Moleculair beeldvormend hersenonderzoek:

wat heeft het ons geleerd over verslaving?

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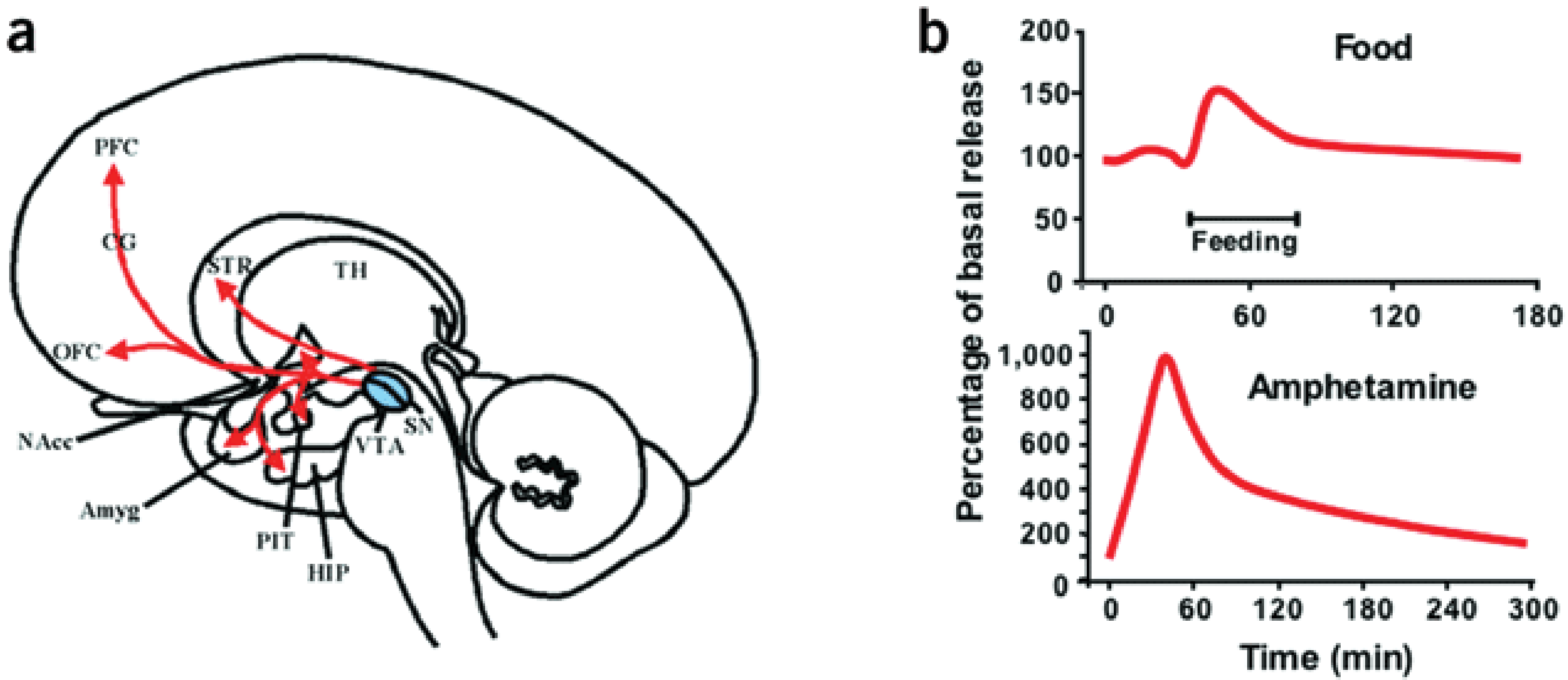
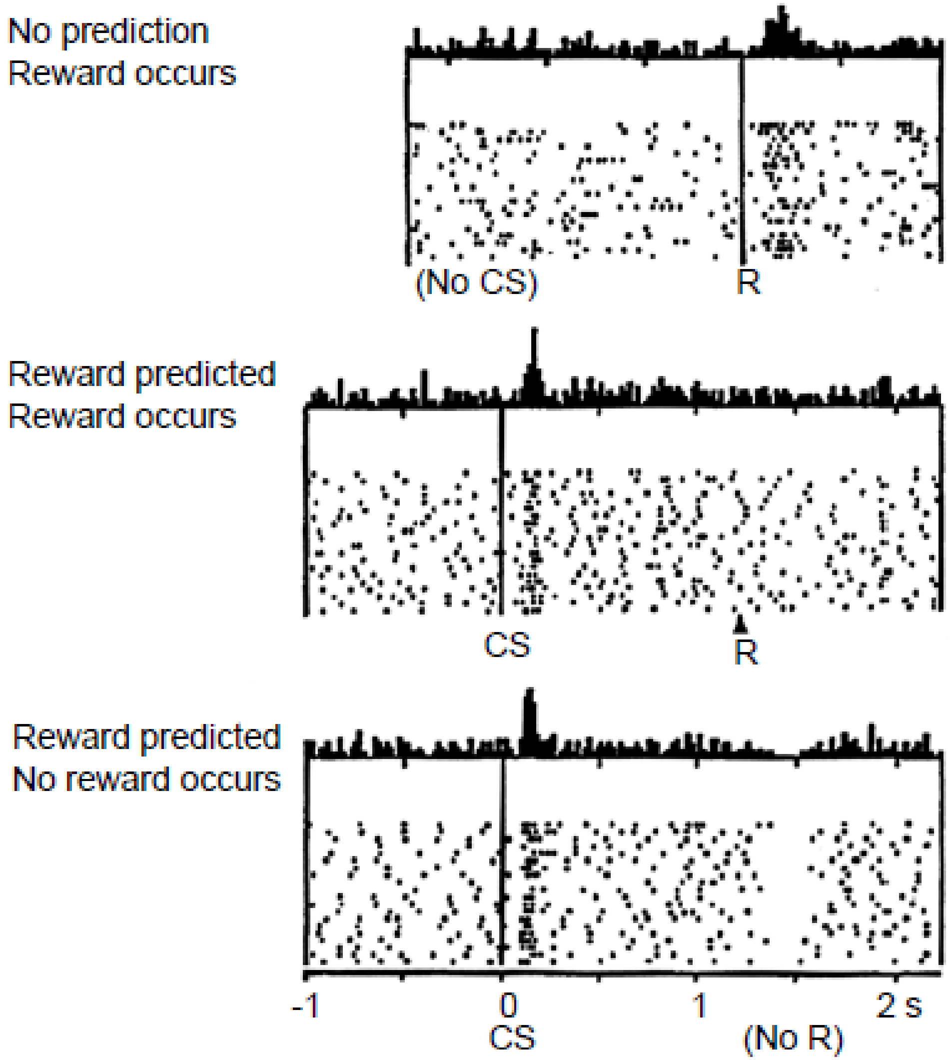
Disclosure belangen spreker

(potentiële) belangenverstrengeling	Zie hieronder
Voor bijeenkomst mogelijk relevante relaties met bedrijven	Bedrijfsnamen
• Onderzoeksgeld • Consultant	• GE Healthcare

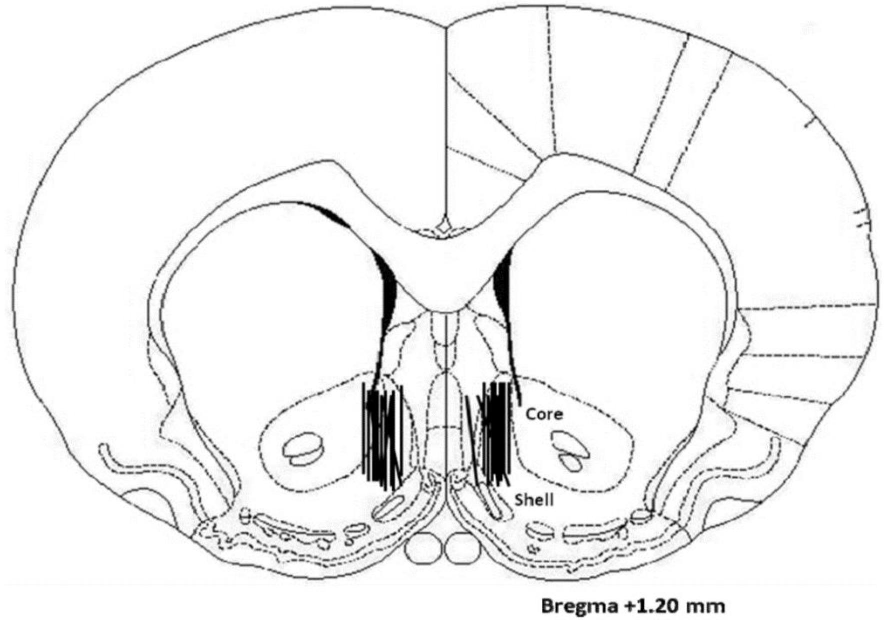
Volkow and Wise, *Nature Neurosc* 2005

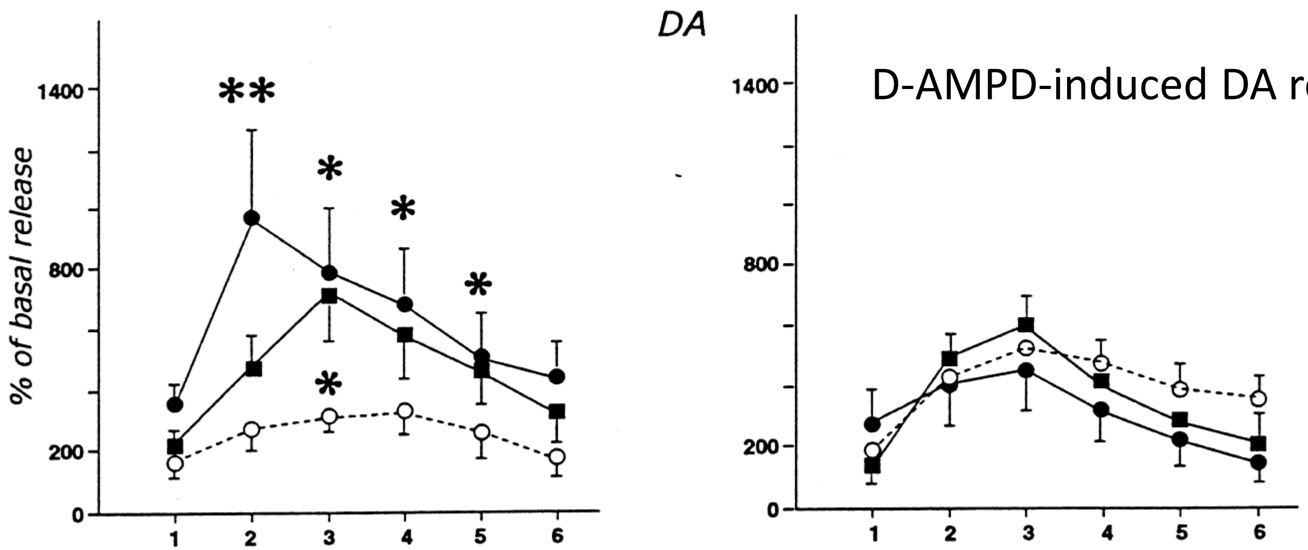


Do dopamine neurons report an error in the prediction of reward?



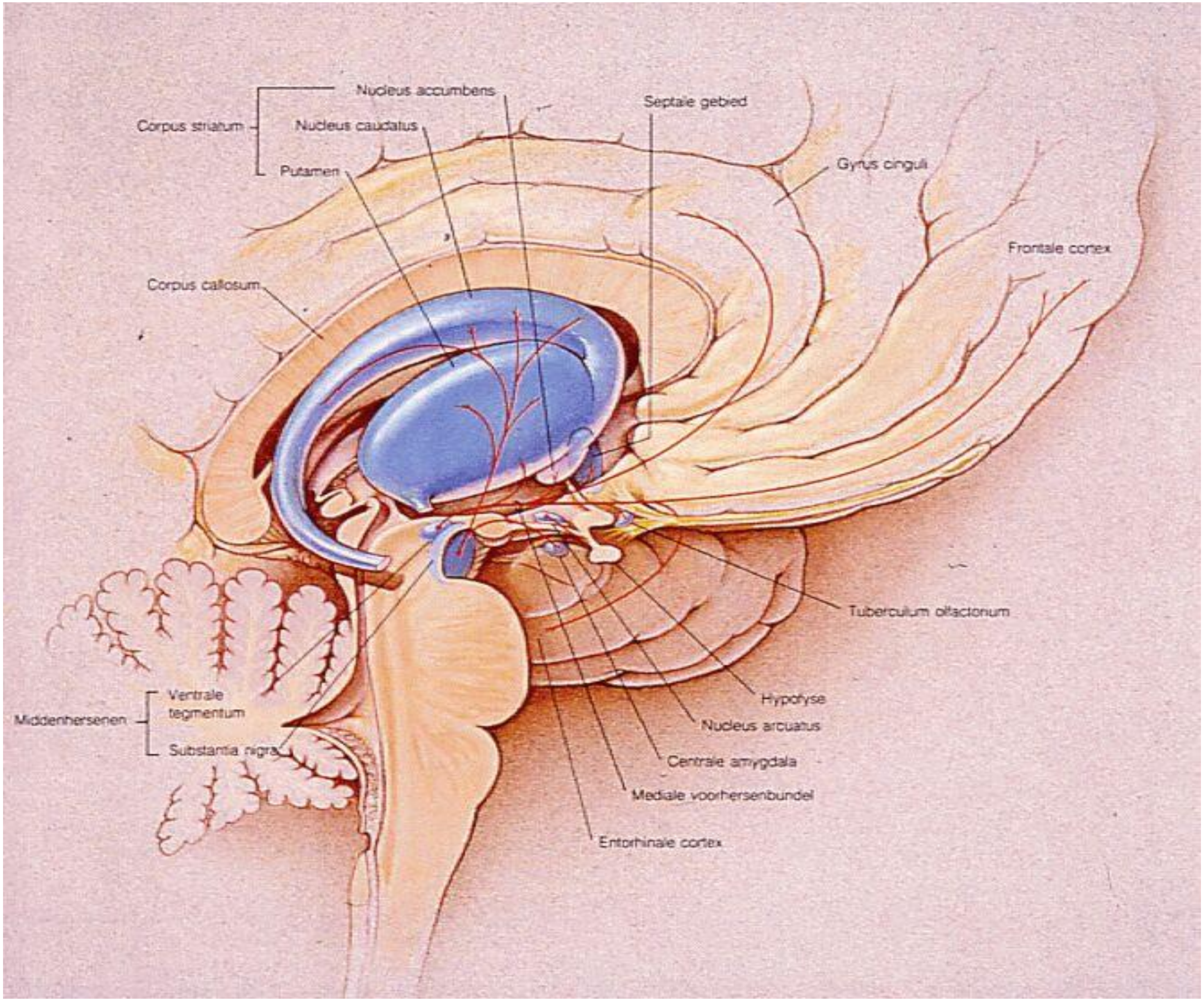
Schultz et al., *Science* 1997





D-AMPD-induced DA release in rats

Rada et al., *Brain Sci* 2012; Laviola et al., *Pharmacol Biochem Behav* 2001



Nucleus accumbens
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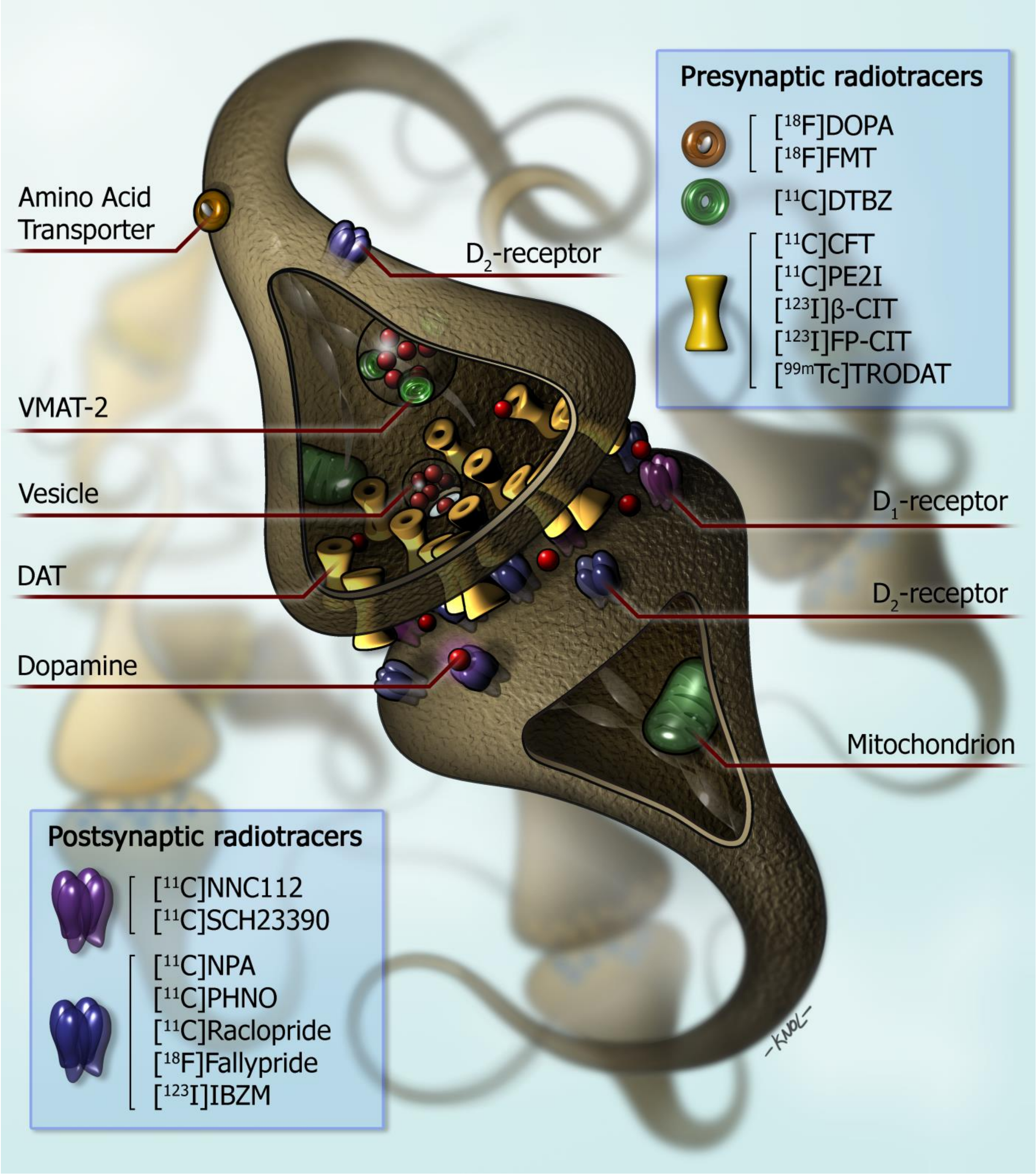


