Functional imaging and dopamine transmission in addiction

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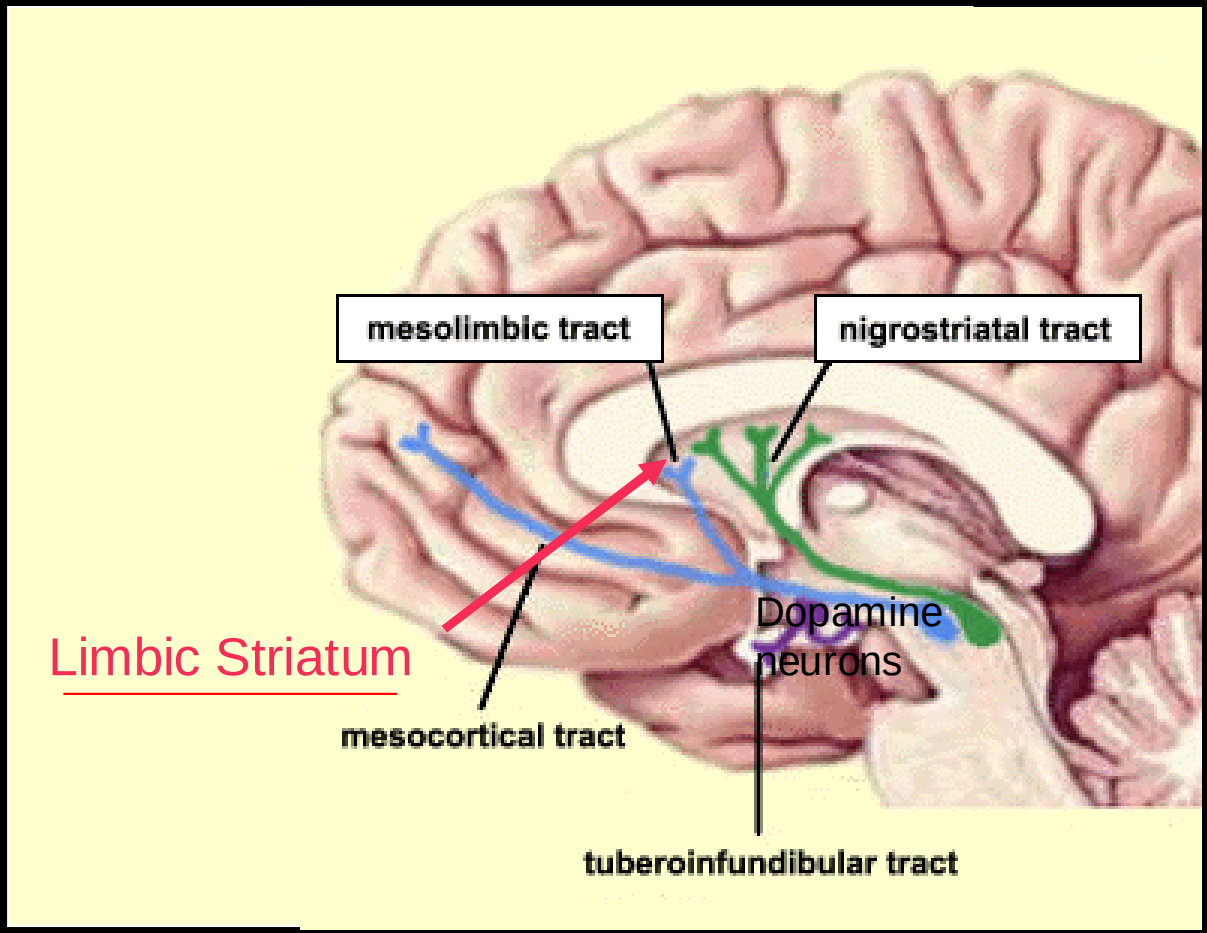
Dopamine and addiction:

The dopamine neurons of the midbrain project to the striatum:
1.mesolimbic tract
2.nigrostriatal tract

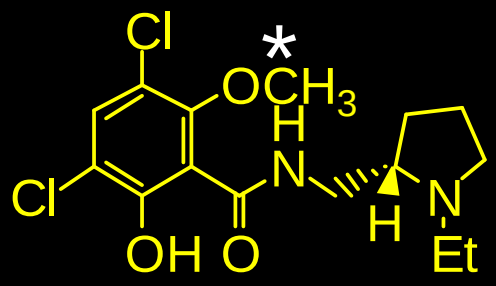
Dopamine signaling in the limbic striatum (mesolimbic tract) is important in drug addiction.



