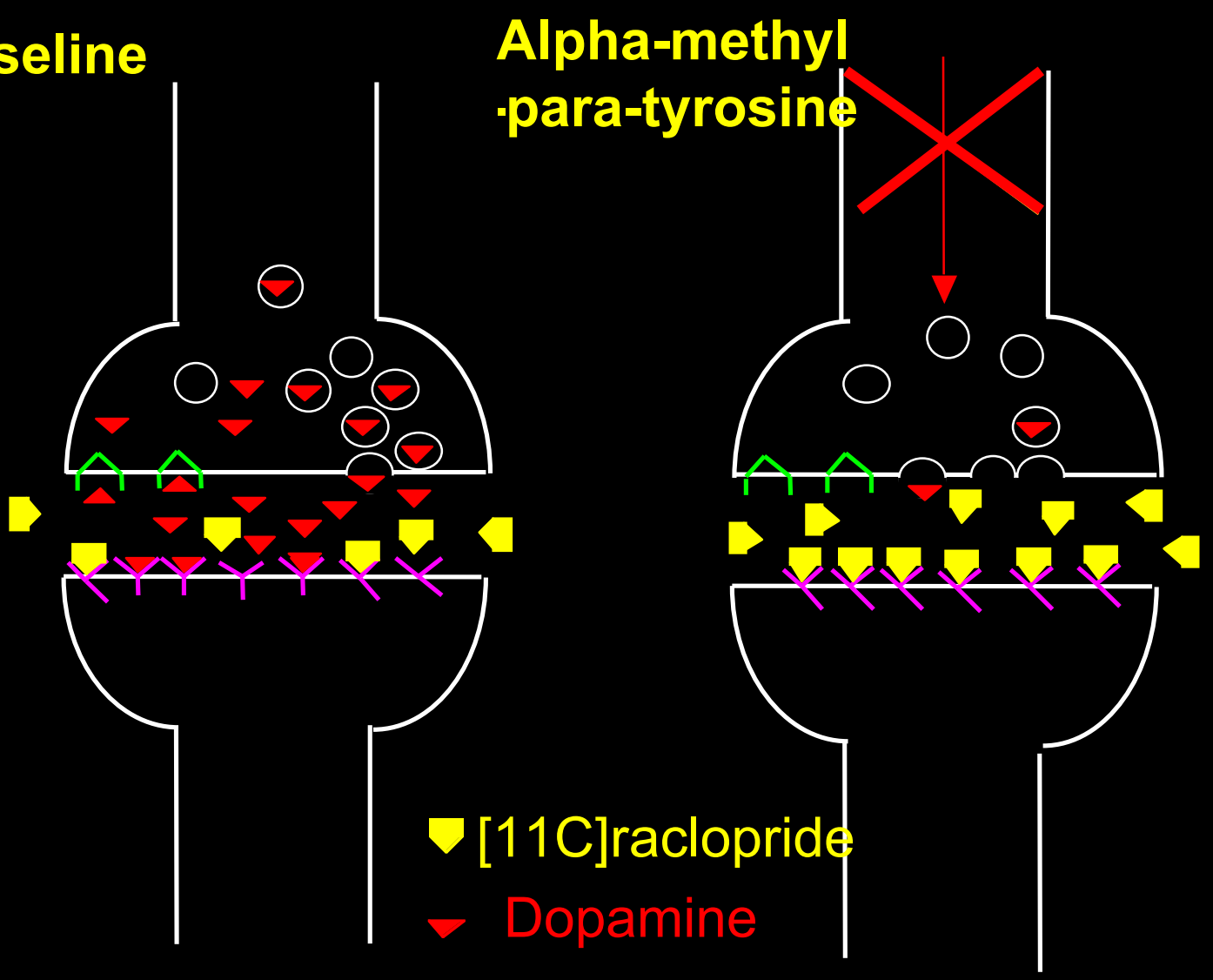
Dopamine D2/3 receptors and addiction:
What could explain reduced D2/3 levels and reduced dopamine release?