Booij et al., 2014

DA release: amphetamine challenge imaging

Breier et al., *PNAS* 1997

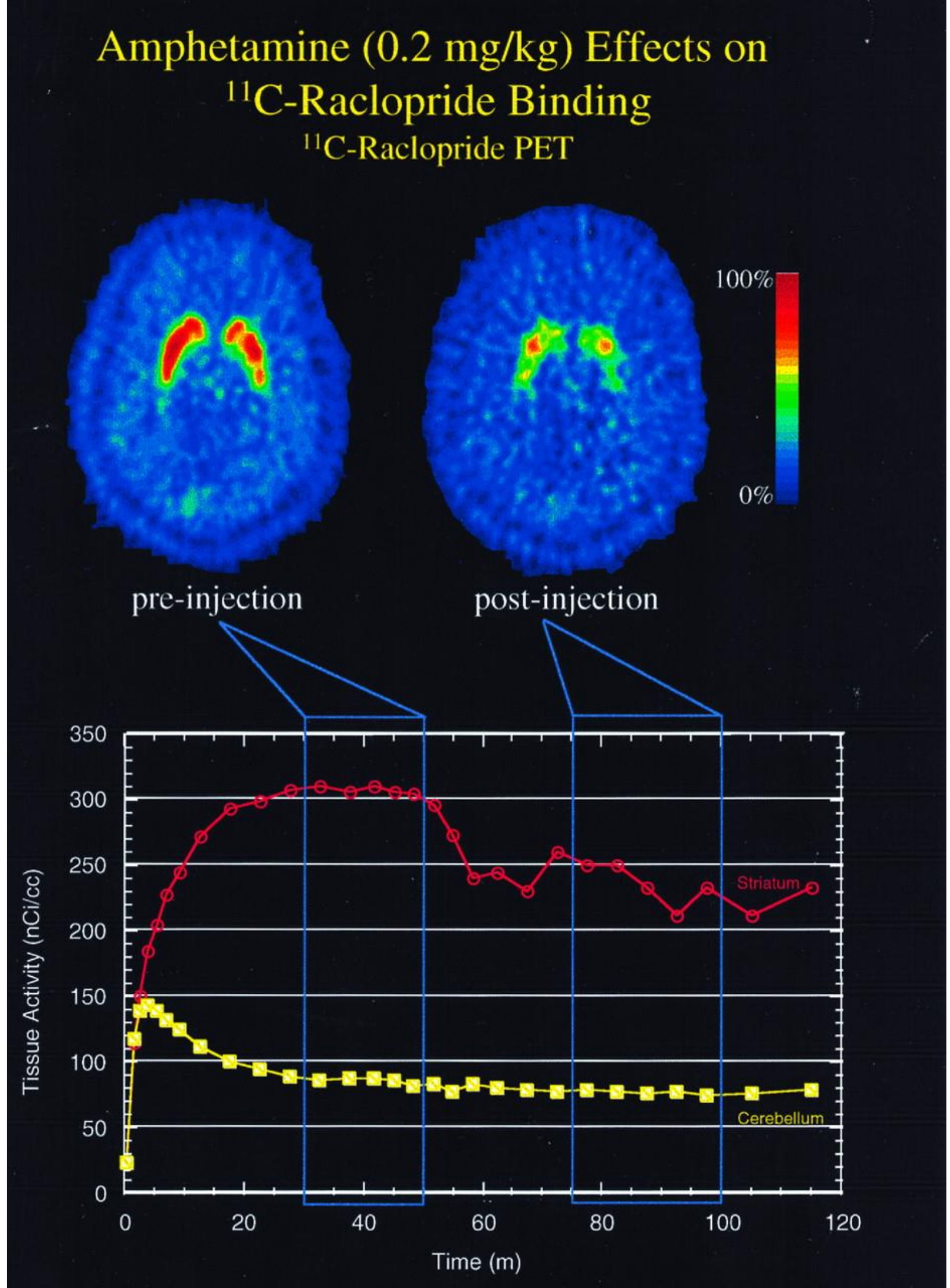


Table 1. Effects of two doses of amphetamine (0.2 and 0.4 mg/kg) on striatal extracellular dopamine levels (nmol/liter) in four Rhesus monkeys

Monkey	Baseline	0.2 mg/kg	% baseline	0.4 mg/kg	% baseline
1	5.9	43.6	+632.2	114.4	+1820.5
2	4.6	51.6	+1006.9	120.0	+2470.7
3	6.6	14.4	+116.5	65.4	+881.3
4	4.5	8.3	+84.1	17.6	+288.5
Mean (±SEM)	5.4 (±0.5)	29.5 (±10.6)	+459.9* (±221.4)	79.3 (±23.9)	+1365.2* (±485.0)

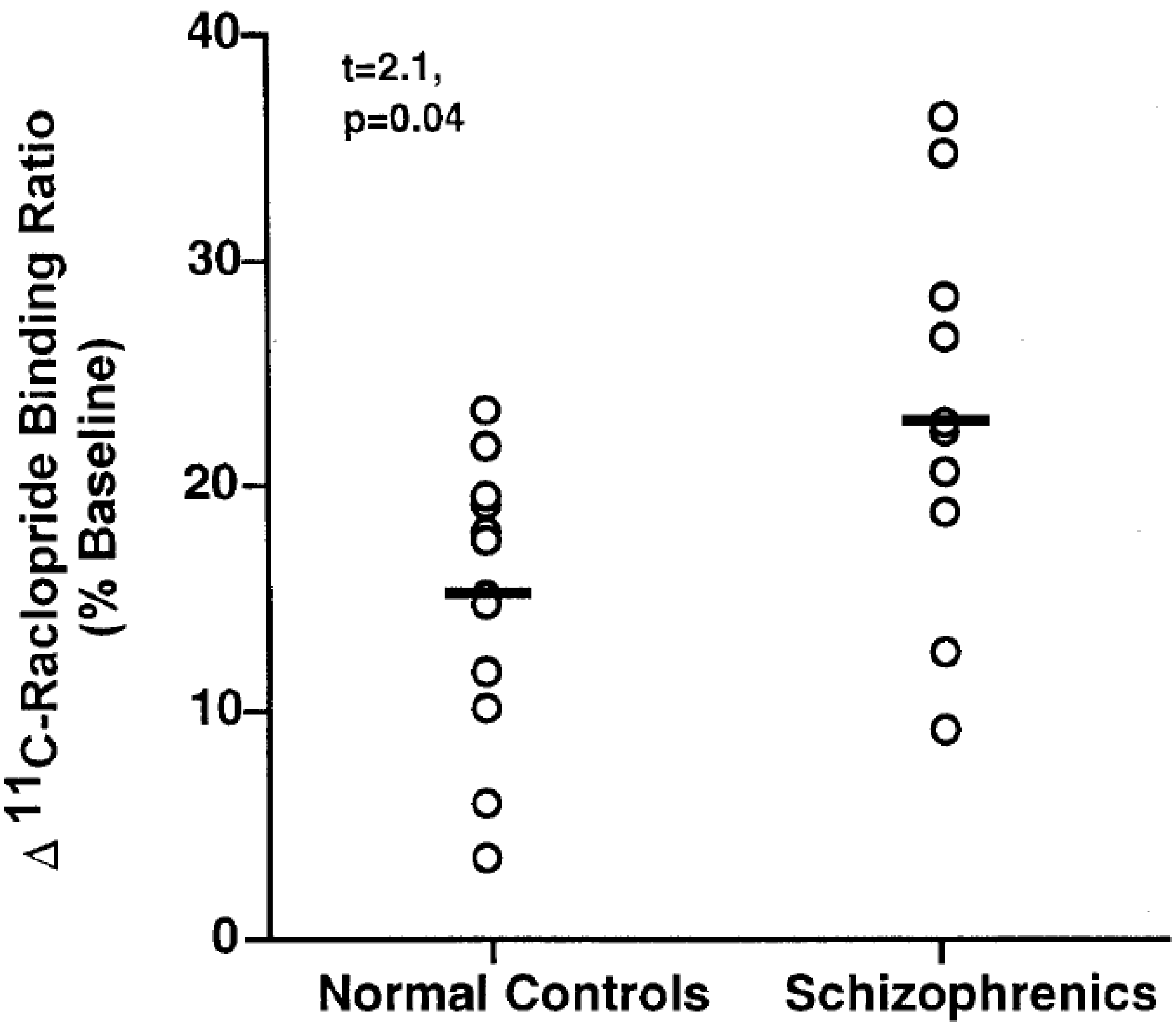
*t = 3.3, P = 0.045; % baseline, 0.2 mg/kg vs. % baseline, 0.4 mg/kg.

Table 2. Effects of two doses of amphetamine (0.2 and 0.4 mg/kg) on [^{11}C]raclopride binding ratios (striatum/cerebellum −1) in four Rhesus monkeys

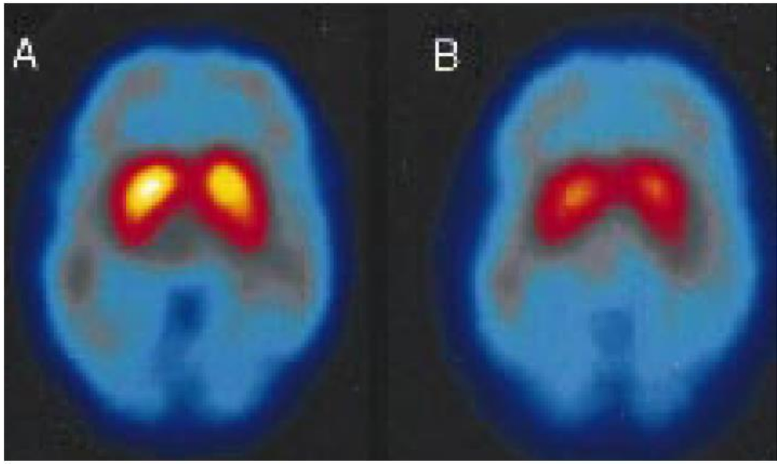
Monkey	Baseline	0.2 mg/kg	% baseline	Baseline	0.4 mg/kg	% baseline
1	1.9	1.6	−17.5	1.8	1.2	−33.3
2	2.0	2.1	+4.9	1.9	1.8	−7.8
3	1.7	1.4	−19.2	1.6	1.2	−25.5
4	2.3	2.1	−10.1	2.1	1.7	−18.4
Mean (±SEM)	2.0 (±0.1)	1.8 (±0.1)	−10.5* (±5.5)	1.8 (±0.101)	1.4 (±0.1)	−21.3* (±5.4)

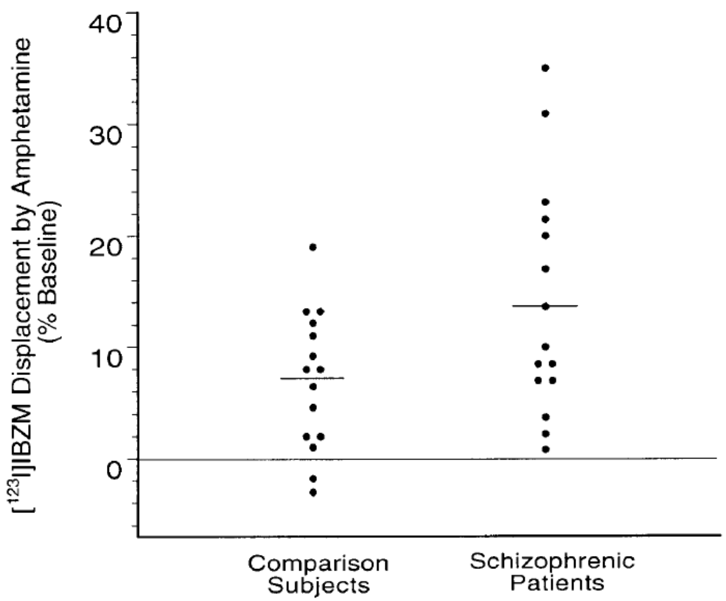
*t = 5.0, P = 0.015; % baseline, 0.2 mg/kg vs. % baseline, 0.4 mg/kg.