From thebrain.mcgill.ca

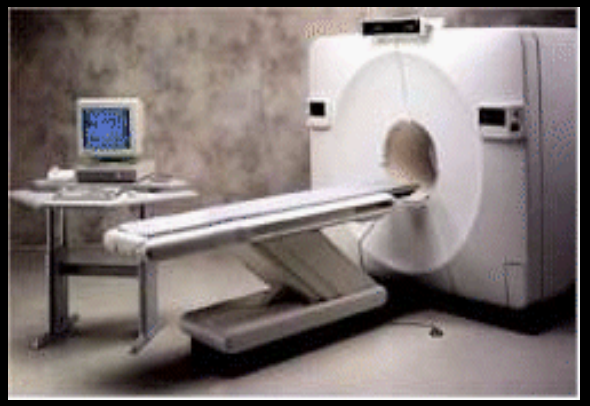
PET Neuroreceptor Imaging

Radiotracer

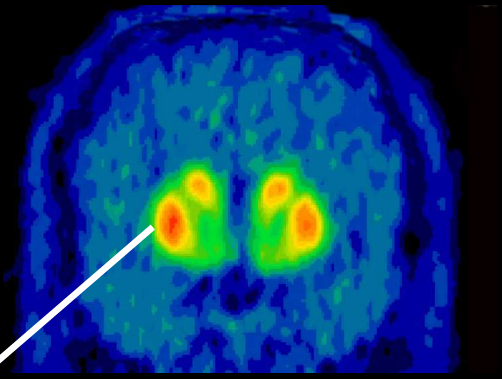


[11C]raclopride

PET camera

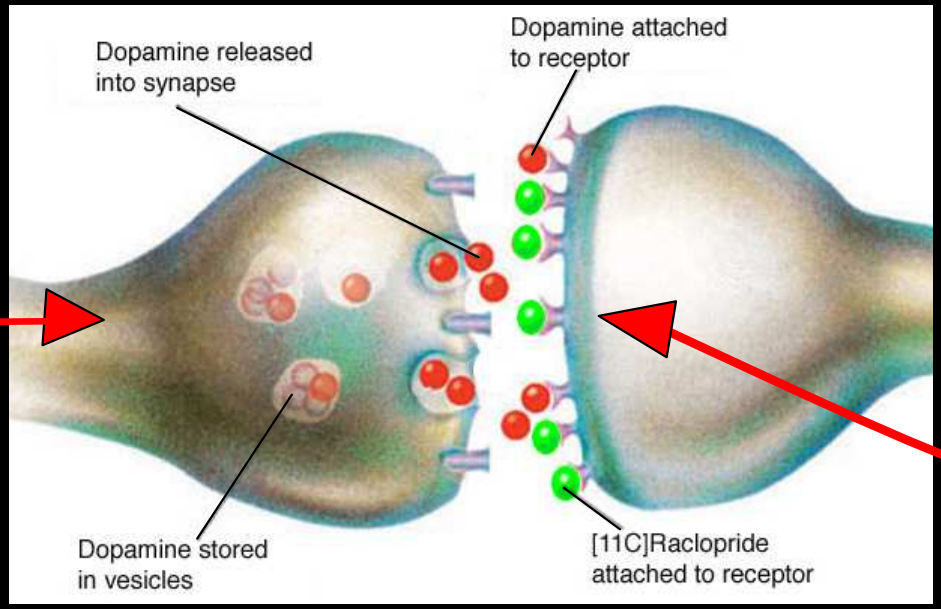


PET Image



Dopamine receptors (D2/3) in the striatum

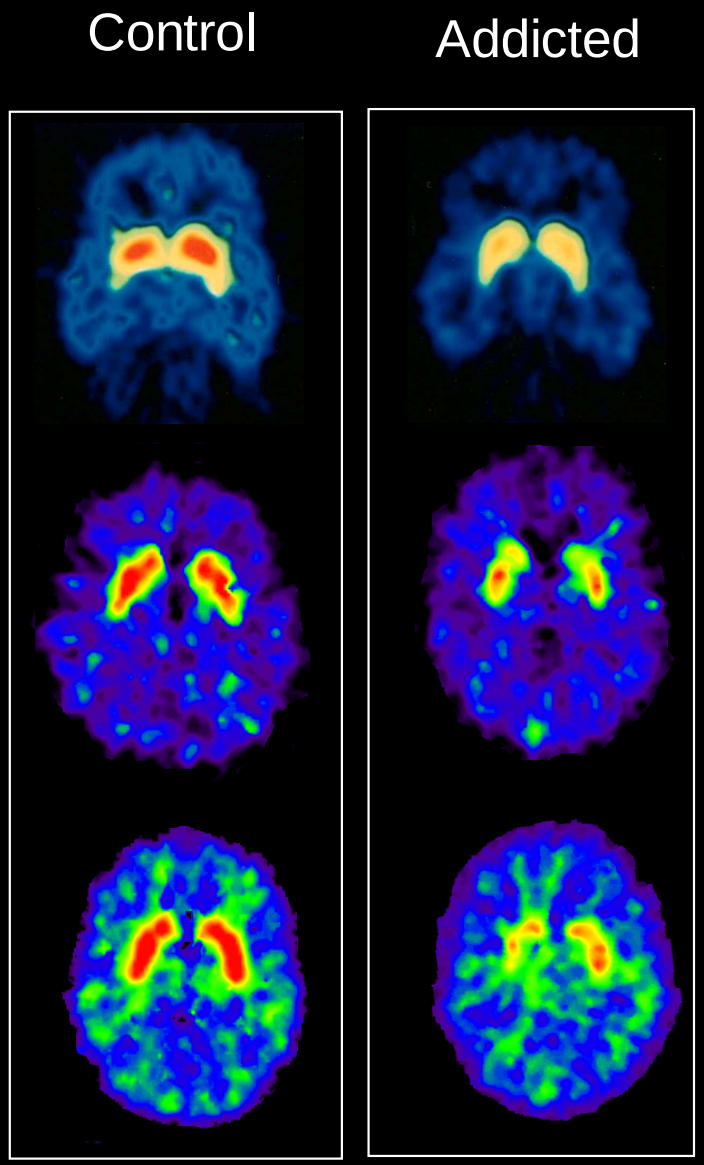
Synapse



Dopamine neuron from the midbrain

Neuron in the striatum, expresses dopamine D2/3 receptors

D2/3 receptors are decreased in addiction

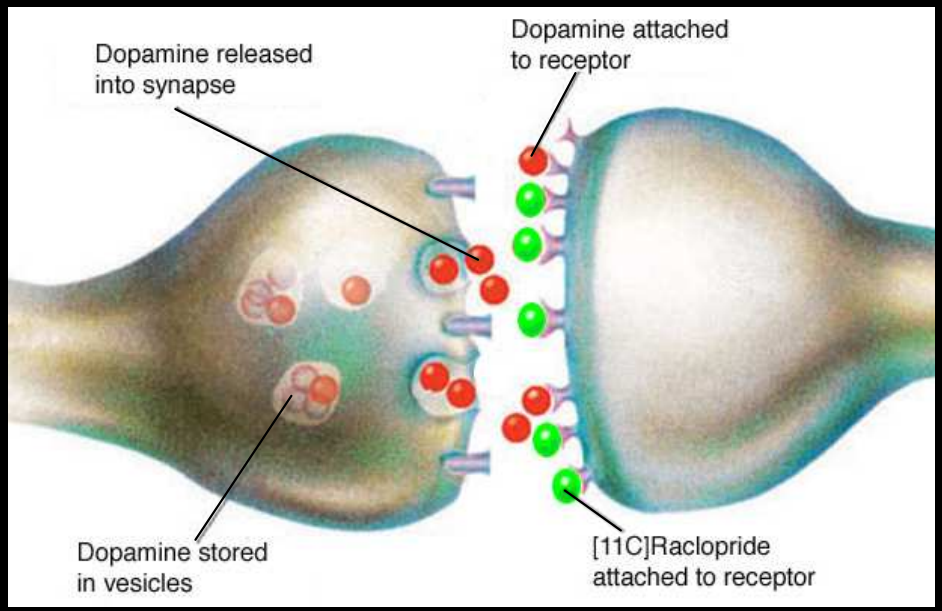


In each case, the addicted group has a 10 - 20% reduction in dopamine D2/3 receptors measured with PET.

This has been seen in cocaine, heroin, alcohol and methamphetamine dependence and obesity

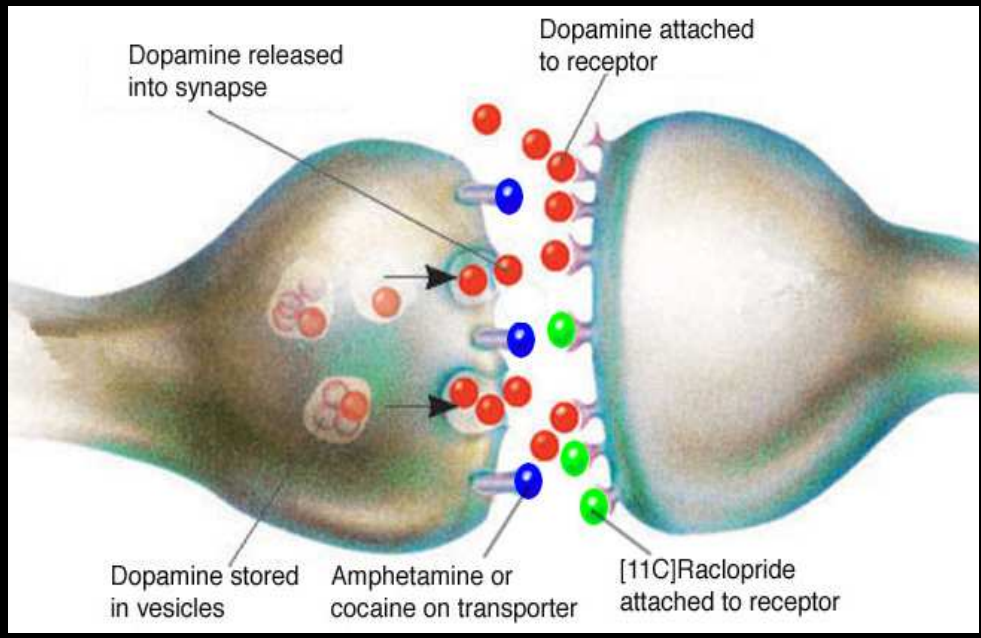
Volkow and Wang et al, 1990-2000

PET also images dopamine in the synapse

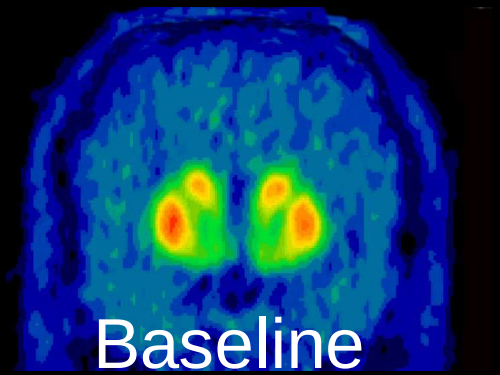


Dopamine neuron (from midbrain)

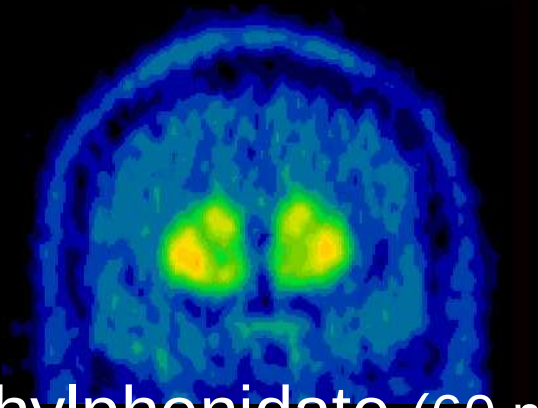
Medium Spiny GABA neuron of striatum



more dopamine = less [11C]raclopride binding

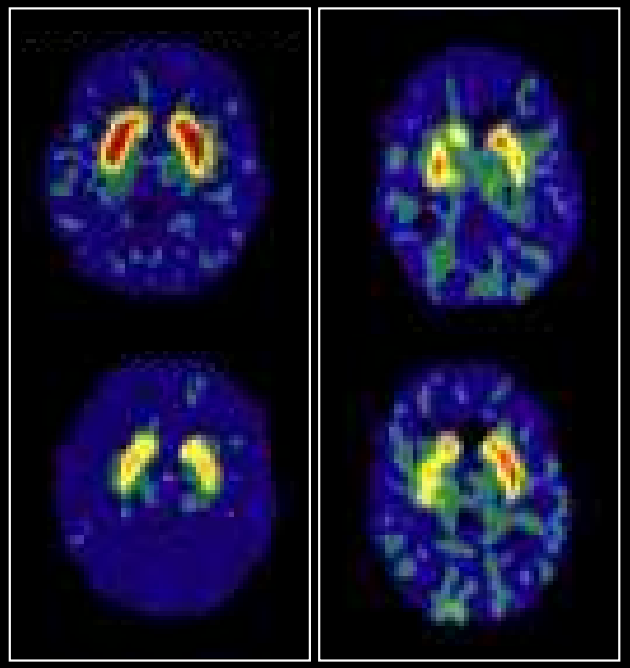


Baseline



Methylphenidate (60 mg PO)

Dopamine transmission in cocaine dependence



Volkow et al. 1997 Nature

The cocaine dependent subject has little change in [11C]raclopride binding after methylphenidate = low synaptic dopamine signalling.

The decrease in [11C]raclopride binding in the control subject = increased dopamine in the synapse

Dopamine: correlation with cocaine seeking behavior

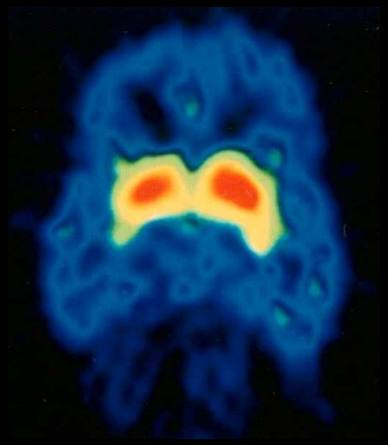
Methods:

- Cocaine dependent subjects hospitalized 3 weeks (n= 24, 39 ± 3 yrs, 19M/5 F)
- Chronic (years = 16.1 ± 4.4) and heavy (280 ± 108 $/wk) users
- Non-treatment seeking
- Healthy control comparison group (n= 24, 39 ± 3 yrs,19M/5 F)

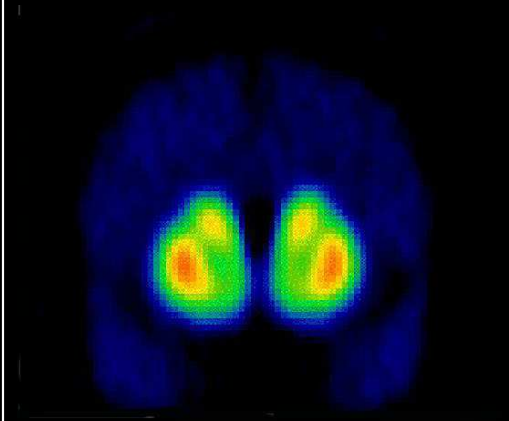
- PET scans performed with [^{11}C]raclopride - before and after 0.3 mg/kg amphetamine (similar to methylphenidate challenge) - to measure dopamine release (synaptic dopamine signaling)
  - CD subjects after 2 weeks abstinence
  - HC scanned as outpatients