Fewer D2/3 receptors available for ligand binding could be due to is often conceived as “fewer receptors” but could also be due to:

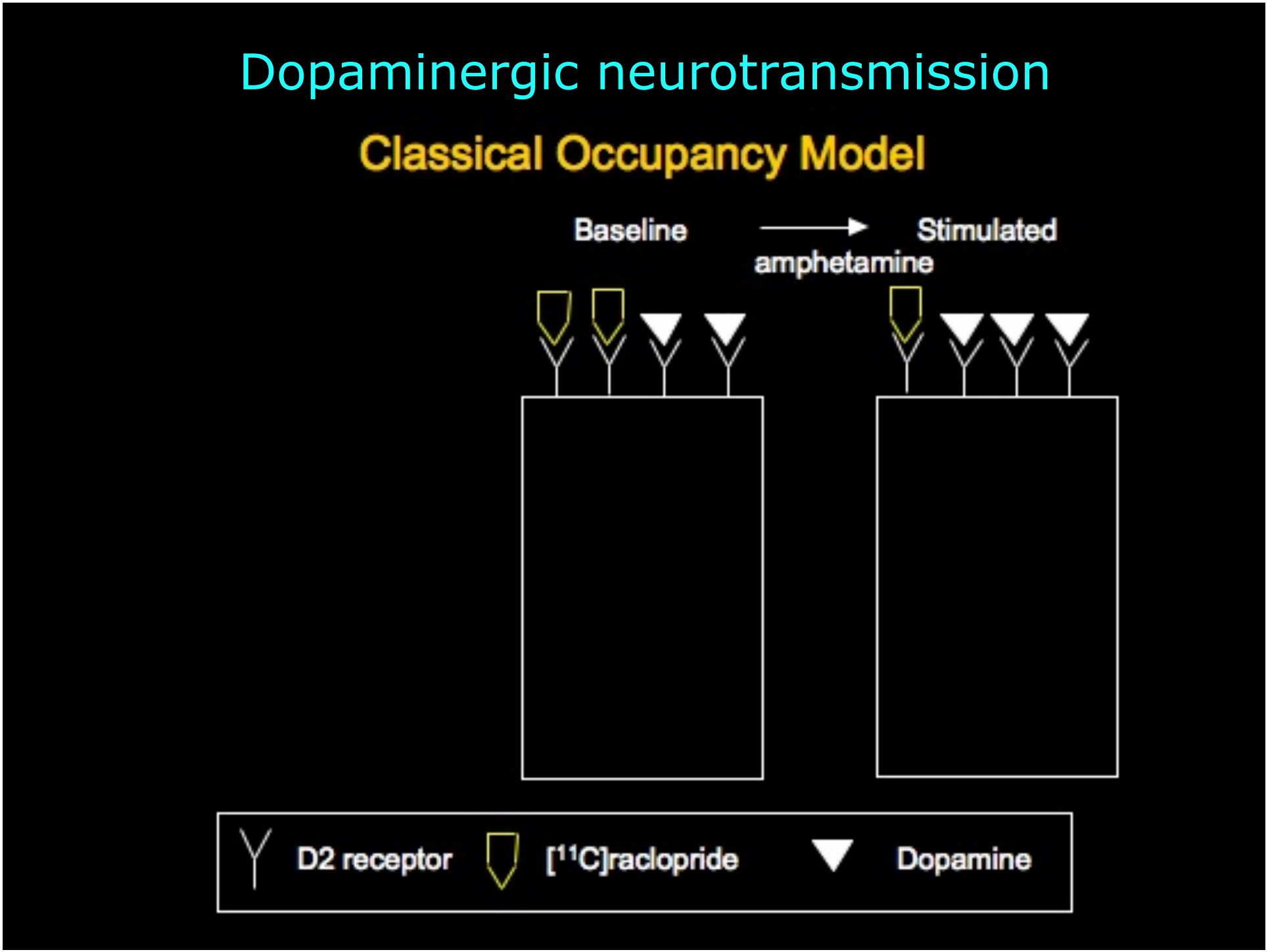
- More dopamine in the synapse ?
- Poorer affinity of D2/3 receptors for dopamine ?