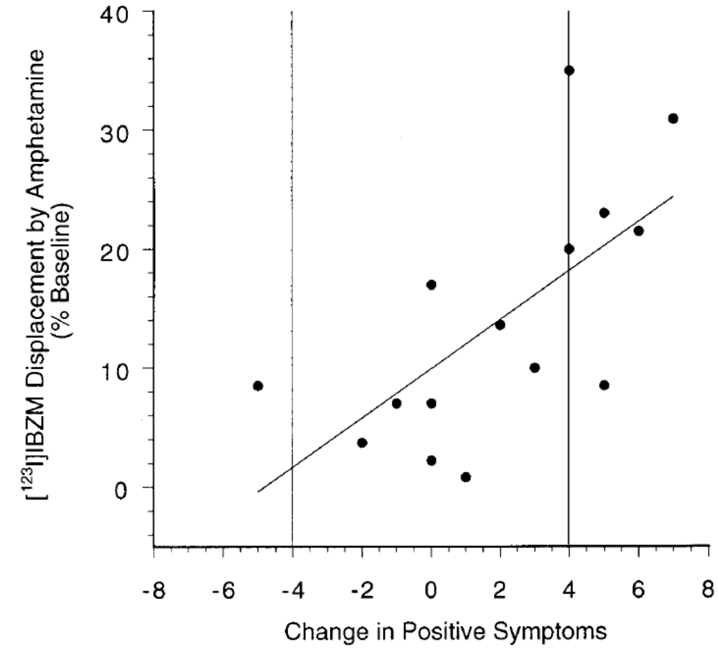
Breier et al., *PNAS* 1997



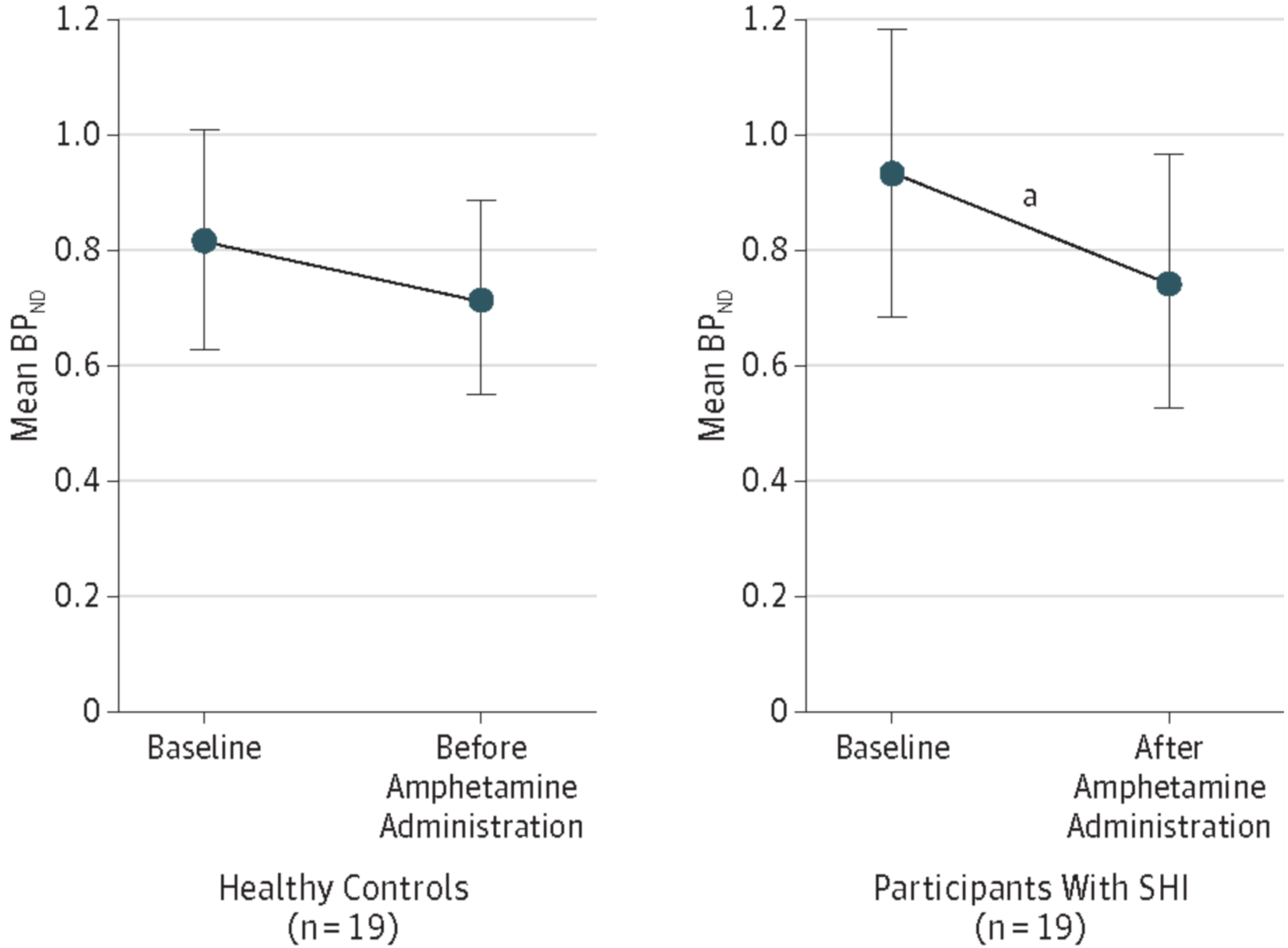
Breier et al., *PNAS* 1997







Abi-Dargham et al.,
Am J Psychiatry 1998



Gevonden et al., *JAMA Psychiatry* 2014

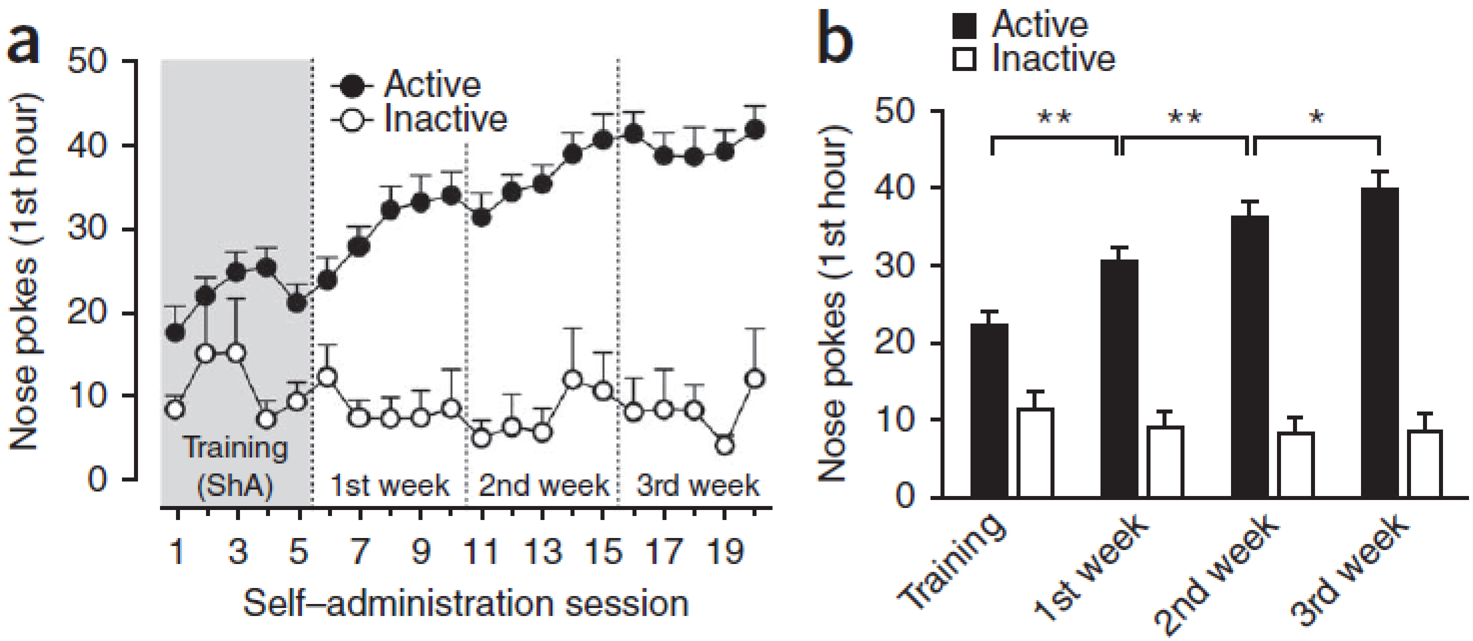
Dopaminergic dysfunction in cocaine users

Functional and Anatomical Subdivision	Healthy Subjects (N=24) Mean Change (%)	Healthy Subjects (N=24) SD	Cocaine-Dependent Participants (N=24) Mean Change (%)	Cocaine-Dependent Participants (N=24) SD	Group Difference (%)	p[a]
Limbic striatum (ventral striatum)	-12.4	9.0	-1.2	7.3	11.2	< 0.001
Associative striatum	-6.7	5.7	-2.6	6.6	4.1	0.03
Precommissural dorsal caudate	-4.6	6.2	-2.8	7.8	1.8	0.39
Precommissural dorsal putamen	-8.7	7.0	-1.0	6.5	7.7	< 0.001
Postcommissural caudate	-6.9	7.8	-6.3	10.7	0.6	0.82
Sensorimotor striatum: postcommissural putamen	-14.1	7.8	-4.3	7.5	9.8	< 0.001
Striatum	-9.5	5.9	-3.0	6.5	6.5	0.001

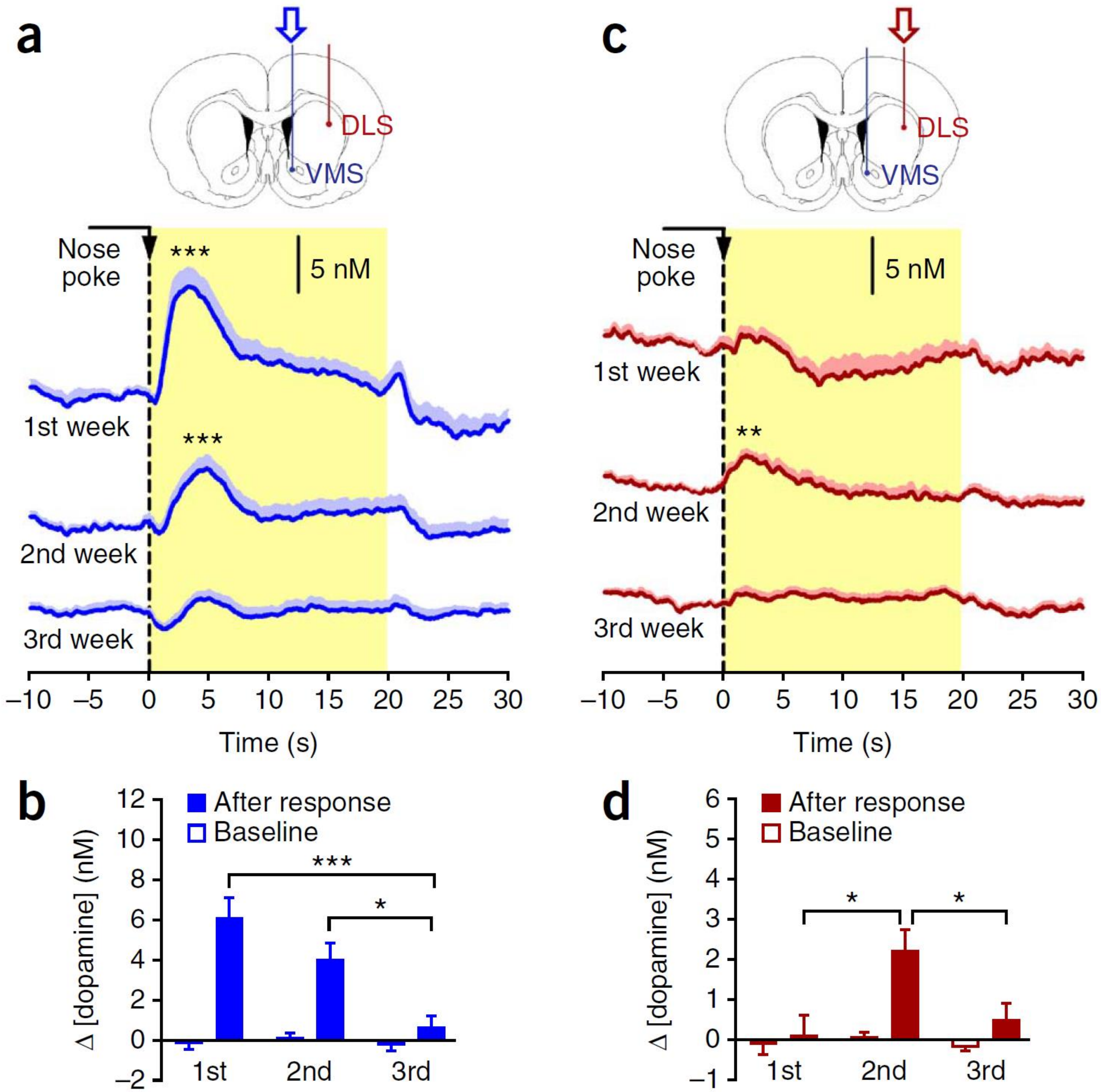
[a] Unpaired t test.

Martinez et al., *Am J Psychiatry* 2007

Excessive cocaine use in rats

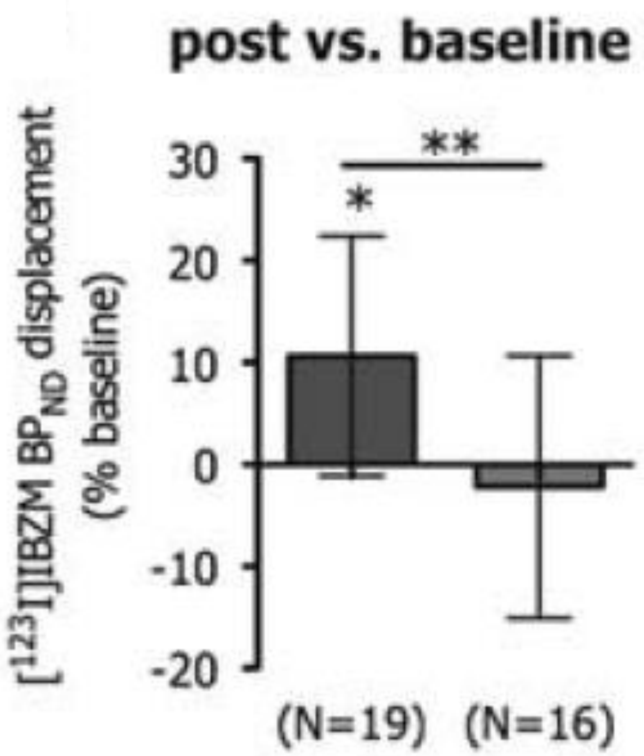


Willuhn et al., *Nature Neurosc* 2014



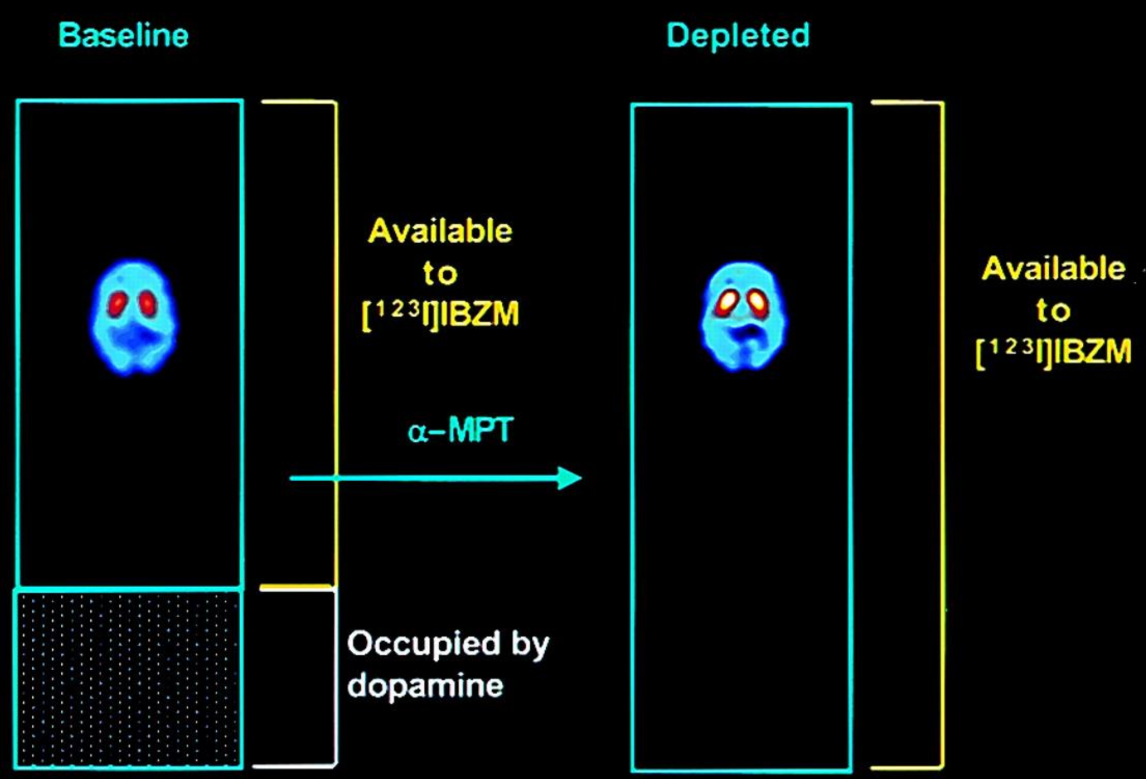
Willuhn et al.,
Nature Neurosc 2014

Dopaminergic dysfunction in dexamphetamine users

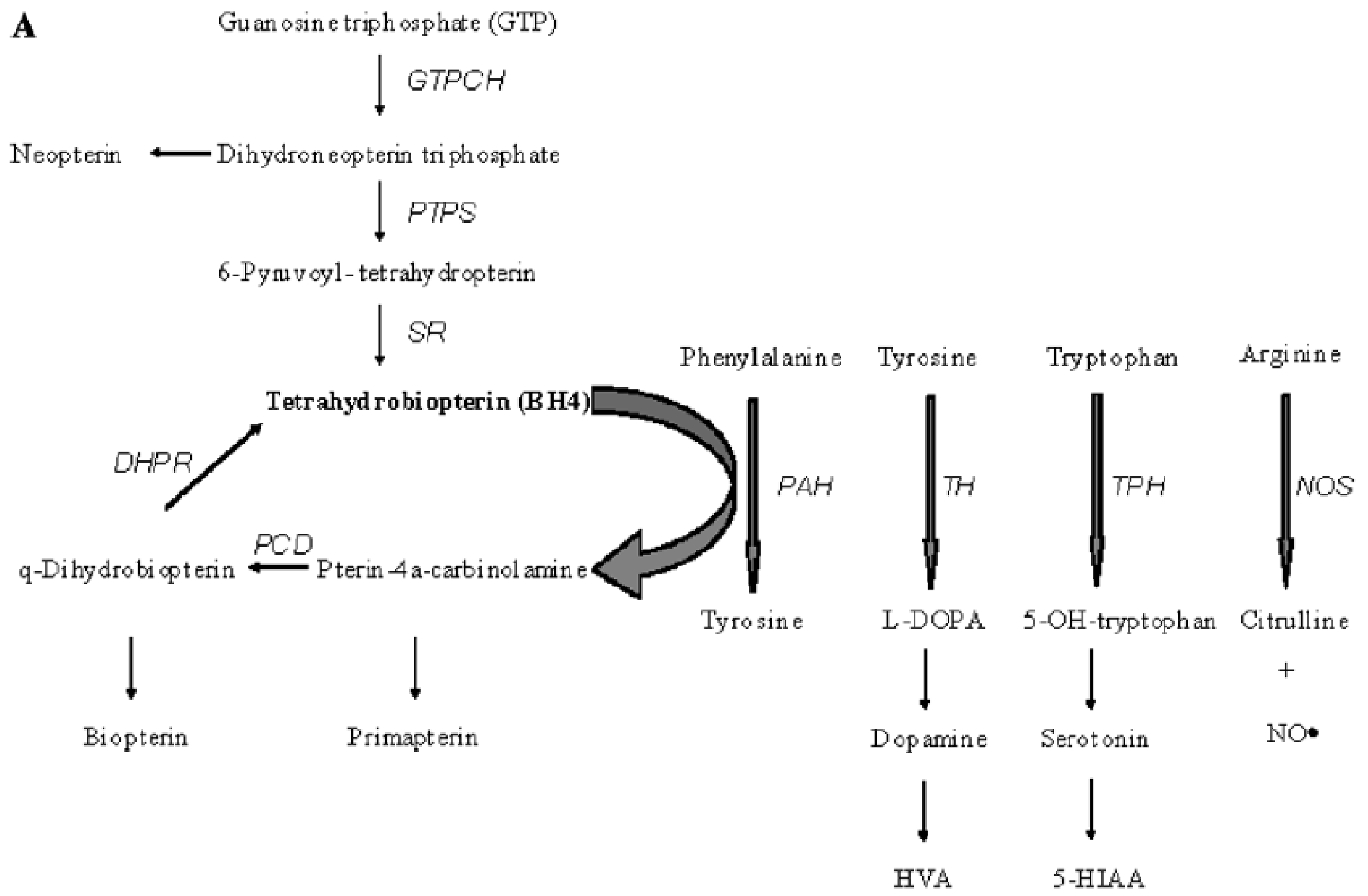


Schrantee et al., *Neuropsychopharmacol* 2015

Dopamine depletion by α-methyl-*para*-tyrosine



Abi-Dargham et al., *PNAS* 2000

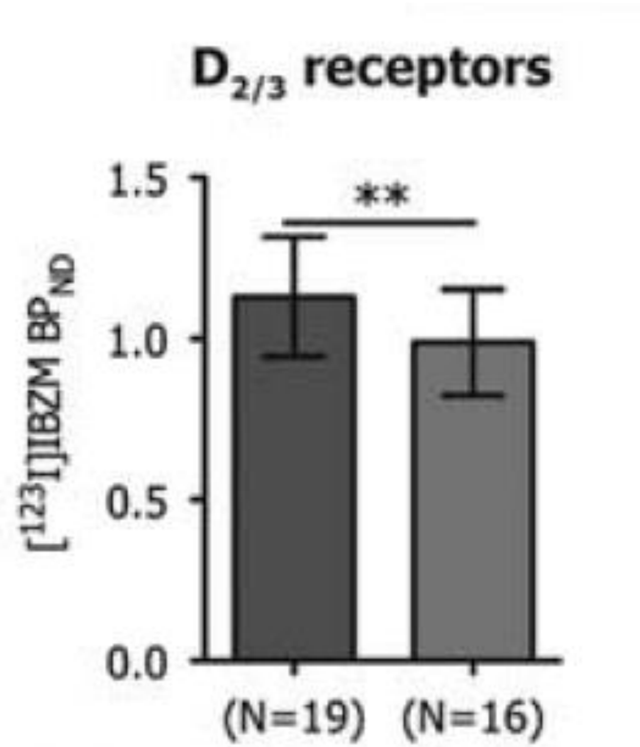


Abeling et al., *Mol Gen Metab* 2006

Martinez et al., *Am J Psychiatry* 2009

TABLE 3. Estimated Occupancy of D_2/D_3 Receptors Measured as AMPT-Induced Change in $[^{11}C]$Raclopride Nondisplaceable Binding Potential