Following the PET scans, the cocaine dependent subjects performed cocaine self-administration sessions - to investigate the correlation between neurobiology and drug taking

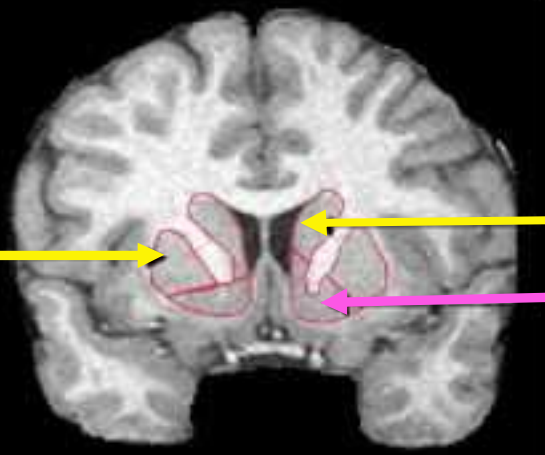
PET Methods: Striatal Subdivisions



Low Resolution PET

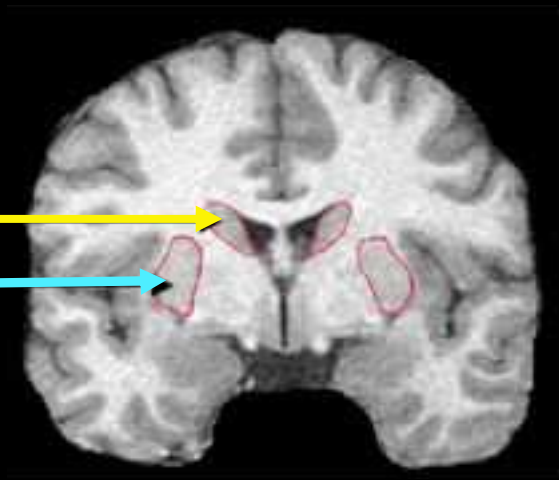


High Resolution PET



Rostral to Anterior Commissure (AC) - 6mm

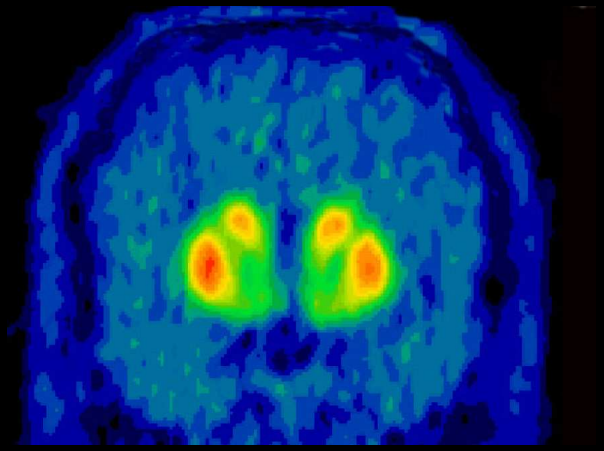
Motivation/Reward
Drug use



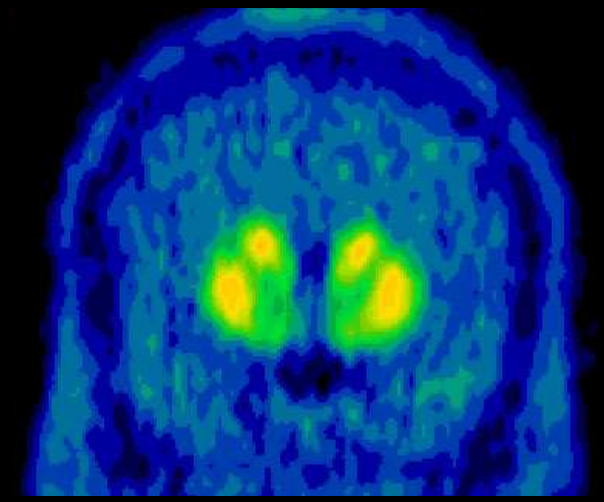
Caudal to Anterior Commissure (AC) - 3mm