Both have recently been tested !

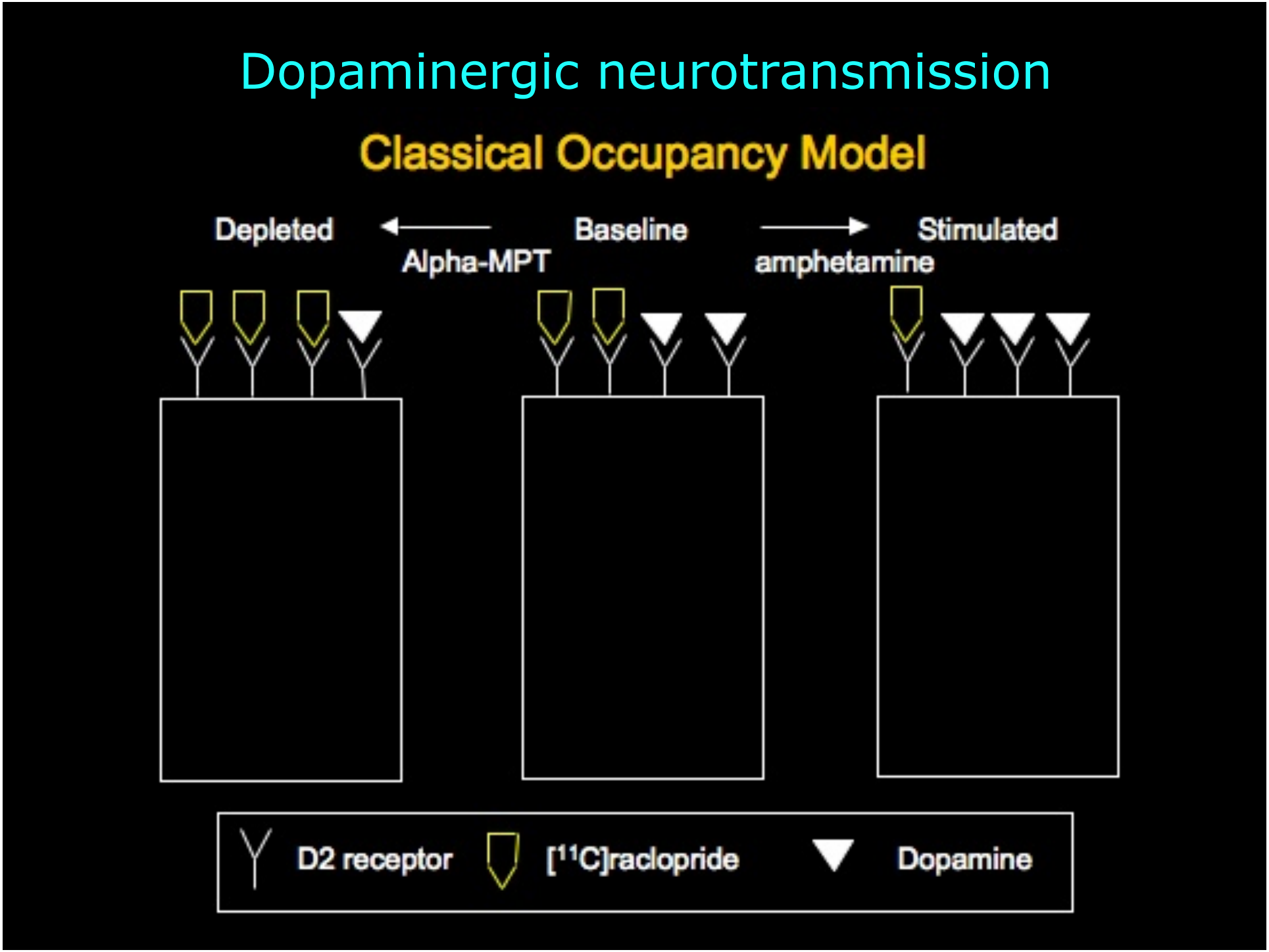
Dopaminergic neurotransmission



Dopaminergic neurotransmission



Dopaminergic neurotransmission



Dopamine D2/3 receptors and addiction: What could explain reduced D2/3 levels and reduced dopamine release?