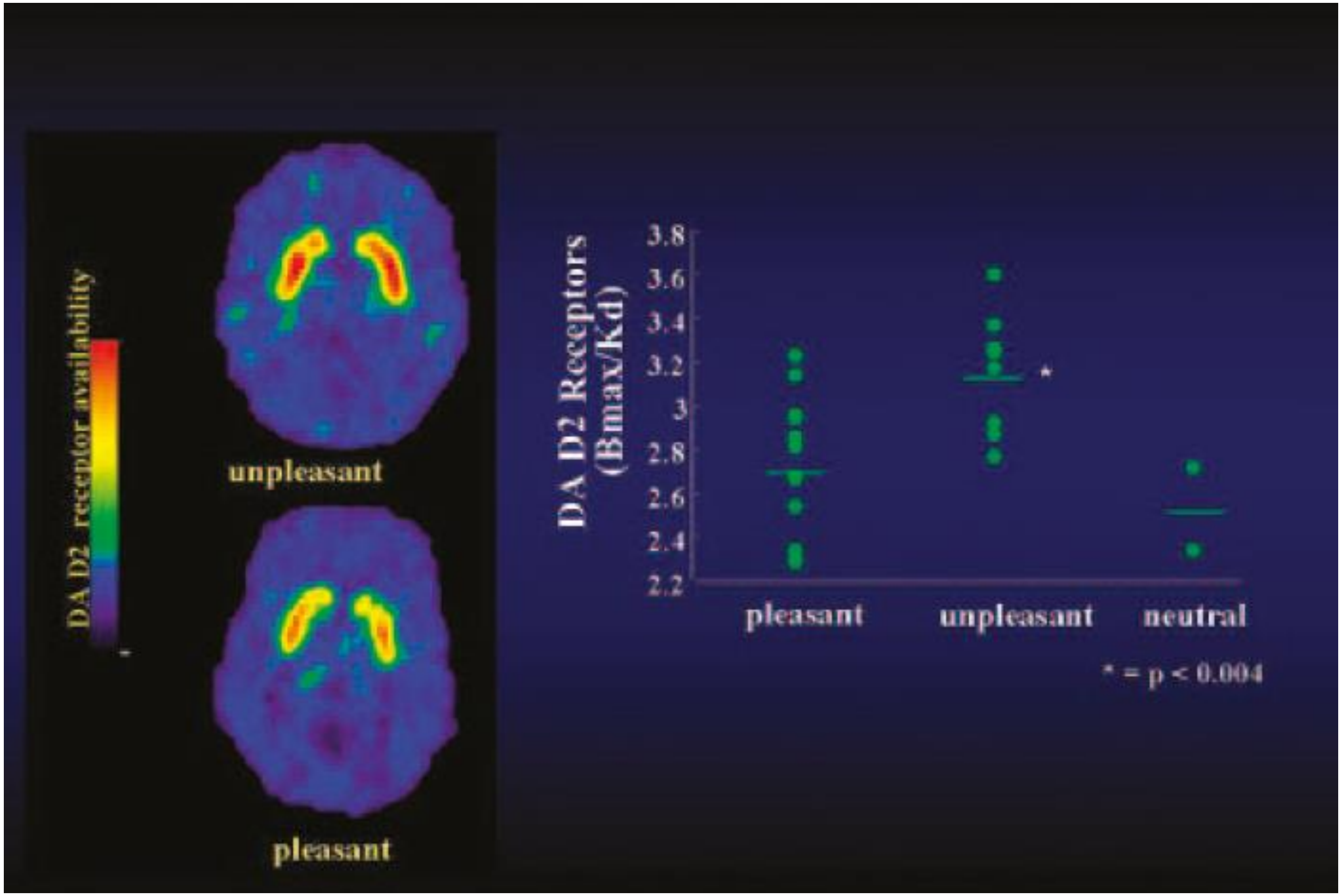
	Increase in Nondisplaceable Binding Potential (%)				
	Healthy Comparison Subjects (N=15)		Cocaine-Dependent Subjects (N=15)		
Striatal Subdivision	Mean	SD	Mean	SD	Unpaired t test (p)
Ventral striatum	10.6	6.5	3.4	7.4	0.007
Precommissural dorsal caudate	9.8	4.7	4.0	9.7	0.04
Precommissural dorsal putamen	10.5	4.8	4.7	7.6	0.02
Postcommissural caudate	12.2	9.4	9.0	10.3	0.43
Postcommissural putamen	12.3	5.4	6.7	6.1	0.01
Striatum	11.1	4.4	5.7	5.9	0.009



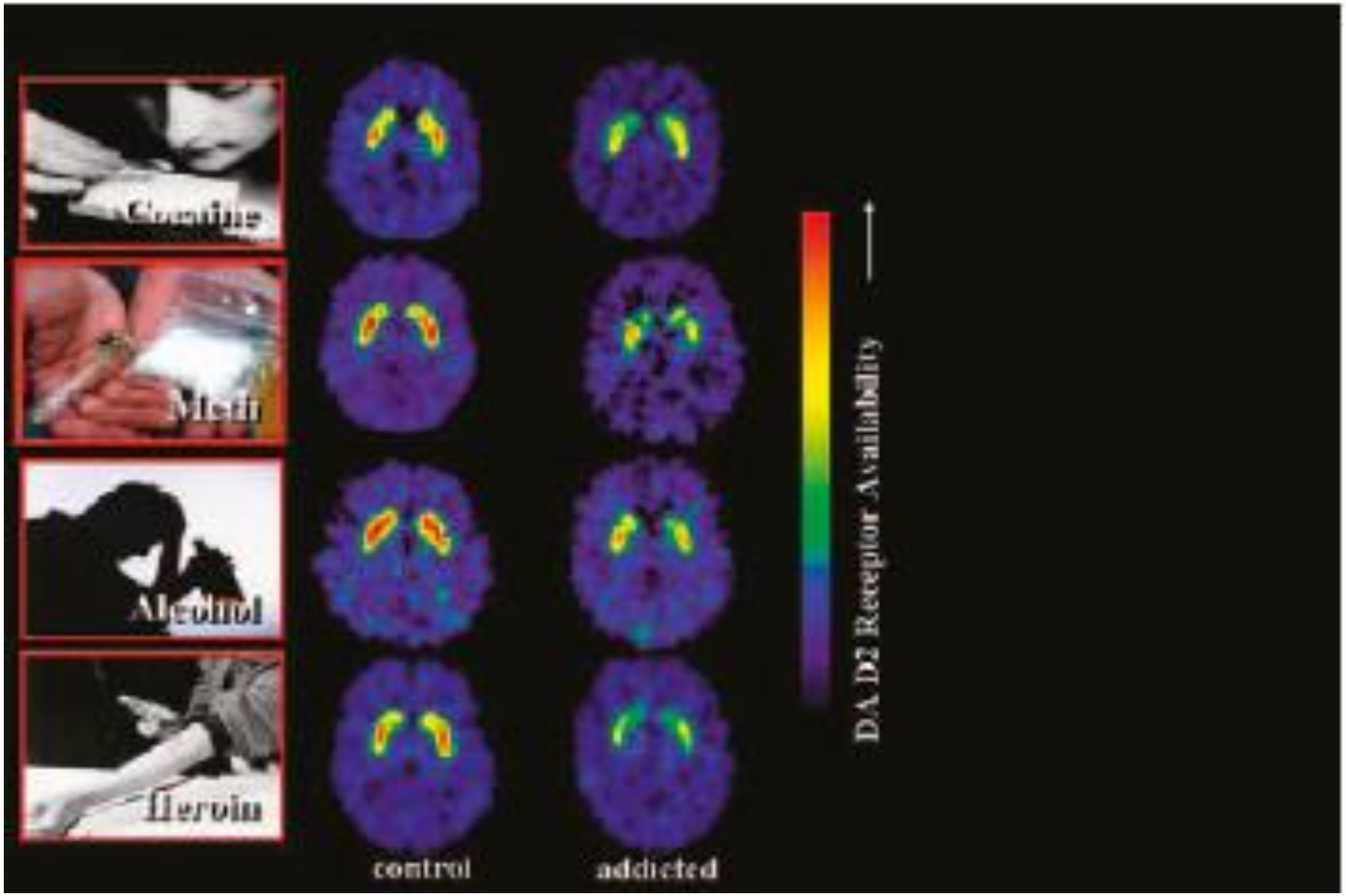
"More control subjects liked the acute administration of dAMPH (ie, experienced a "pleasant feeling") than dAMPH users"

"...the lower the $D_{2/3}$ availability, the more pleasant the dAMPH administration was experienced, only in controls..."

Schrantee et al., *Neuropsychopharmacol* 2015

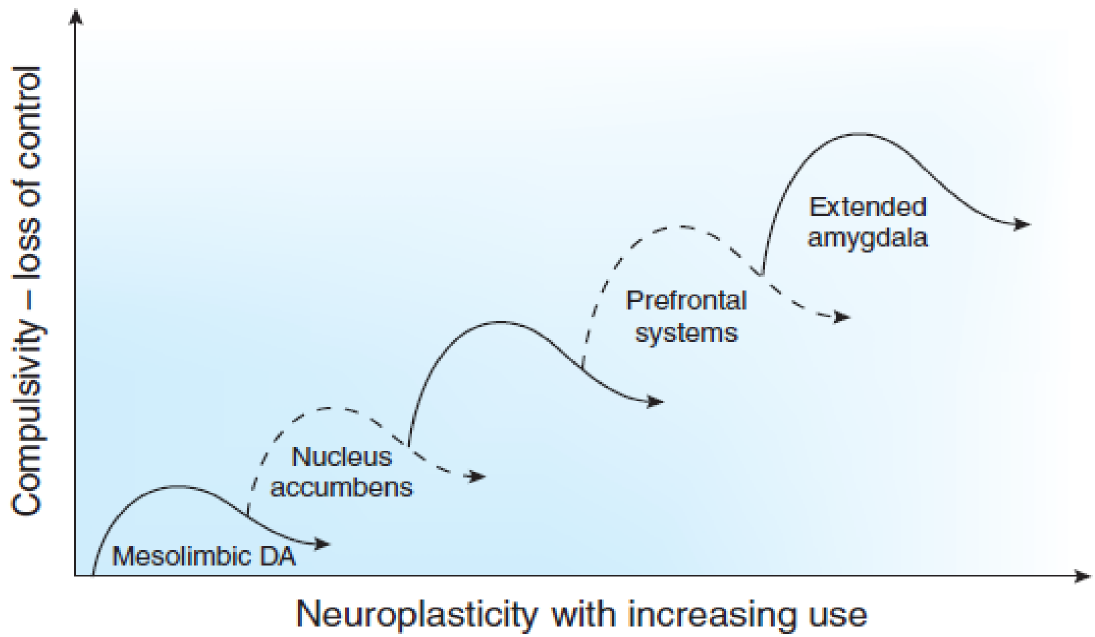


Volkow, *J Nucl Med* 2004



Volkow, *J Nucl Med* 2004

Koob and Volkow *NNP* 2009



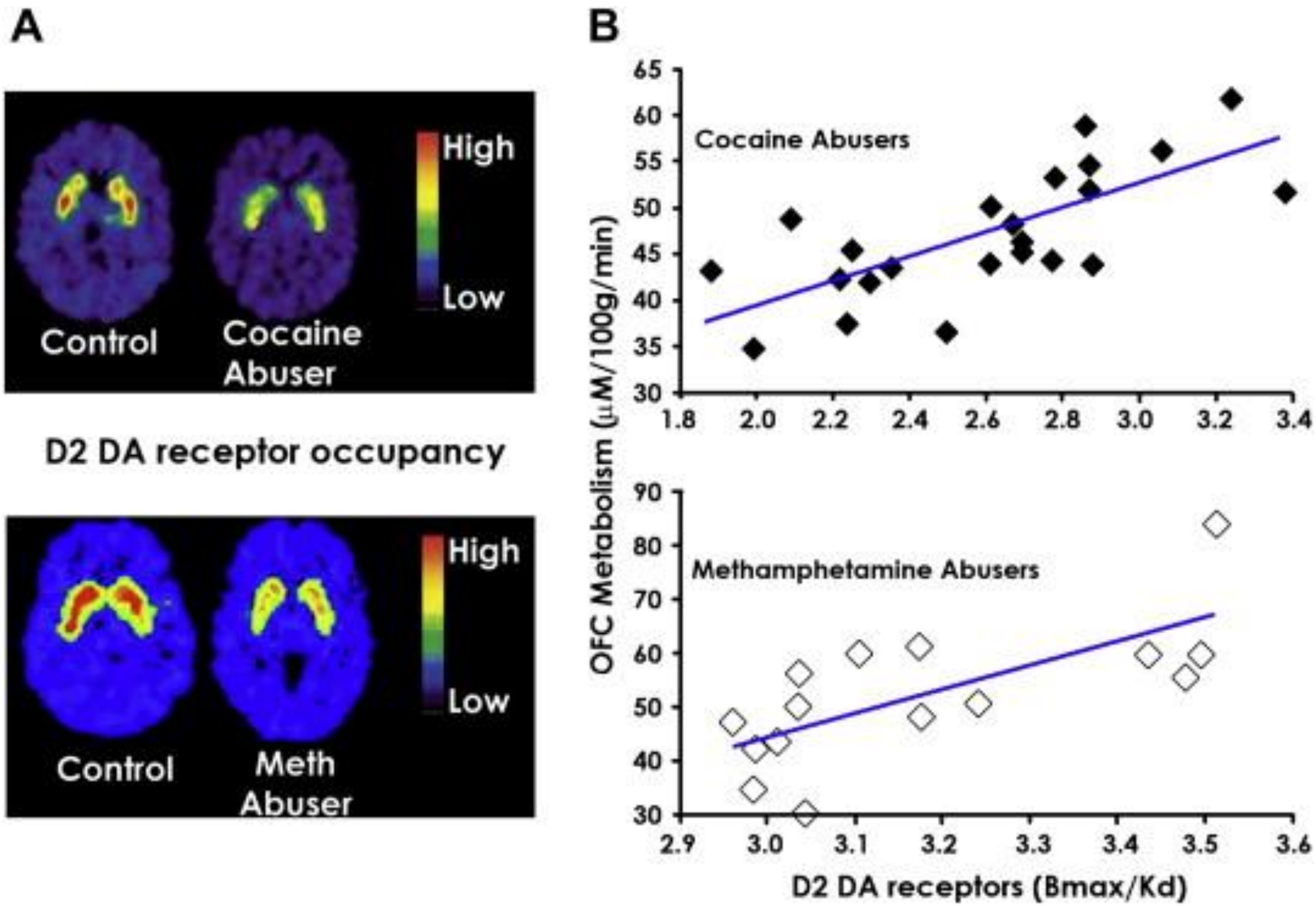
"Wanting" is separate from "liking" (pleasure)

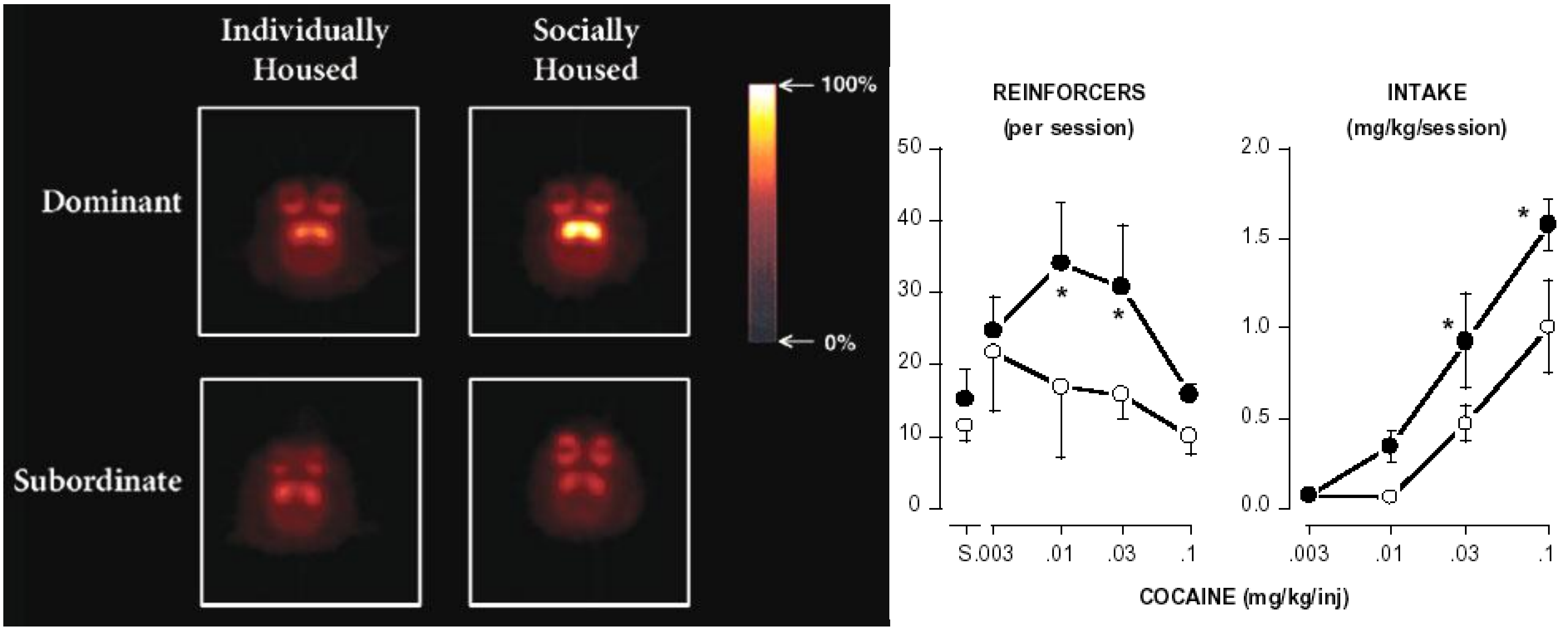
Neuroadaptations: incentive salience: stimuli become attractive and "wanted" ("craving"). Incentive sensitisation theory (Robinson/Berridge)