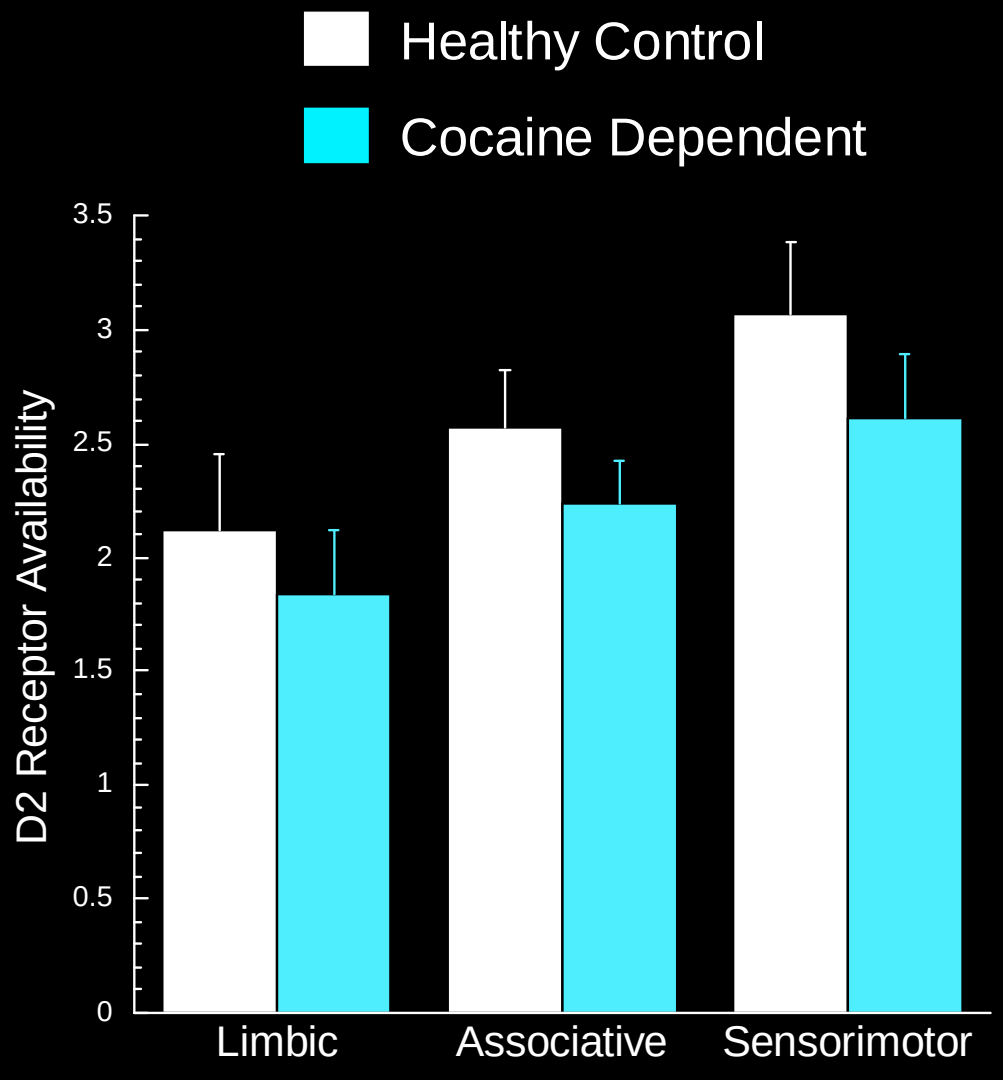
Results: Dopamine D2/3 receptors

Healthy Control



Cocaine Dependent

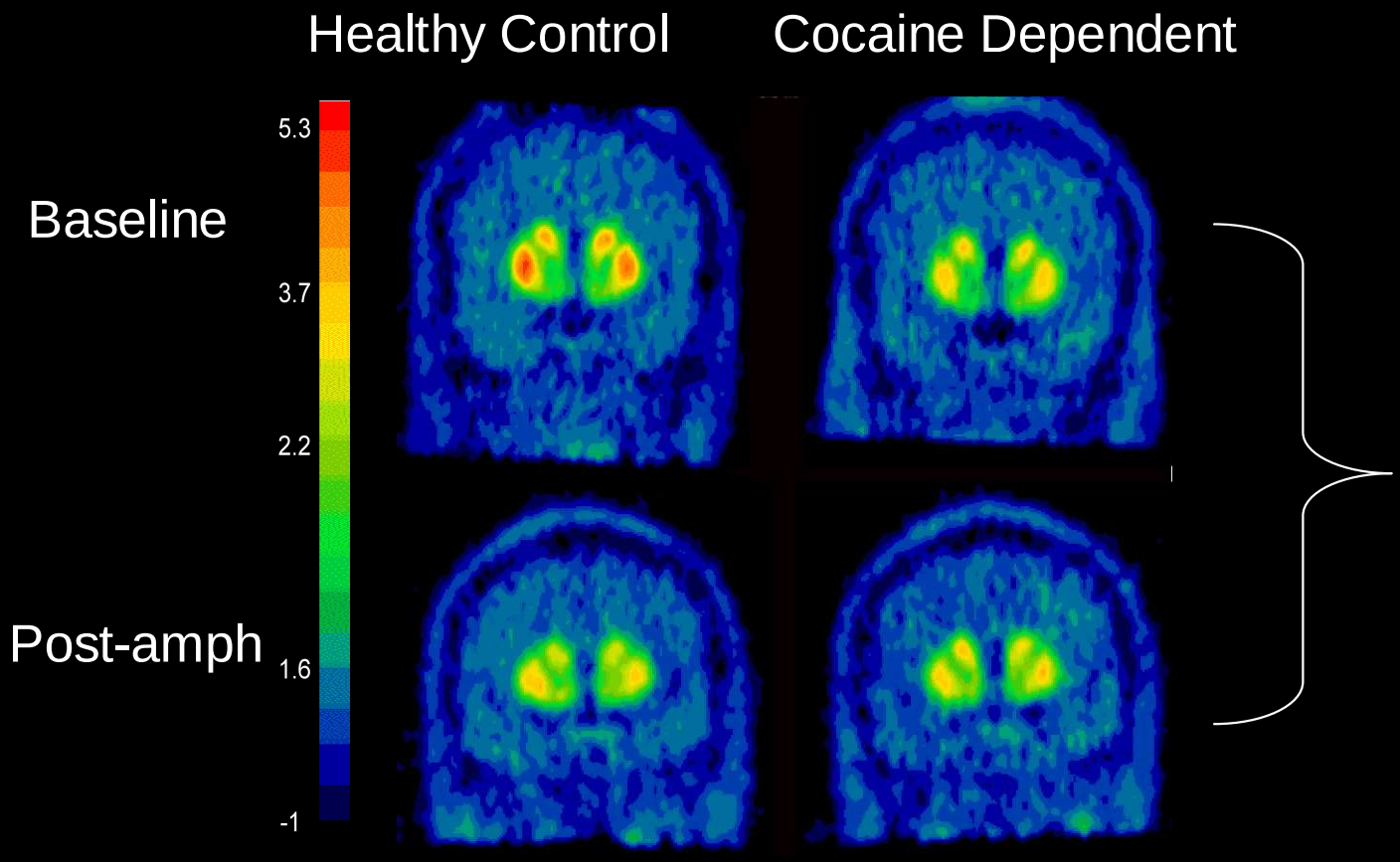




Difference: 16.5% 14.7% 18.4%

Martinez et al, 2004 Neuropsychopharm

Synaptic dopamine in cocaine dependence

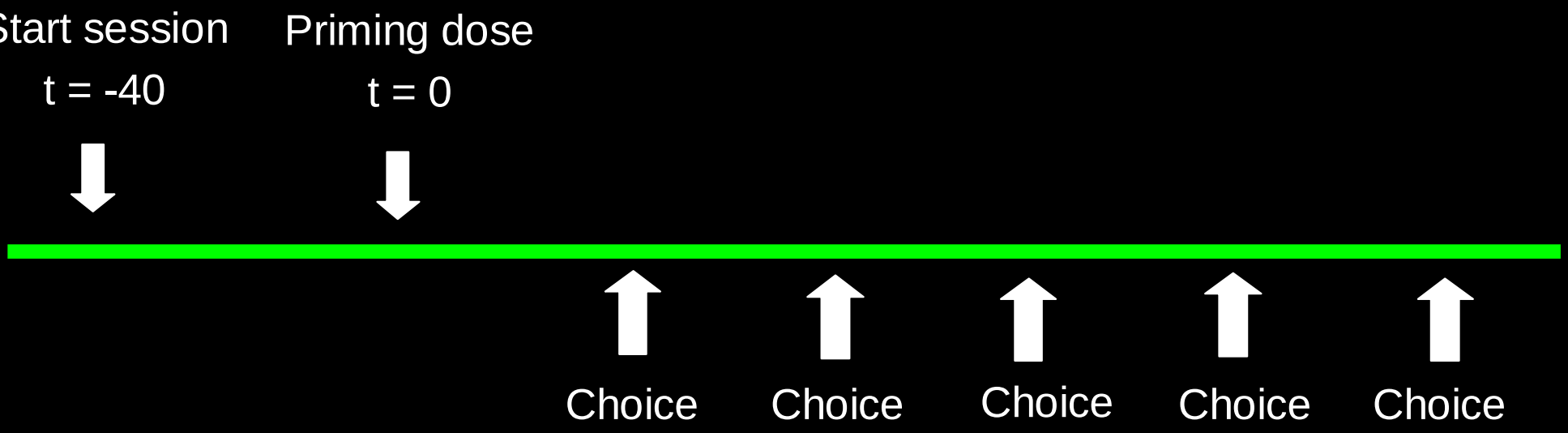


Comparison of pre- and post-amphetamine: CD subjects had little difference in signal between the two scans = blunted dopamine release (decreased synaptic dopamine signaling)

	Control	Cocaine	p
Limbic	-12.4 ± 9.0%	-1.3 ± 7.3%	<0.001
Associative	-6.9% ± 5.7%	-2.7% ± 6.8%	0.027
Sensorimotor	-14.1 ± 7.8%	-4.4 ± 7.7%	0.0001

Methods: Laboratory Model of Relapse

Cocaine self-administration sessions: Non-treatment seeking cocaine dependent subjects given the choice between low dose smoked cocaine vs $5 USD (€ 4.2)



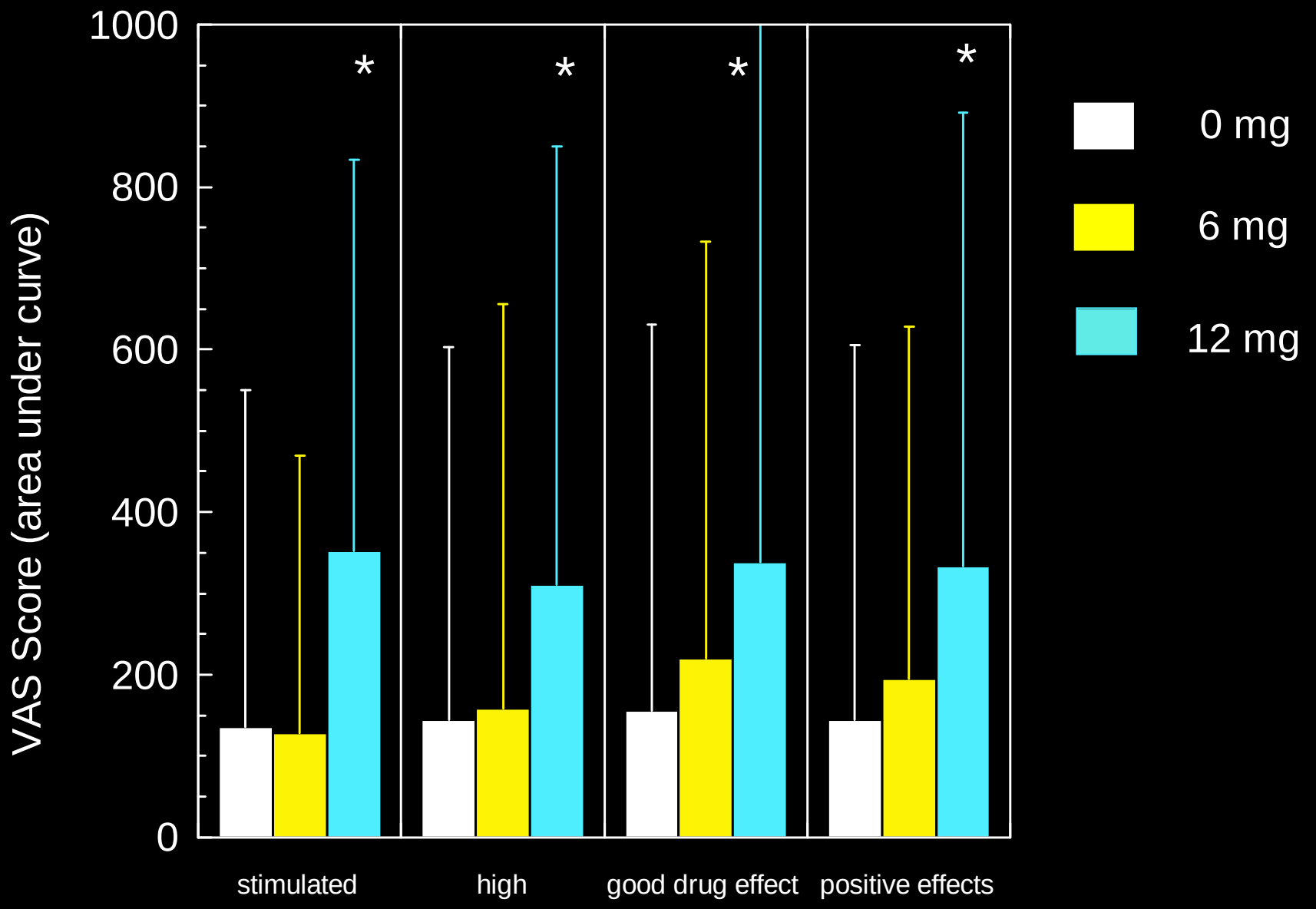
Each subject performed 3 choice sessions: with 0, 6, 12 mg (1 session each dose)

1st dose (t = 0) is priming dose

5 choices at 14 min intervals (dose vs $5 voucher)