- More dopamine (DA) in the synapse ?
- Poorer affinity of D2/3 receptors for DA ?

- Martinez et al, 2009: Depletion study in CDPs vs CTRs using 11C-raclopride before and after AMPT (DA depleting agent).

- CDPs showed less change (smaller increase) in post-AMPT vs baseline 11C-raclopride binding when compared to CTRs.
- This indicates lower levels of endogenous DA relative to CTRs.
- Thus, the low baseline D2/3 levels in (cocaine) addicts cannot be attributed to differences in the percentage of D2/3 receptors occupied by DA...
- ....and the lower DA levels in CDPs may have masked even greater differences between CDPs and CTRs.

Dopamine D2/3 receptors and addiction: What could explain reduced D2/3 levels and reduced dopamine release?

- More dopamine (DA) in the synapse ?
- Poorer affinity of D2/3 receptors for DA ?
- Narendran et al. 2011:

By comparing binding of 11C-raclopride (antagonist ligand binding to high and low affinity D2 receptor states) and 11C-NPA (agonist ligand only binding to high affinity states of D2) the fraction of D2 in high affinity state was calculated in cocaine addicted patients and matched controls.

Thus no support for difference in receptor affinity states in addicted patients.

Dopamine D3 receptors and addiction

- Dopamine D2 or D3 receptors?

- So far: No distinction in human in-vivo imaging studies

<u>Dopamine D3 receptors; pre-clinical and post-mortem:</u>

- Increased binding in cocaine overdose fatalities.
- Upregulation of striatal dopamine D3 gene expression in rats after years of alcohol drinking.
- Selective dopamine D3 receptor blockade reduces ethanol preference and consumption in rat and mouse.
- Same blocker reduces nicotine and opiate seeking behaviours and cue-induced use of cocaine.

Dopamine D3 receptors (DRD3) in alcoholism

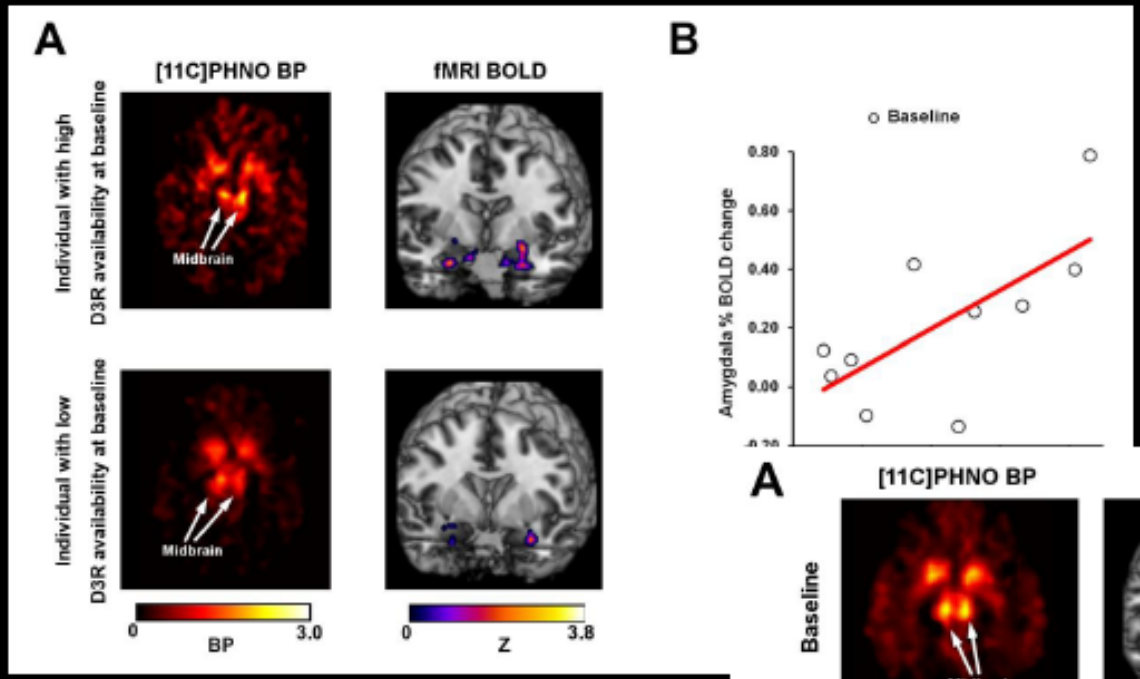
• Dopamine D3 can now be measured with PET in humans using the DRD3 preferring D2/3-agonist radioligand, 11C-PHNO in some brain regions.
If 11C-PHNO is used in combination with a selective DRD3-blocker, D3 can be assessed in all dopaminergic brain regions (Searle et al. 2010).