- Prefrontal cortex (orbitofrontal cortex/anterior cingulate gyrus), involved in salience attribution/inhibitory control

- Disruption linked to compulsive behavior and poor impulse control

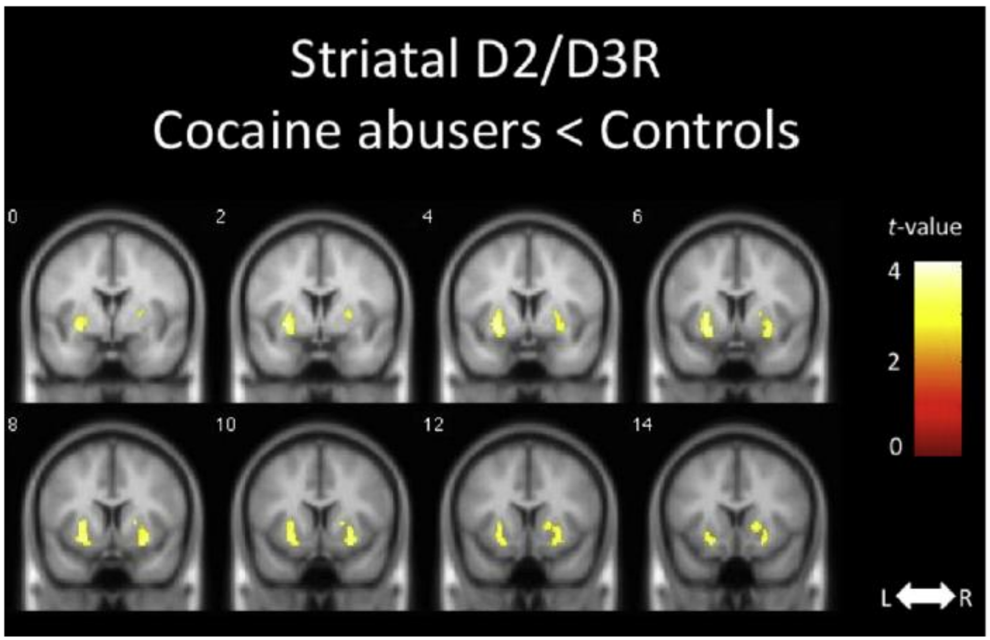
Volkow et al., *Neuropharmacology* 2009

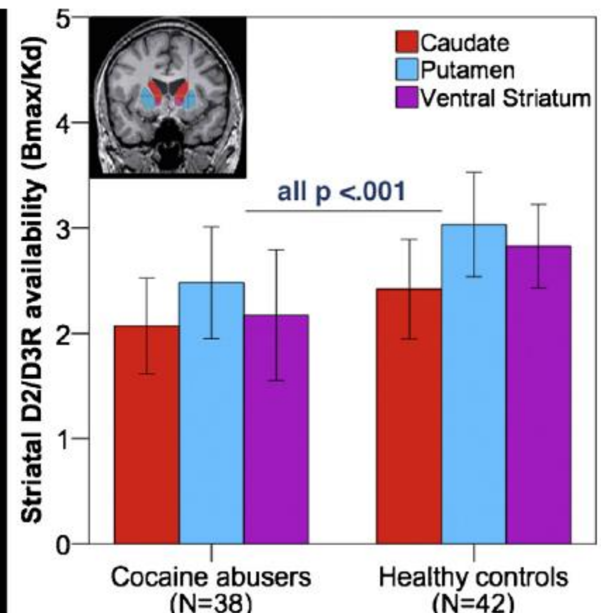




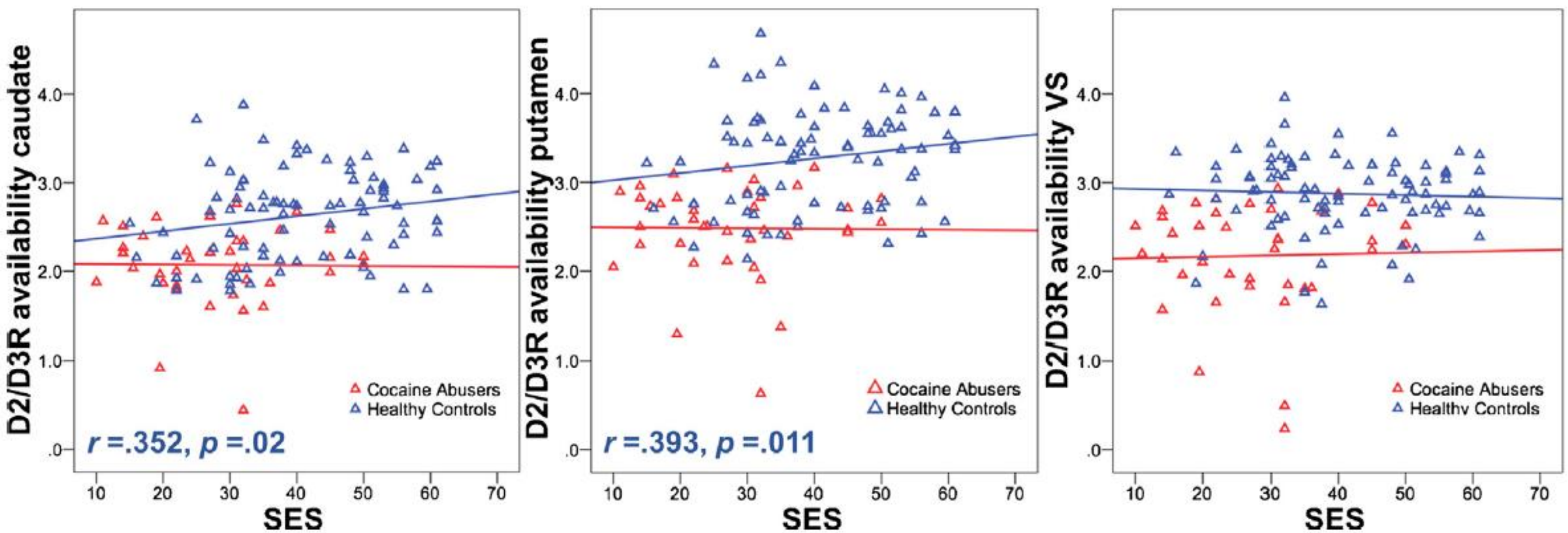
Morgan et al., *Nature Neurosc* 2002

Wiers et al., *Neurosc Letters* 2016

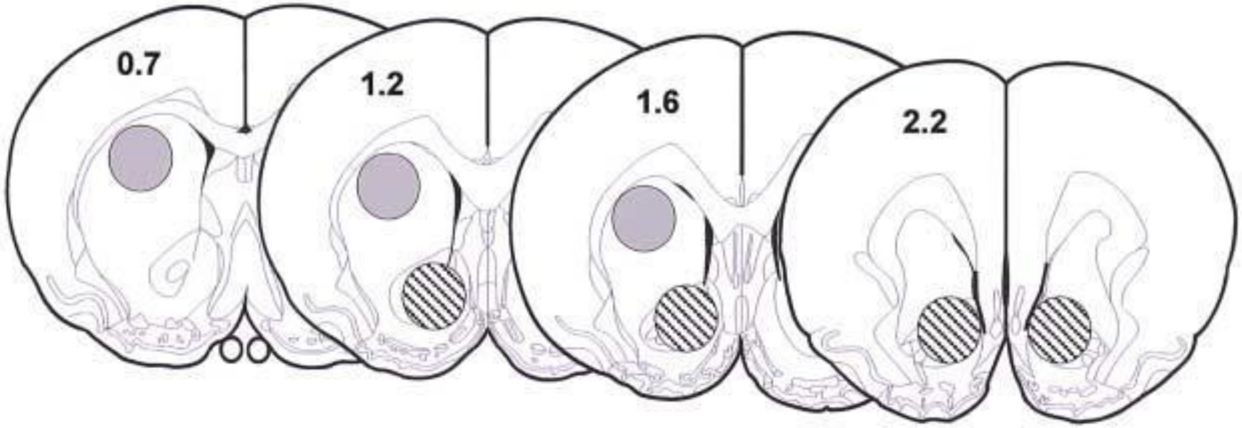


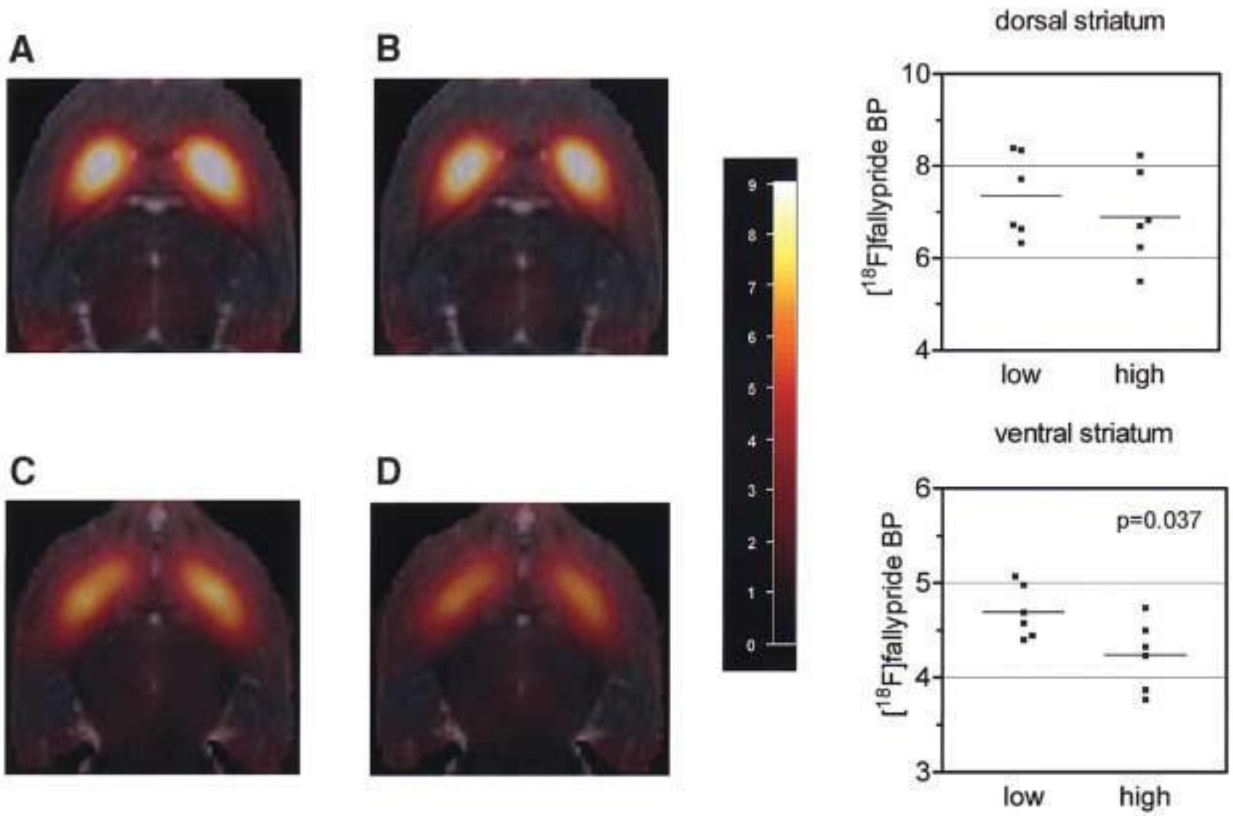


Wiers et al., *Neurosc Letters* 2016

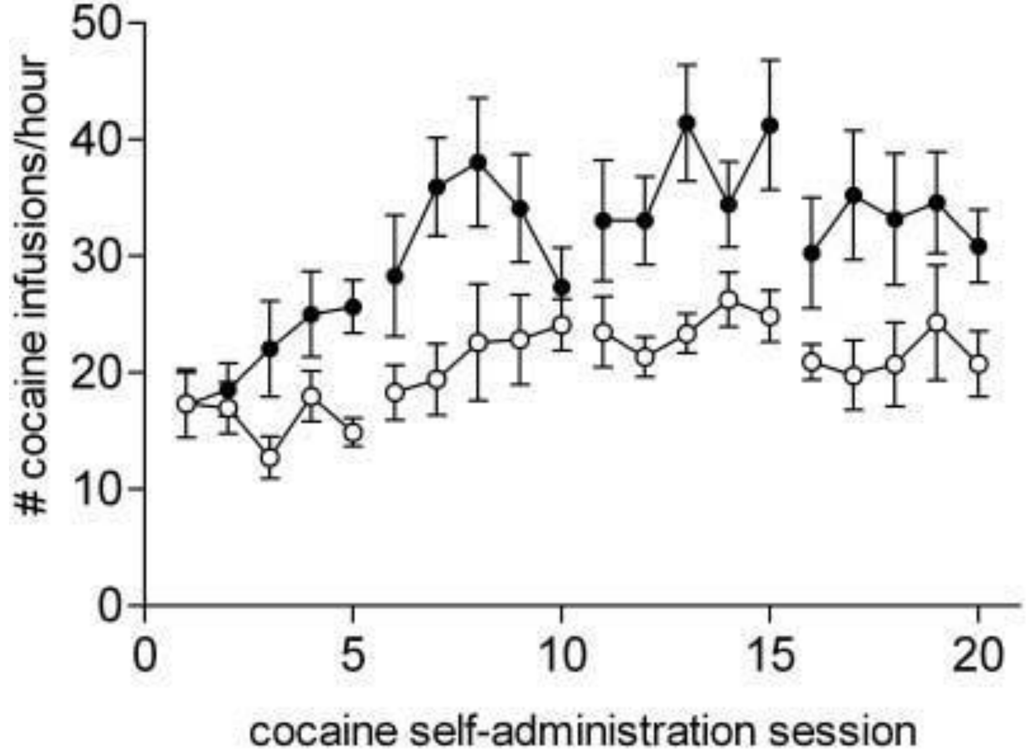


SES: socioeconomische status

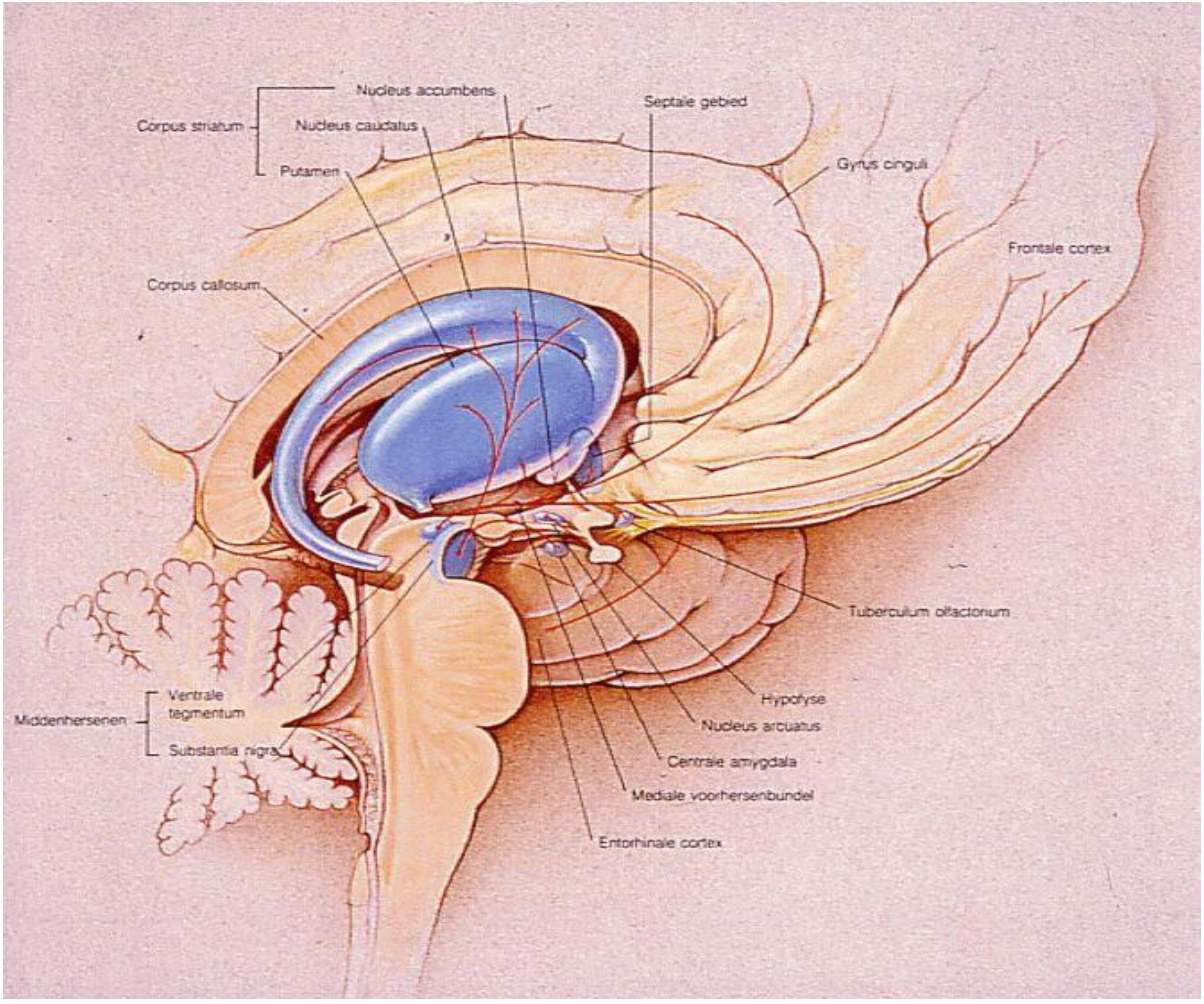