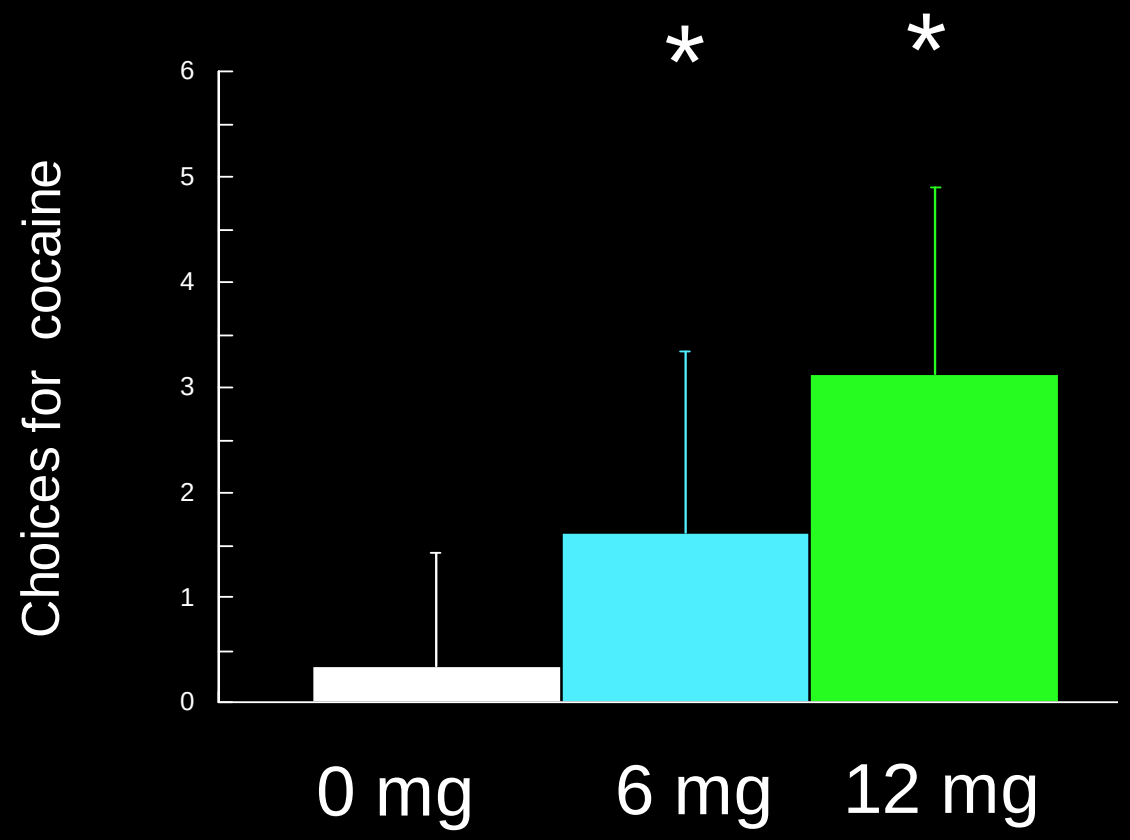
Self-administration sessions serve as a model of relapse: subject given choice of cocaine vs money following a priming dose -

Positive effects of cocaine



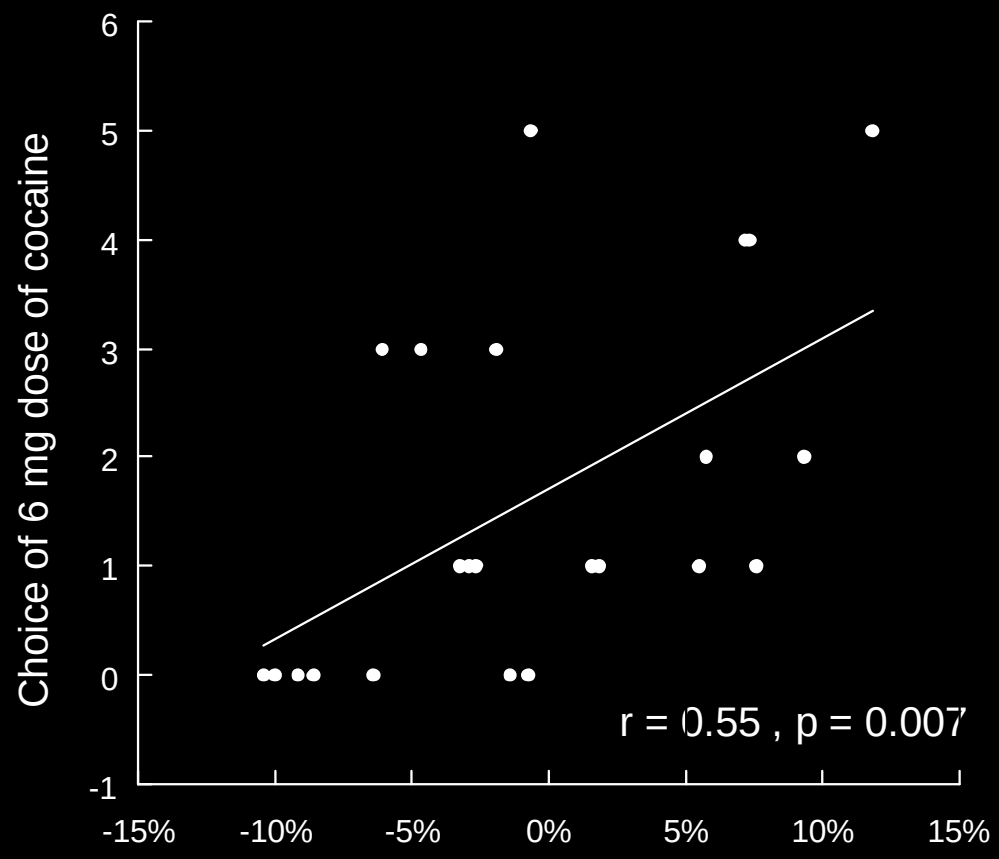
Subjective effects of 6 mg not different than placebo

Cocaine self-administration results - choice for cocaine

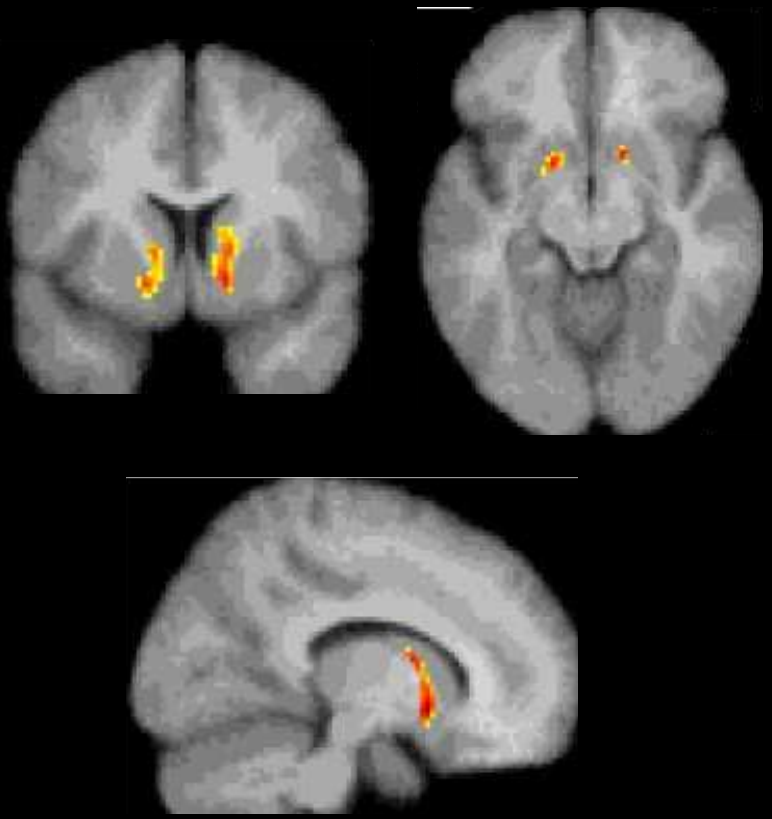


Even though the positive subjective effects of the 6 mg smoked dose of cocaine were the same as the 0mg dose, subjects still chose the 6 mg dose over $5 USD (€ 4.2).

Synaptic dopamine and choice for cocaine



Change in [11C]raclopride binding due to methylphenidate administration



In the limbic striatum: correlation between choice for cocaine and dopamine release (change in synaptic dopamine)

Results:

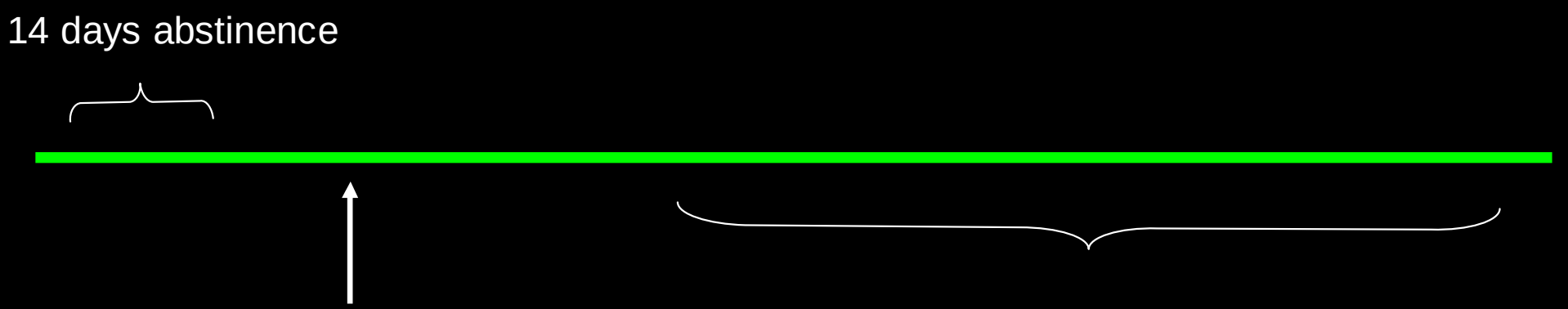
1) This data showed that dopamine release (synaptic dopamine signaling) in the limbic striatum predicted the choice to self-administer cocaine: low dopamine transmission = more choices for cocaine over money

2) Importantly, $5 >> 6 mg smoked cocaine (in NYC). Decreased dopamine = lack of response to a reward other than cocaine.

3) Is this a model for relapse? Does this finding apply to treatment seeking subjects in the clinic?

4) Can dopamine transmission in the limbic striatum predict the response to a treatment that uses alternative rewards to replace cocaine use?