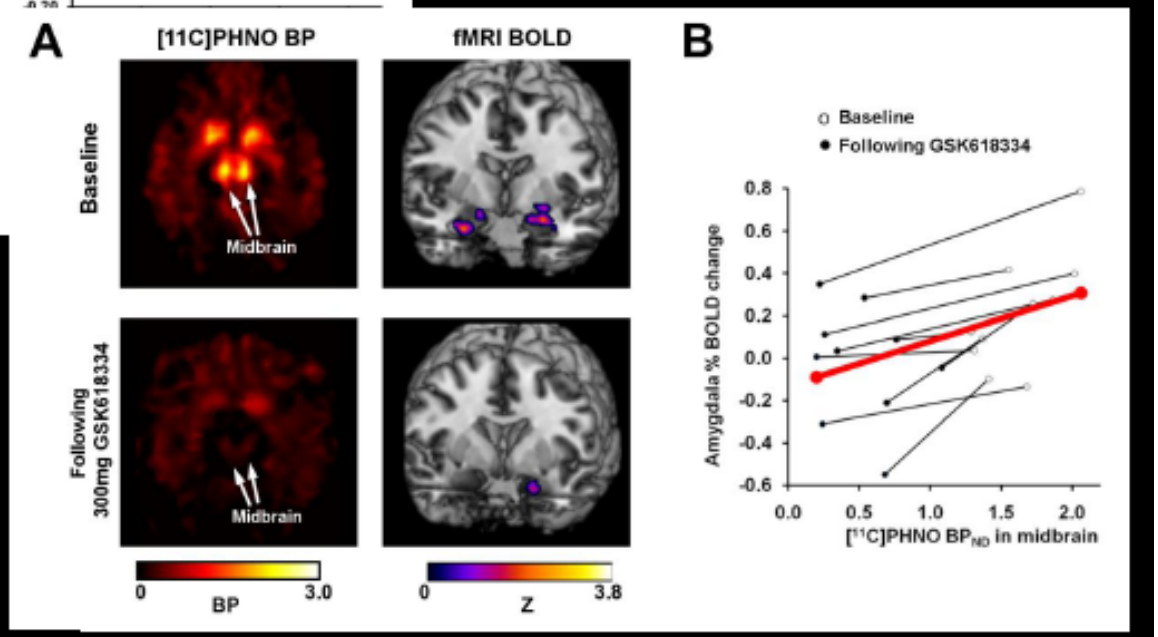
In methamphetamine users (Boileau et al 2012):
• Increased D3 in midbrain

In alcohol dependent patients (manuscript under prep):
• No difference in midbrain D3, but increased in hypothalamus.

• No significant striatal group differences.

D_3R Availability Predicts Amygdala Response To Monetary Reward





Beaver et al., submitted

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