Dalley et al., *Science* 2007



Dalley et al.,
Science 2007



Corpus striatum
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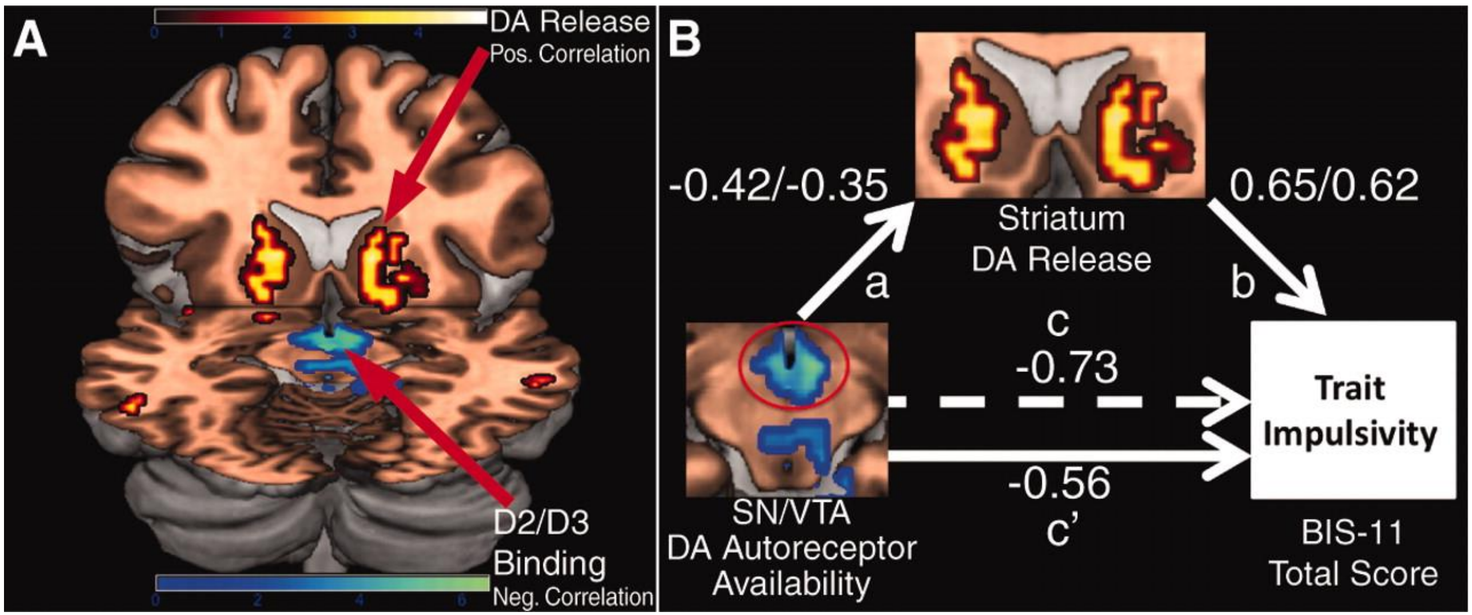
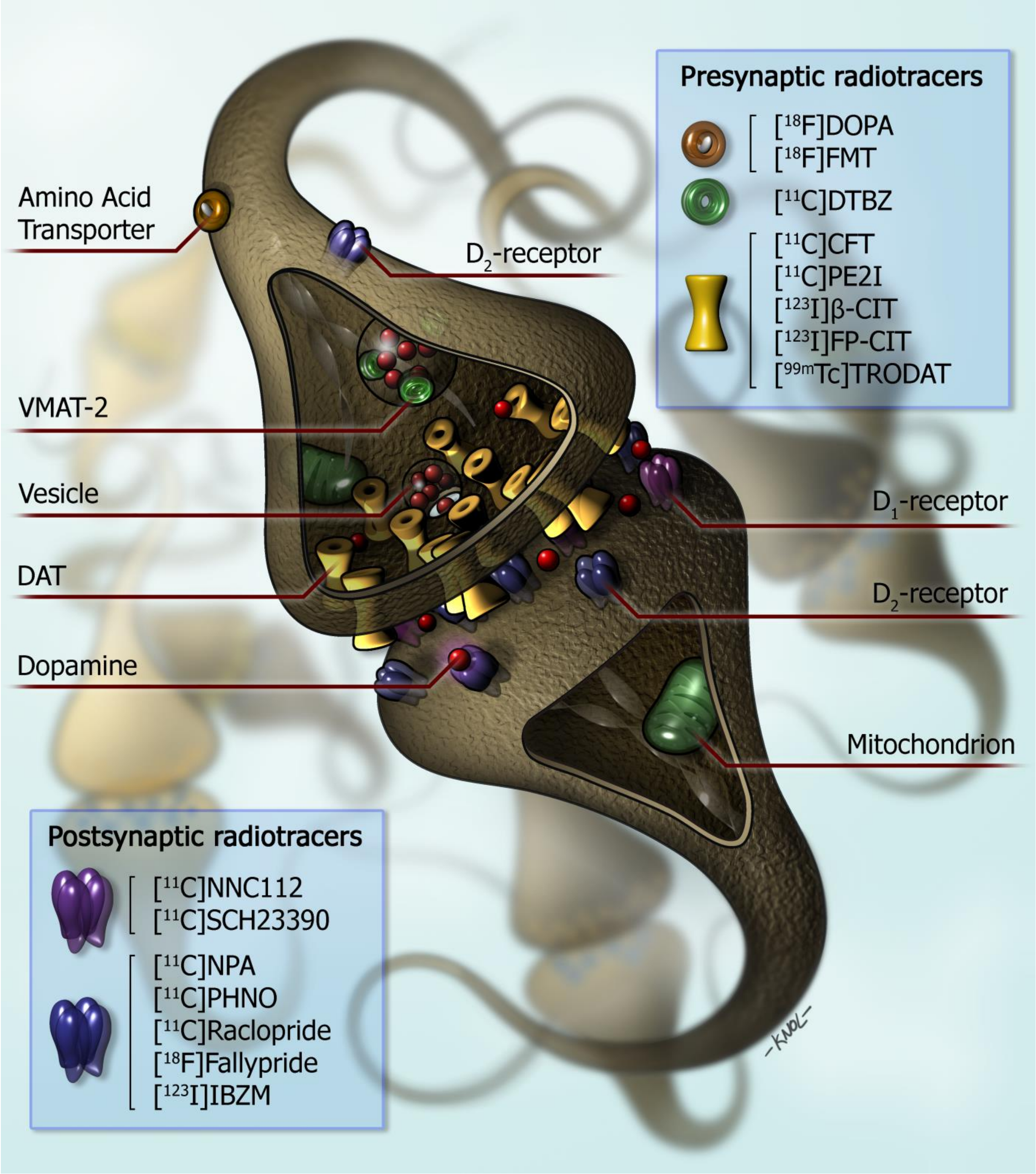
Substantia nigra

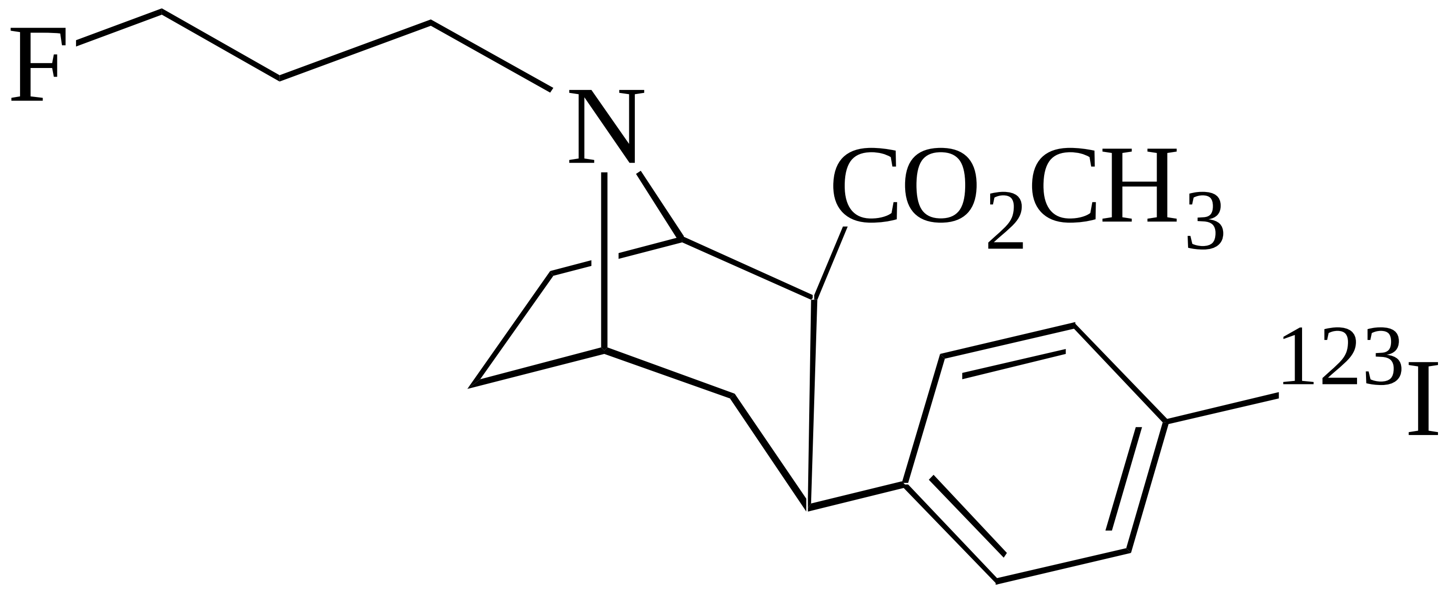
Buckholtz et al., *Science* 2010



Positive correlation DA release
and drug-wanting



Booij et al., 2014

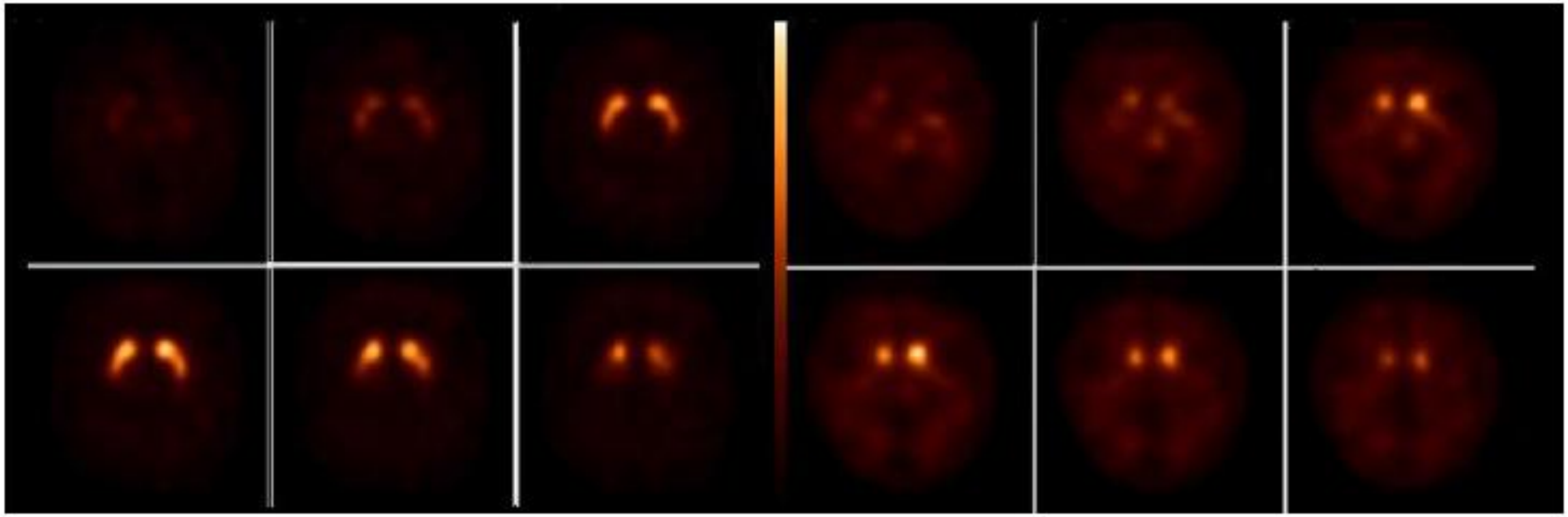


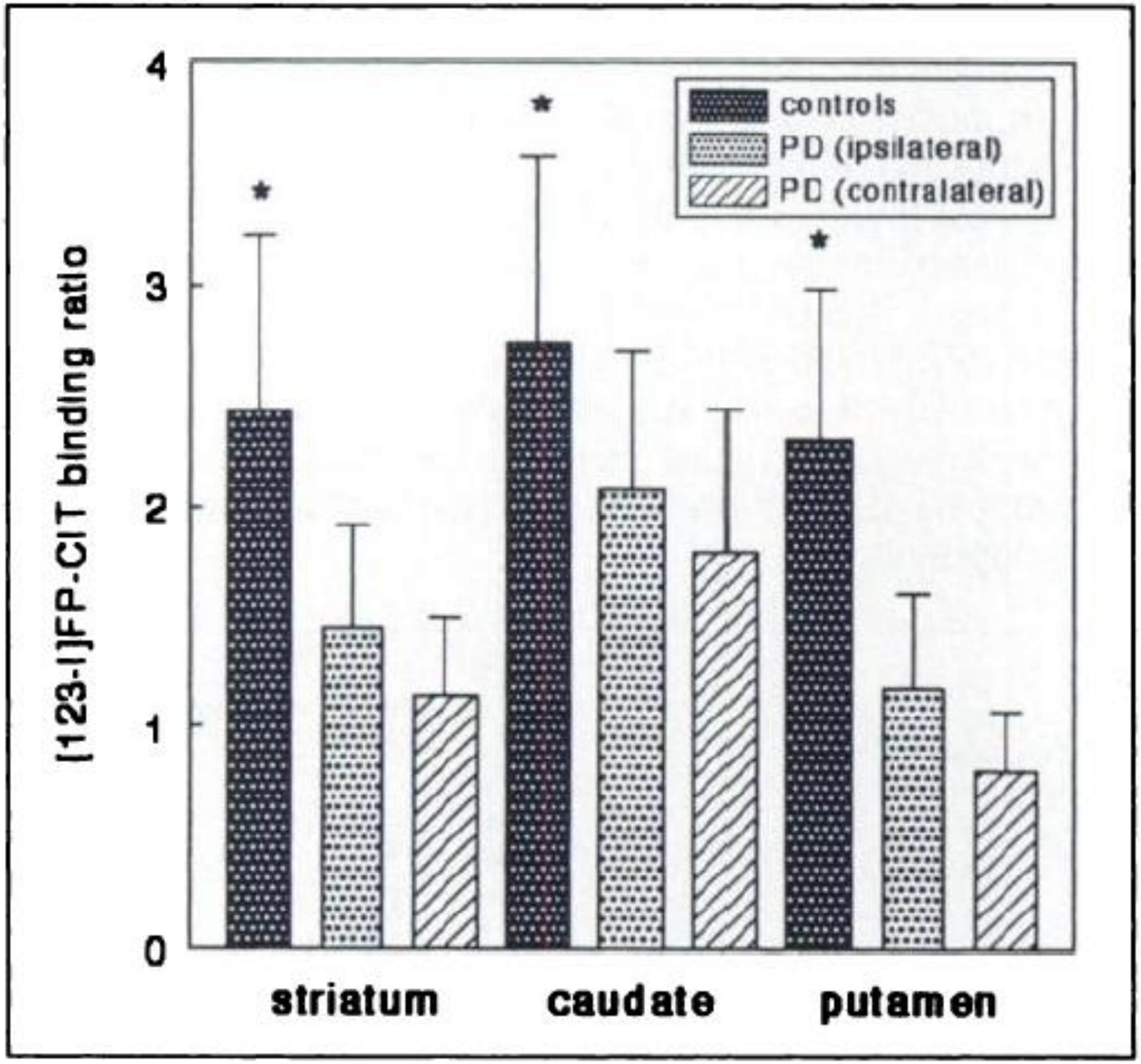
[^{123}I]FP-CIT: DaTSCAN

Affinity (Ki) to dopamine transporter: 3.50 (0.39) n*M*

(Abi-Dargham et al., 1996)

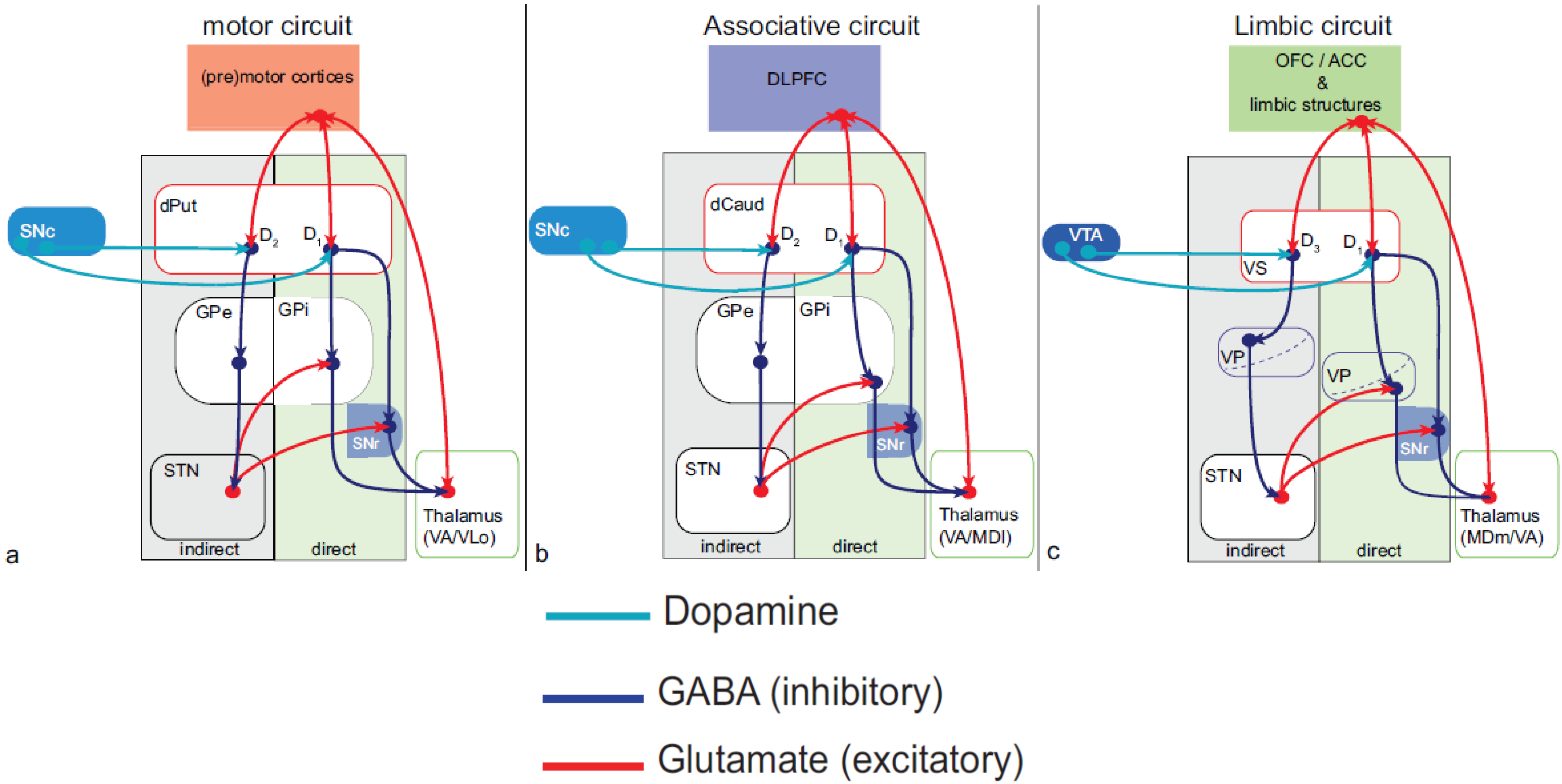
Suwijn et al., *Parkinsonism Relat Disord* 2014