Treatment: CM/CRA



- Participants attend the clinic 3 days a week for 12 weeks
- Each visit: urine tested for cocaine, subjects earn money for negative urine = contingency management (CM) - range $0 - $977.50 (€ 820) over 12 weeks.
- Therapy: Community reinforcement approach (CRA) which seeks to replace cocaine use with personal goals and social/vocational skills.
- This treatment has been used previously in human studies of cocaine dependence with success (Higgins ST, Arch Gen Psychiatry. 2003)

Methods:

Treatment seeking cocaine dependent subjects (n= 24, 31 ± 7 yrs,22M/3 F)

Using for 14.3 ± 7.2 years and spending 337 ± 204 $/week

PET scans performed with [^{11}C]raclopride :

1. Measure dopamine D2/3 receptors
2. Measure dopamine release / synaptic dopamine transmission (Scans performed with [11C]raclopride before and after 60 mg oral methylphenidate)

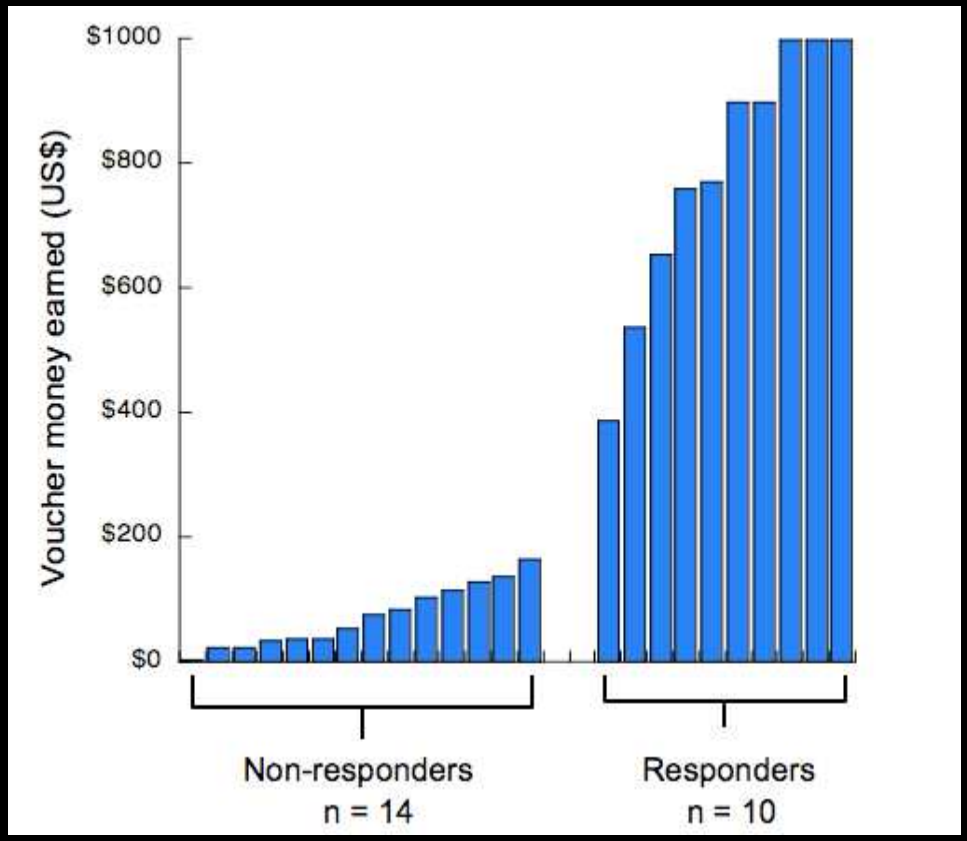
Response to treatment - measured as voucher money earned. More continuous abstinence results in more money earned - range $0 to $977.50 (€ 820)

Hypothesis:

Dopamine receptors and synaptic dopamine will be lower in cocaine dependent subjects who fail to respond to treatment compared to the subjects who respond to treatment

Less dopamine transmission in the limbic striatum = greater likelihood of relapse

Results: Response to treatment



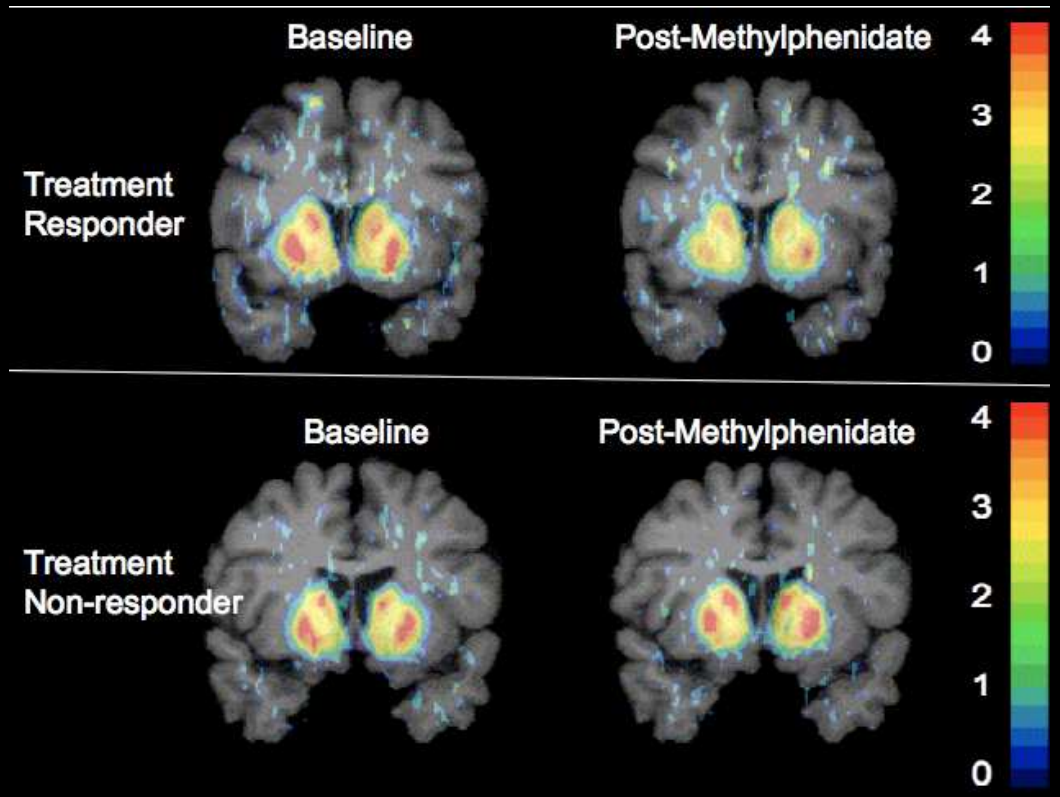
Money earned for cocaine-negative urine samples

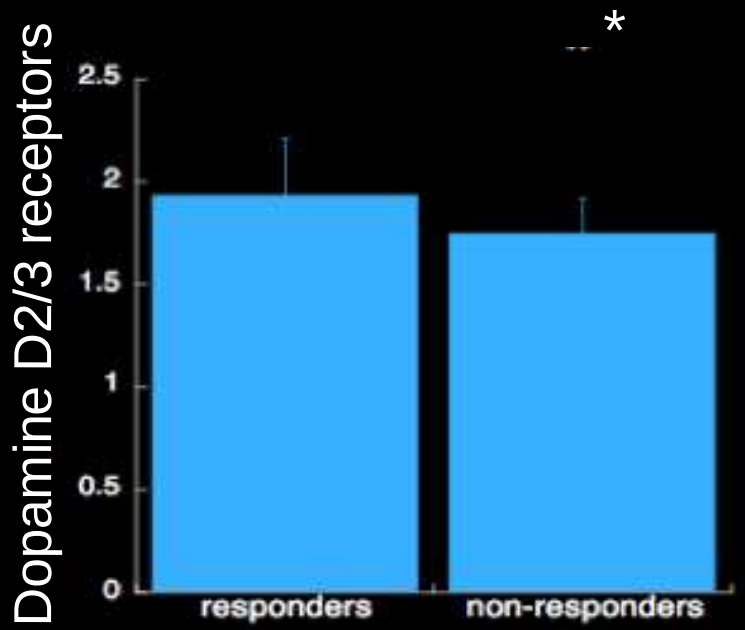
Subjects divided into treatment responders (n=10) vs non-responders (n=14)

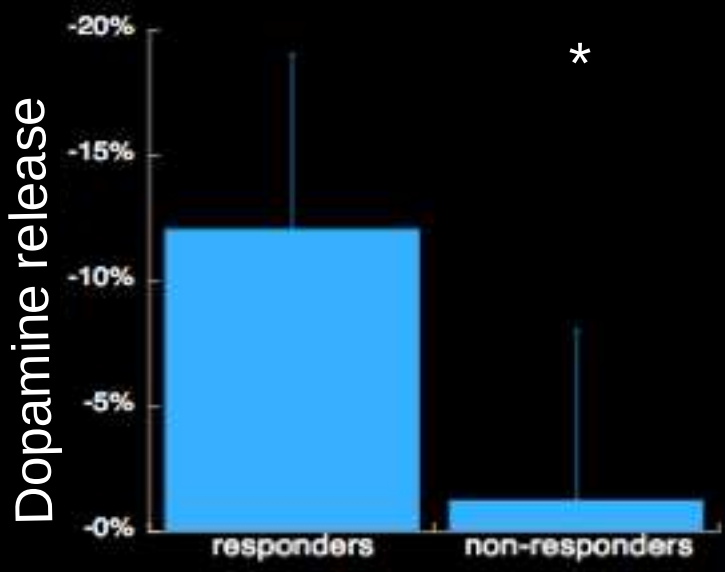
Treatment responders: all 10 had attained abstinence at 12 weeks, and had continued abstinence after 6 months

Non-responders: none reported abstinence at 12 weeks or 24 weeks

Results: Treatment response







Treatment responders had higher dopamine D2/3 receptors (10%) and higher synaptic dopamine release in the limbic striatum

Can PET imaging improve treatment?