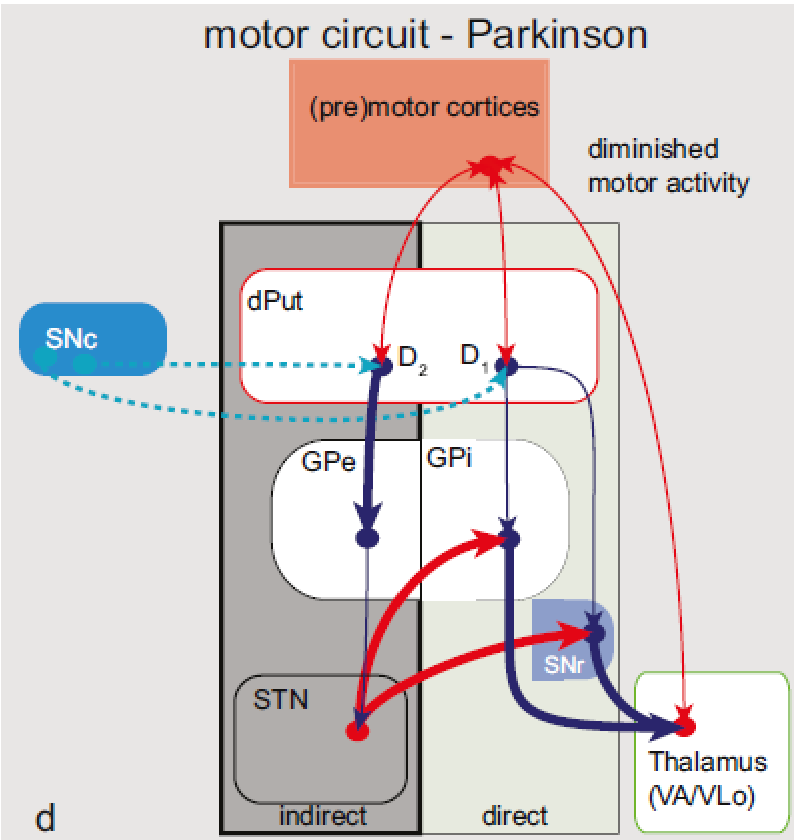
Tissingh et al., *J Nucl Med* 1998

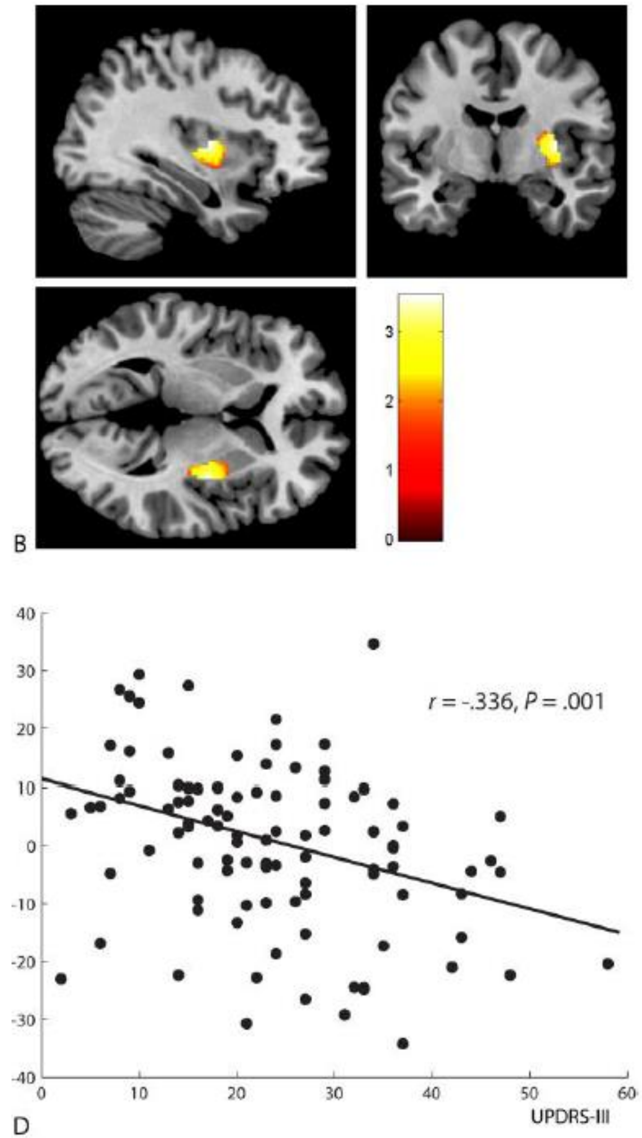
Coordination goal-directed behaviour by dopaminergic cortico-striatal-thalamocortical circuits (parallel/segregated)



Vriend et al., *Neurosc Biobehav Rev* 2014

Vriend et al., *J Neurol Neurosurg Psychiatry* 2014
Vriend et al., *Neurosc Biobehav Rev* 2014





Cognitive deficits in PD

Cognitive deficits in PD affect visuospatial, attentional, executive and memory functions due to abnormal neurotransmitter systems (DA and ACh) and Lewy bodies (cortical and subcortical)

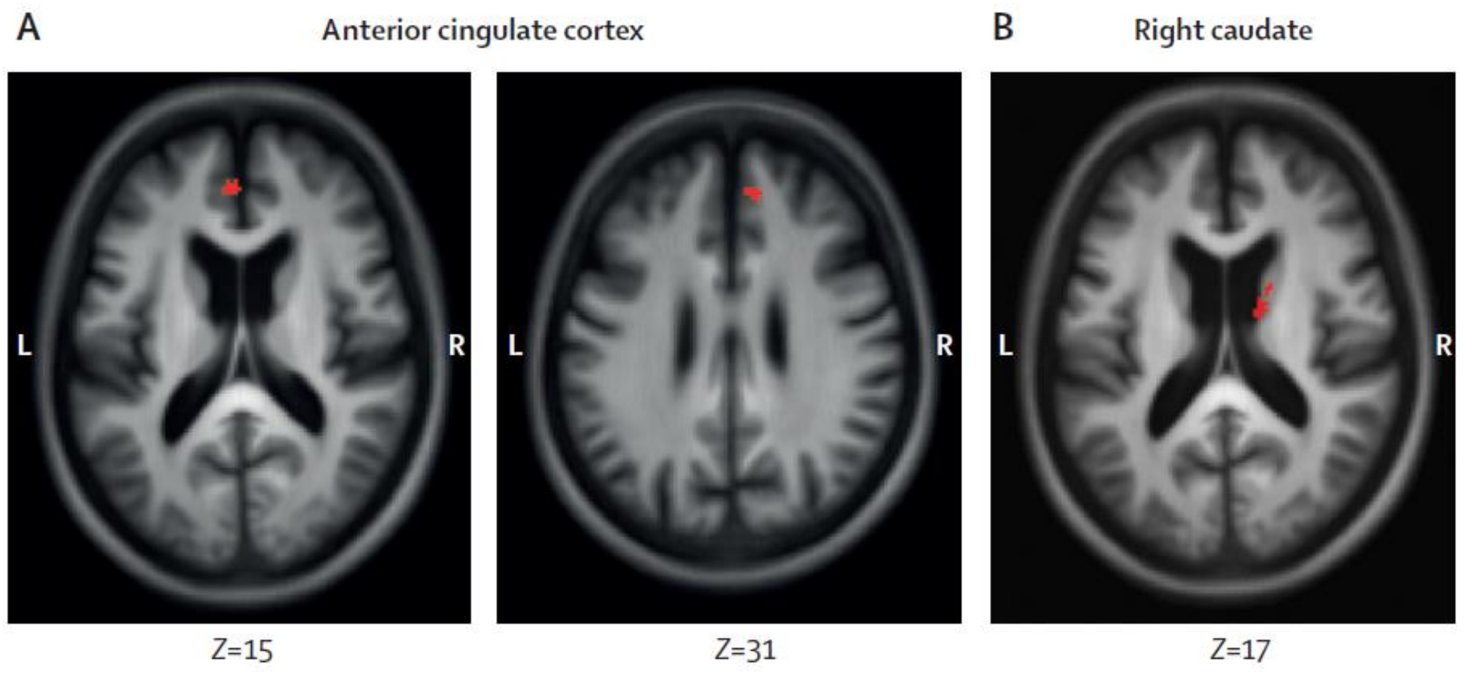
“Dual Syndrome” hypothesis:
Dopaminergic corticostriatal deficits affect executive functions (planning, response inhibition, working memory)
Posterior cortical LB and cholinergic loss affect visiospatial, mnemonic and semantic functions

Janvin *Mov Disord* 2006; Aarland and Kurx, *Brain Pathol* 2010; Pedersen et al., *JAMA neurol* 2013; Kehagia et al., *Neurodegener Dis* 2013

Ekman et al., *Lancet Neurology* 2012

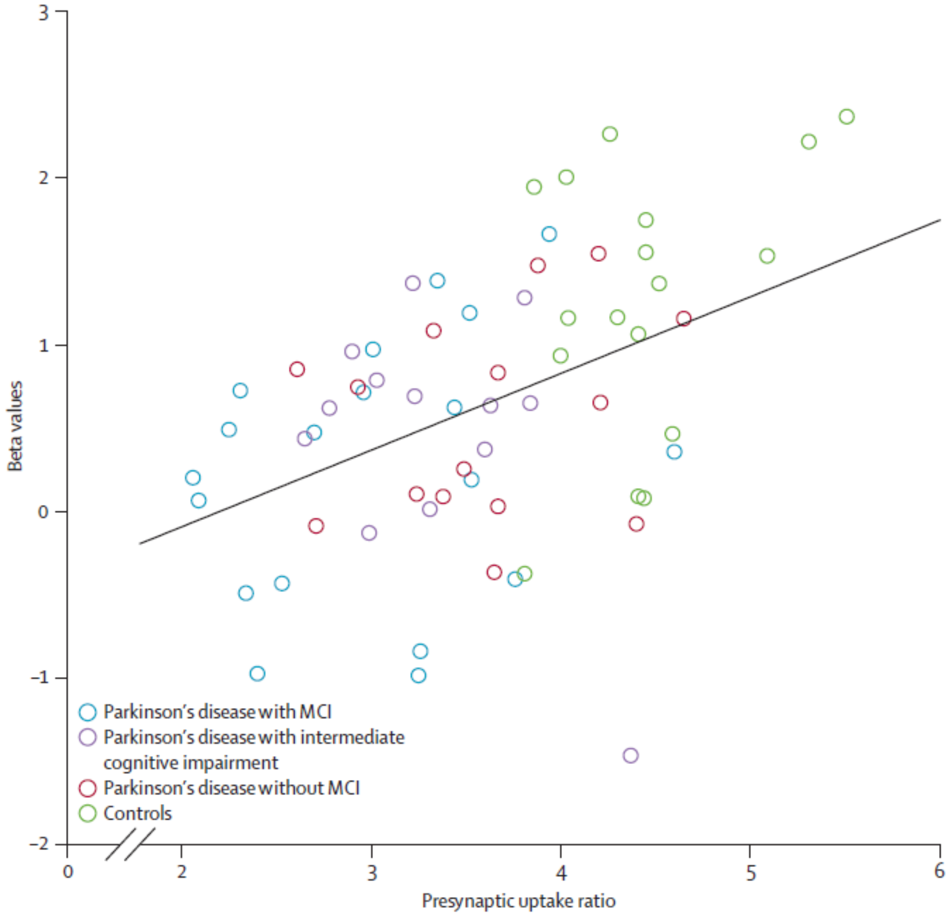
Lower caudate DAT binding in PD and MCI (n=30) versus PD without MCI (n=26)

Working memory test (fMRI) in PD and MCI vs PD without MCI: under-recruitment in anterior cingulate cortex (bilaterally) and right dorsal caudate nucleus

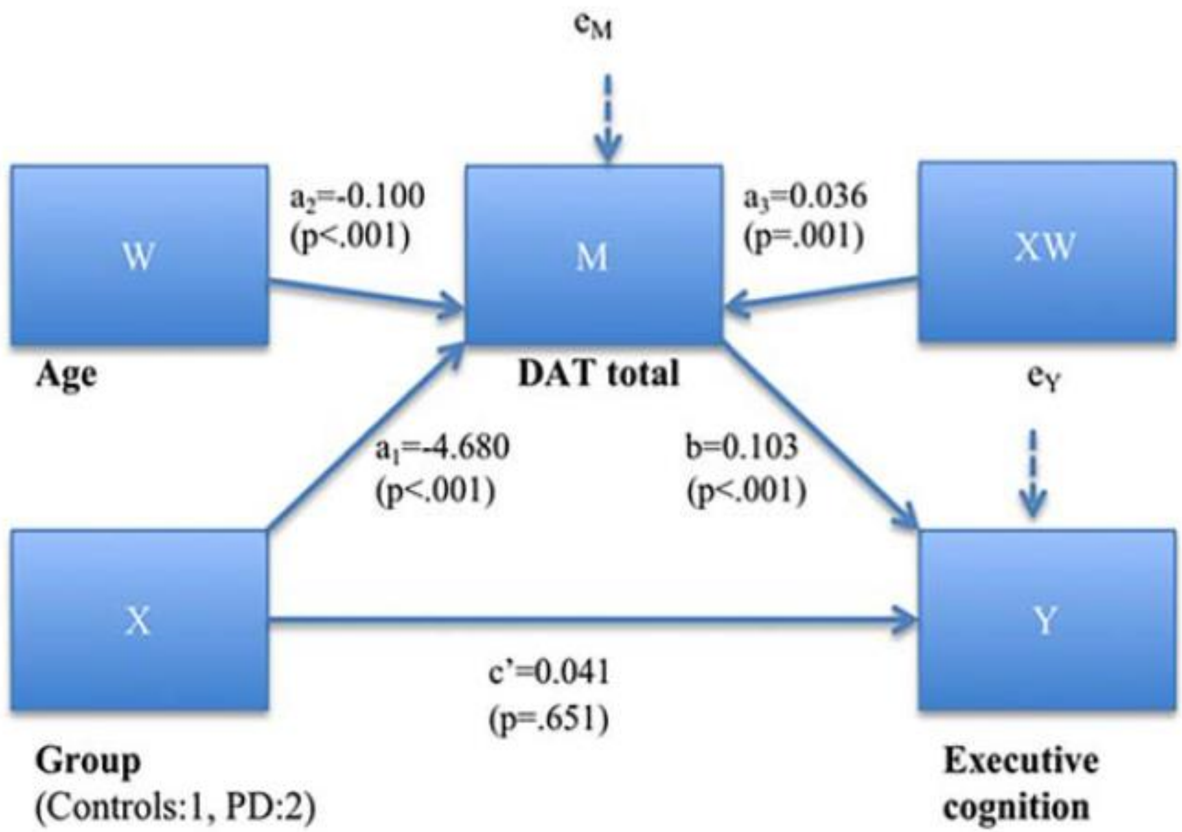


Ekman et al., *Lancet Neurology* 2012

Caudate DAT SPECT correlated with striatal fMRI BOLD signal



Siepel et al., *Mov Disord* 2014



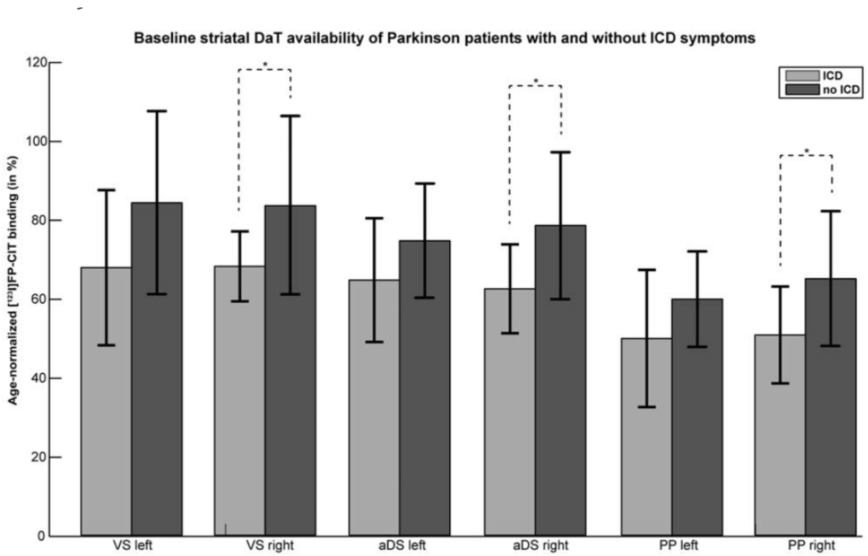
Executive deficit in PD mediated by DAT binding