This study shows that the cocaine dependent subjects who failed treatment:

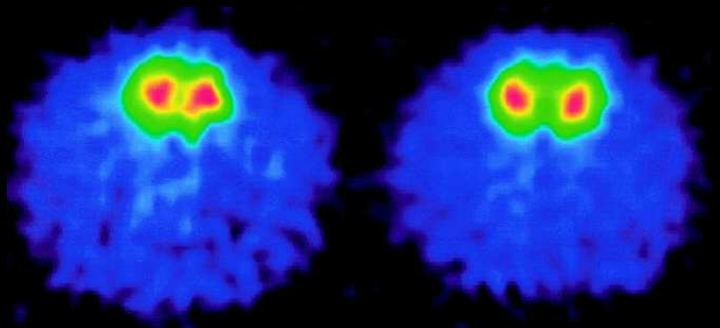
1) Lower dopamine D2/3 receptors in the limbic striatum
2) Lower dopamine release (lower synaptic dopamine signaling)

Low dopamine = failure to respond to a reward other than cocaine

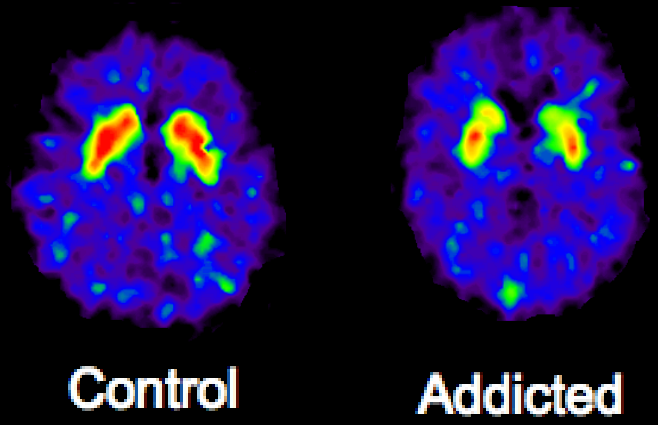
Can we convert non-responders to treatment responders?

1. By increasing dopamine D2/3 receptors?
2. Or increasing dopamine release from the midbrain dopamine neurons
   - and increase the patients response to reward OTHER than cocaine?

Increasing striatal dopamine receptors



(Thanos et al. 2001 2004)

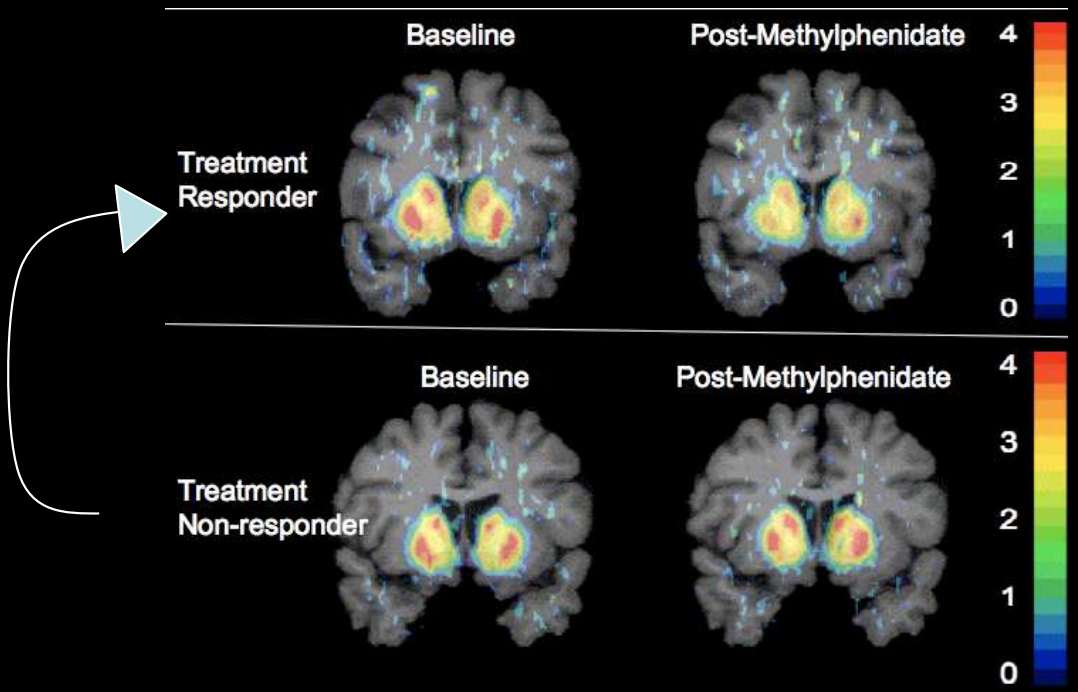


(Volkow et al. 1998)

- Alcohol preferring rats have lower dopamine D2 receptors compared to non-preferring rats.
- Adenovirus- induced increase in dopamine D2 receptors in preferring rats reduced their alcohol intake .
- Similar results in cocaine exposed rodents: adenovirus-induced increases striatal dopamine receptors resulted in less cocaine self-administration.

- However - not a current treatment (requires injection of virus into the brain)

Increase synaptic dopamine ?



Medication to treat cocaine dependence have not shown great success. Many of these studies have used medications that, like methylphenidate, to increase synaptic dopamine -

which may have little effect in treatment refractory cocaine dependent subjects

Schmitz et al (2008) reported that treatment of cocaine abusers with levodopa/carbidopa (for Parkinson's disease) and contingency management - resulted in a greater response to treatment compared to placebo.

This suggests that the combination of pharmacology to improve dopamine transmission combined with treatment that uses positive alternatives to cocaine use may provide the best approach for the treatment of cocaine addiction.

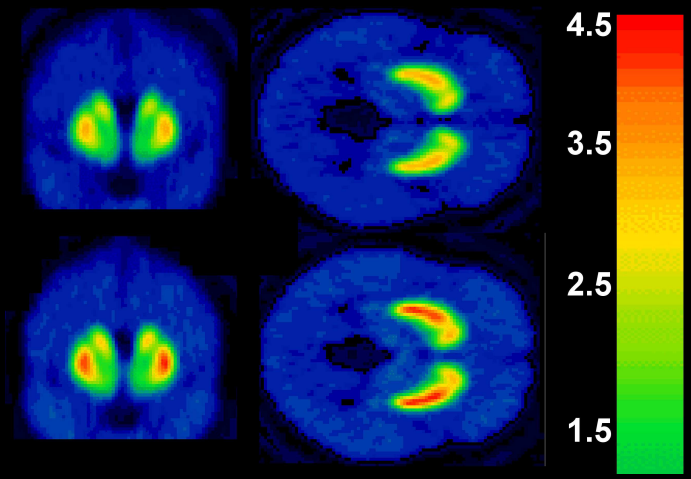
We are also using PET to find other medications that will increase dopamine in refractory patients.

Dopamine transmission in alcohol dependence

Dopamine D2/3 receptors

Alcohol Dependent

Healthy Control



Alcohol dependence is associated with decreased dopamine D2/3 receptors in the striatum (Hietala et al, Volkow et al, Heinz et al, Martinez et al,.)

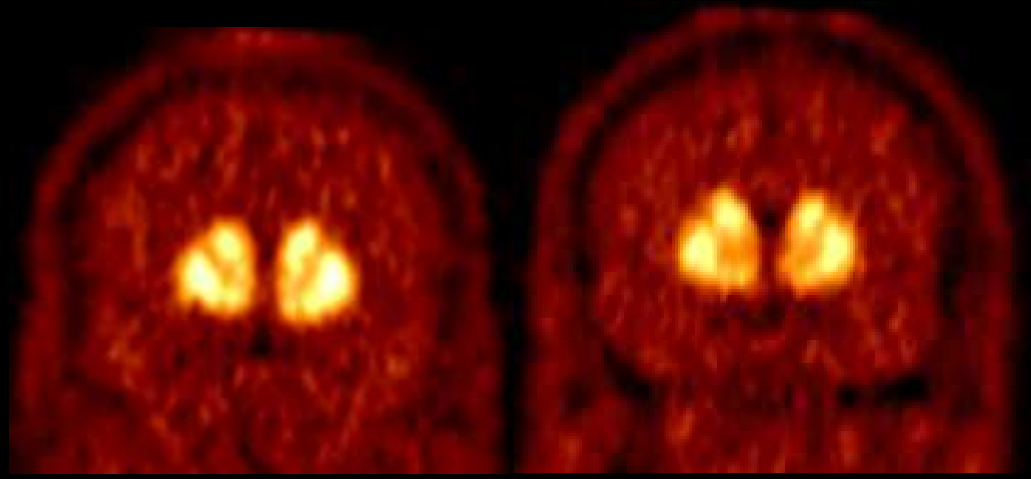
Dopamine release

	Control	Alcohol	p
Limbic	-13.0 ± 8.8%	-5.2% ± 3.6%	0.004
Associative	-6.7% ± 5.4%	-4.6% ± 5.8%	0.32
Sensorimotor	-13.7 ± 7.5%	-12.3 ± 7.3%	0.59

Dopamine release is decreased in the ventral striatum (Martinez et al, Volkow et al).

Dopamine transmission in heroin dependence

Dopamine D2/3 receptors



Healthy Control Heroin Dependent

Heroin dependence was associated with a decrease in dopamine D2/3 receptors in the ventral and dorsal striatum

Dopamine release

	Control	Heroin	p
Limbic	-12.1 ± 9.8%	- 4.1% ± 6.6%	0.02
Assoc	-8.7% ± 6.7%	3.9% ± 6.5%	<0.001
SMotor	-16.0 ± 9.5%	- 4.7 ± 8.2%	<0.001

Synaptic dopamine is also decreased in the striatum

While studies have shown that CM/CRA can be an effective treatment, it is unknown if dopamine predicts response to treatment

Colleagues and Collaborators

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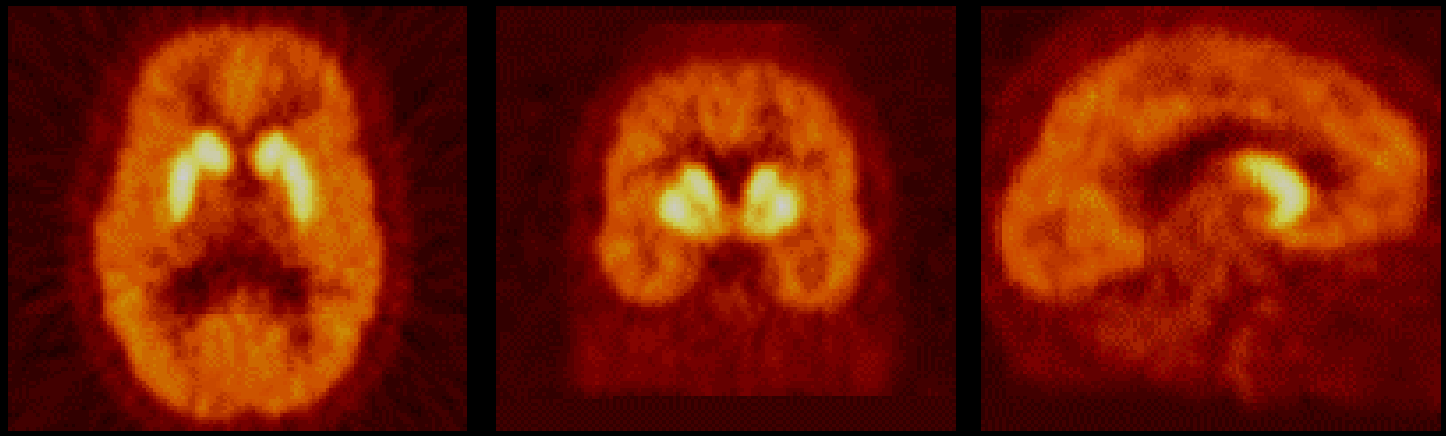
D1 receptors in cocaine dependence

Twenty cocaine dependent subjects scanned with [^{11}C]NNC 112

- Subjects scanned after 14 days inpatient abstinence
- D1 receptor BP_{ND} (= specific binding/non-specific binding)
- 20 healthy controls scanned as a comparison group
- After PET scans: cocaine self-administration sessions

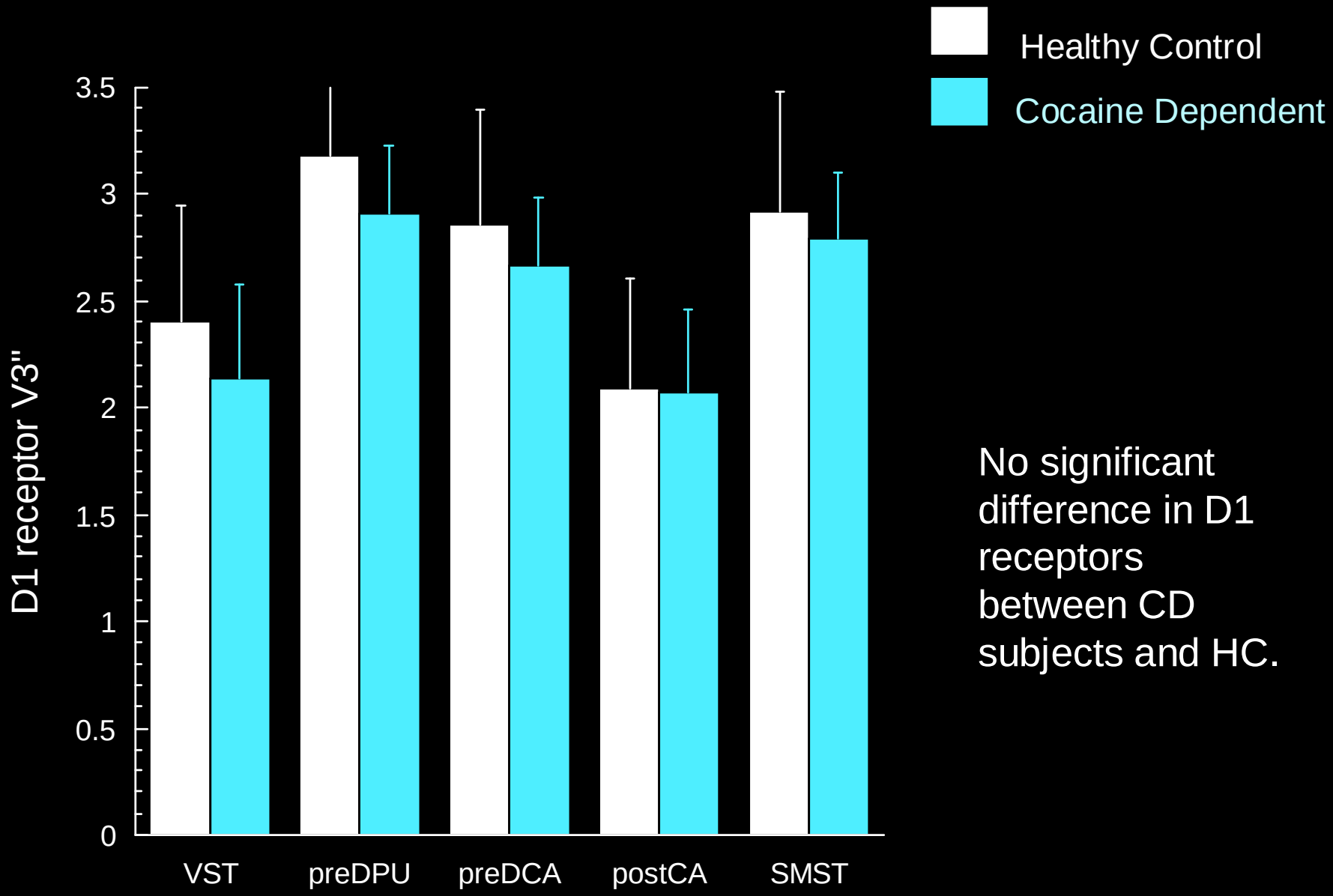


Hypothesis:

Cocaine dependence is associated with a decrease in D1 receptors

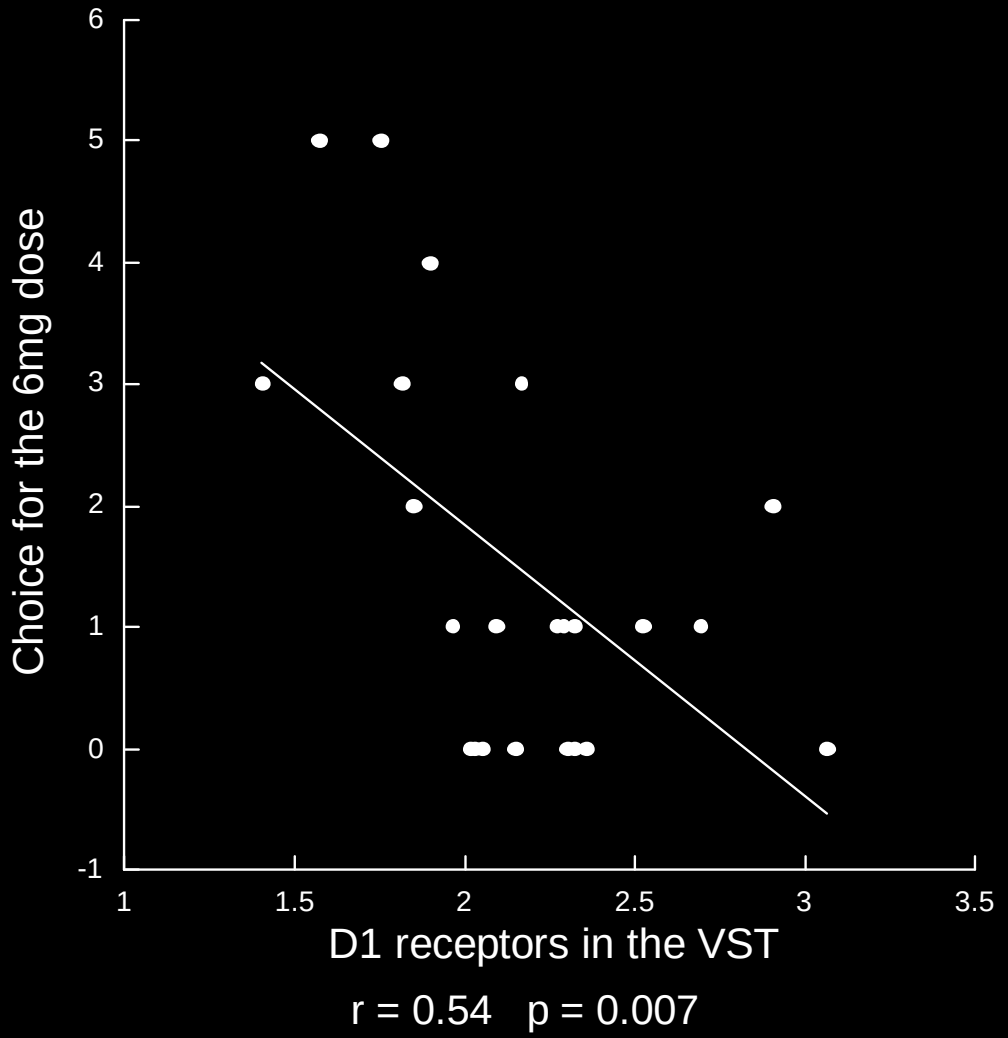
D1 receptor BP would correlate with the choice to self-administer cocaine

Results: D_1 Receptors in Cocaine Dependence



No significant difference in D1 receptors between CD subjects and HC.

D1 receptors and choice of cocaine



Post Hoc analysis of other ROI

Region	r	p
SMST	0.22	0.32
AST	0.39	0.08

Lower D1 receptors - more choices for cocaine