Age moderator; Mediation effect is stronger for younger than older patients

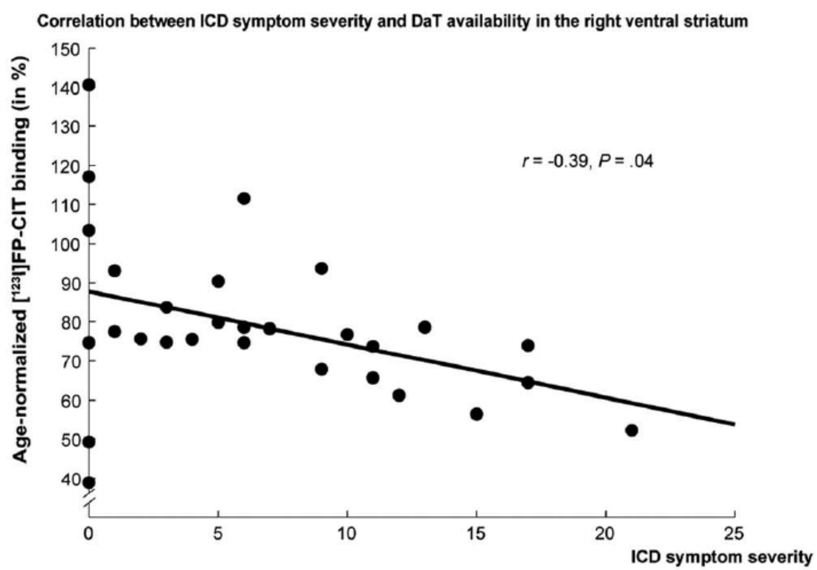
No association DAT and memory or visuospatial functions

158 controls and 339 PD patients from the Parkinson's Progression Markers Initiative (PPMI) study

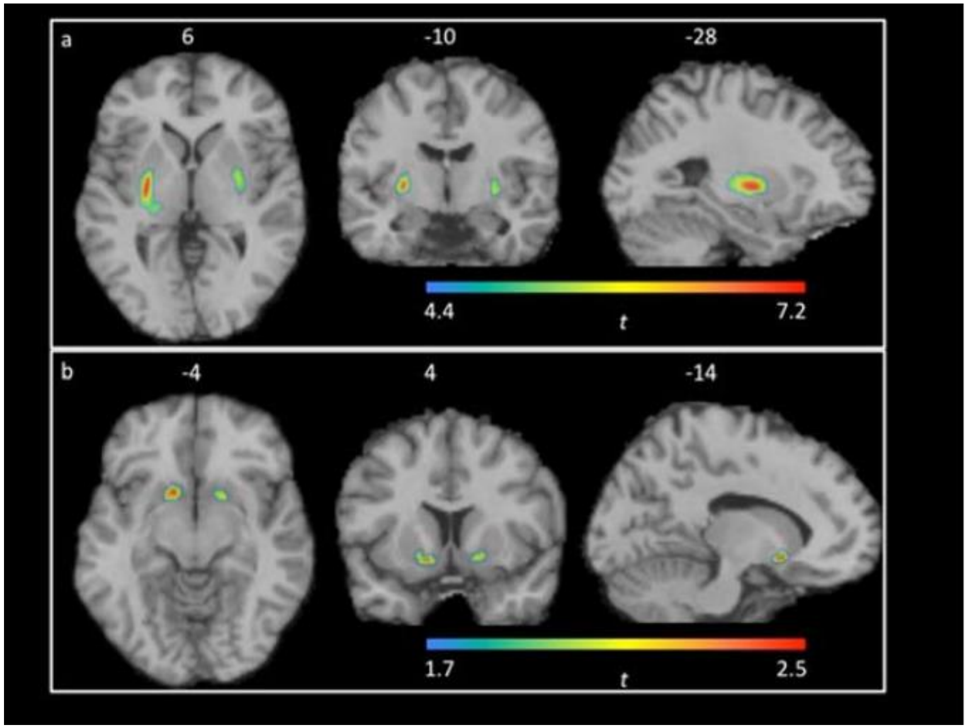
ICD in PD (DAT imaging)



Vriend et al., *Mov Disord* 2014



ICD in PD ($D_{2/3}$ imaging)



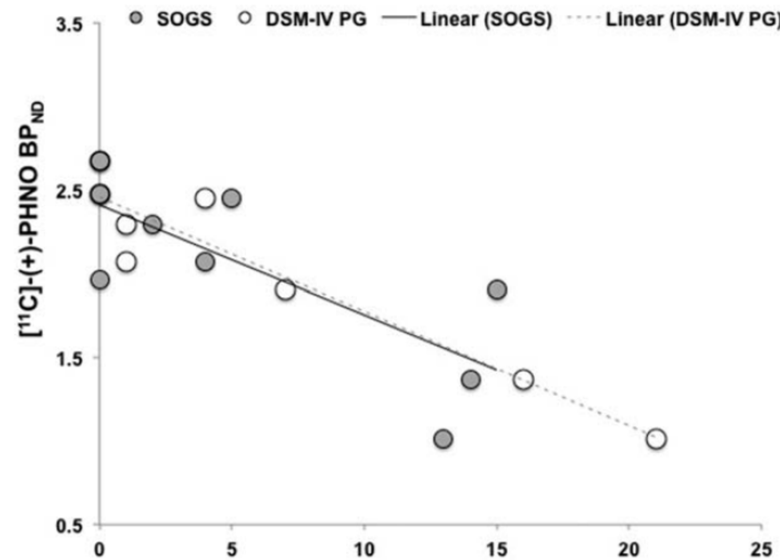
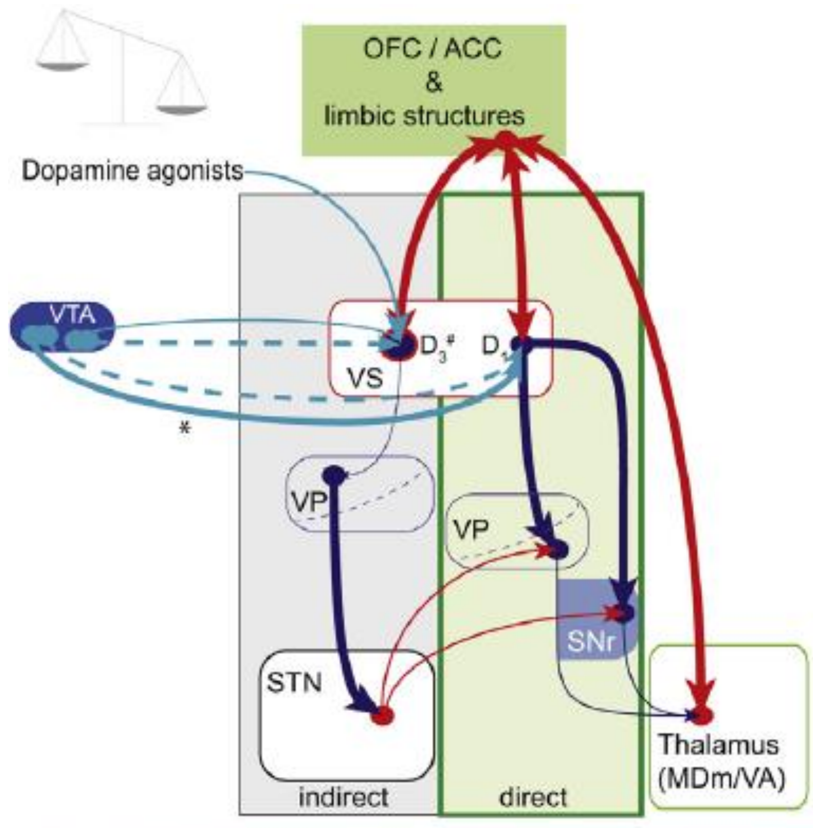


FIG. 3. Correlation between [^{11}C]-(+)-PHNO binding in ventral striatum of Parkinson's patients with impulse control disorders and gambling severity as rated with the South Oaks Gambling Scale (SOGS) and DSM-IV Questionnaire for Pathological Gambling (DSM-IV PG).

Payer et al., *Mov Disord* 2015

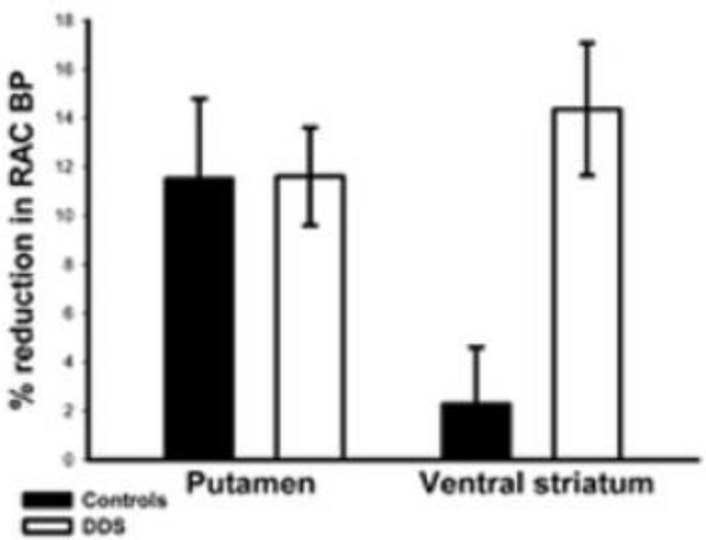
DA agonists (pramipexole; D_3) impair processing of negative feedback during reward learning

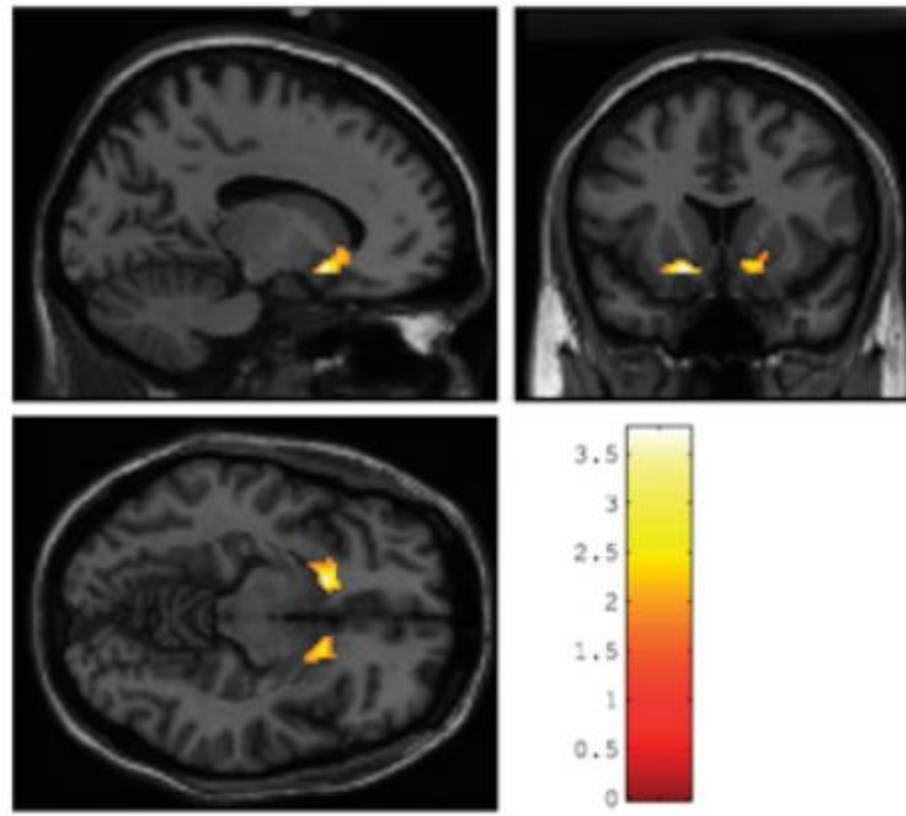


Negative outcomes decrease activity indirect pathway and inhibits potentially harmful behaviour

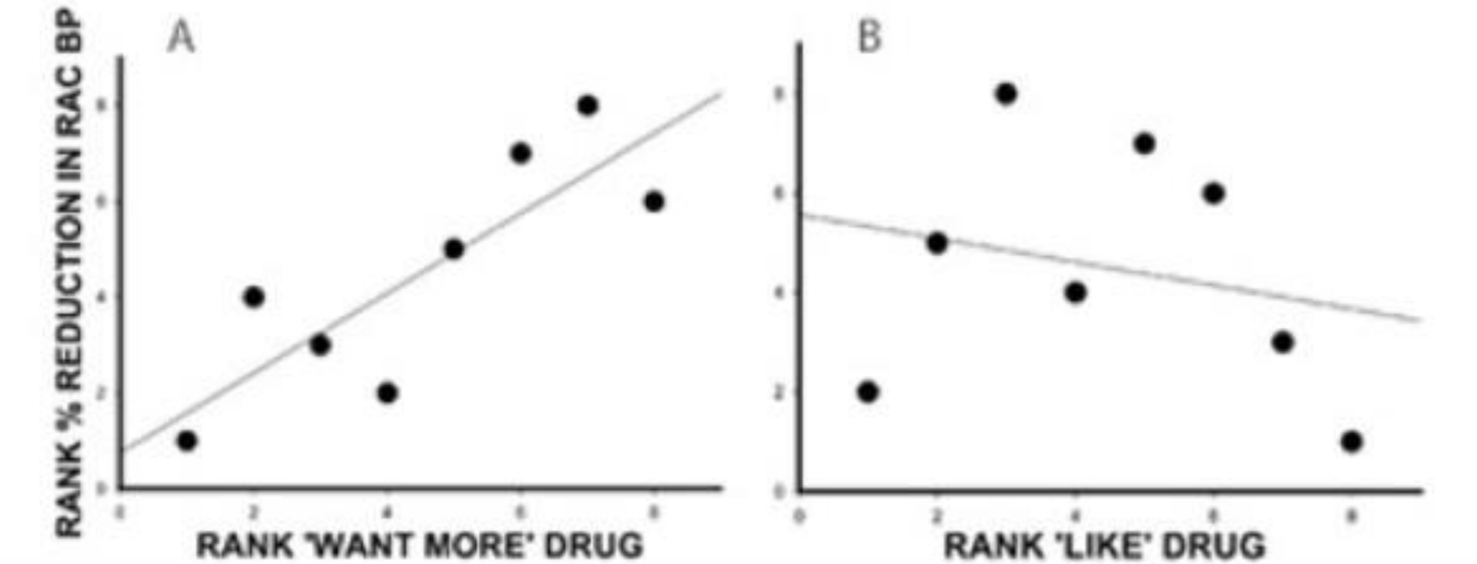
Unexpected rewarding stimuli induce increase activity direct pathway: reward learning

Dopamine dysregulation syndrome in PD; compulsive drug use





Evans et al., *Ann Neurol* 2006



Evans et al., *Ann Neurol* 2006

Martinez et al., *Biol Psychiatry* 2005

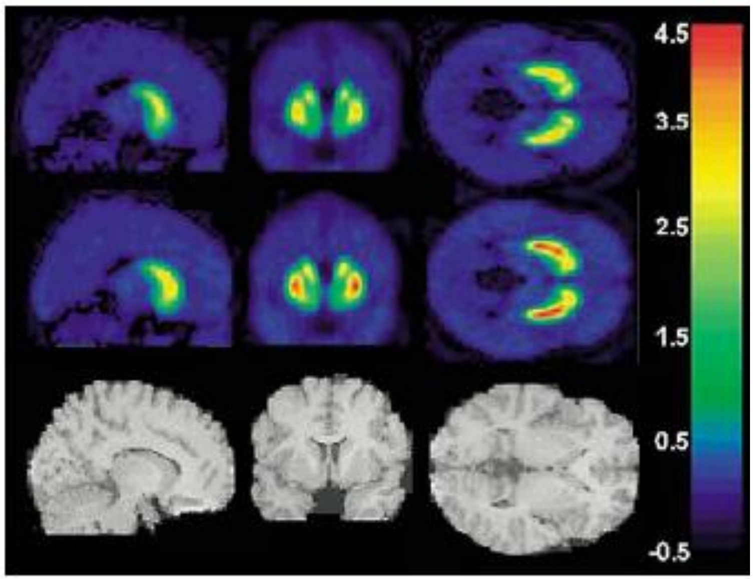


Table 3. [[11]C]Raclopride Specific to Nonspecific Partition Coefficient (V_3'', unitless)

Functional Subdivision	Anatomic Subdivision	HC	AD	Difference	p^a
LST	VST	2.09 ± .24	1.81 ± .27	−13.2%	.006
AST		2.60 ± .28	2.17 ± .27	−16.4%	<.001
	preDCA	2.47 ± .28	2.12 ± .25	−14.4%	.001
	preDPU	3.02 ± .32	2.50 ± .31	−17.3%	<.001
	postCA	1.80 ± .30	1.49 ± .30	−17.1%	.008
SMST	postPU	2.97 ± .31	2.42 ± .32	−18.5%	<.0001
STR		2.65 ± .27	2.21 ± .27	−16.7%	.0001

Values are mean ± SD, *n* = 15 per groups. See Table 1 for abbreviations.
[a]Unpaired *t* test.

Baseline $D_{2/3}$ receptor binding

Martinez et al., *Biol Psychiatry* 2005

Table 4. Percent Change in Amphetamine-Induced [^{11}C]Raclopride Displacement ($\Delta V_3''$)

Functional Subdivision	Anatomic Subdivision	HC	AD	p^a
LST	VST	−13.0 ± 8.8%	−5.2 ± 3.6%	.004
AST		−6.7 ± 5.4%	−4.6 ± 5.8%	.31
	preDCA	−4.2 ± 5.6%	−3.1 ± 5.6%	.60
	preDPU	−8.8 ± 6.7%	−5.6 ± 6.9%	.20
	postCA	−7.8 ± 8.3%	−5.6 ± 8.1%	.46
SMST	postPU	−13.7 ± 7.5%	−12.3 ± 7.3%	.59
STR		−9.4 ± 5.9%	−7.2 ± 5.3%	.28

Values are mean ± SD, n = 15 per groups. See Table 1 for abbreviations.
[a]Unpaired t test.

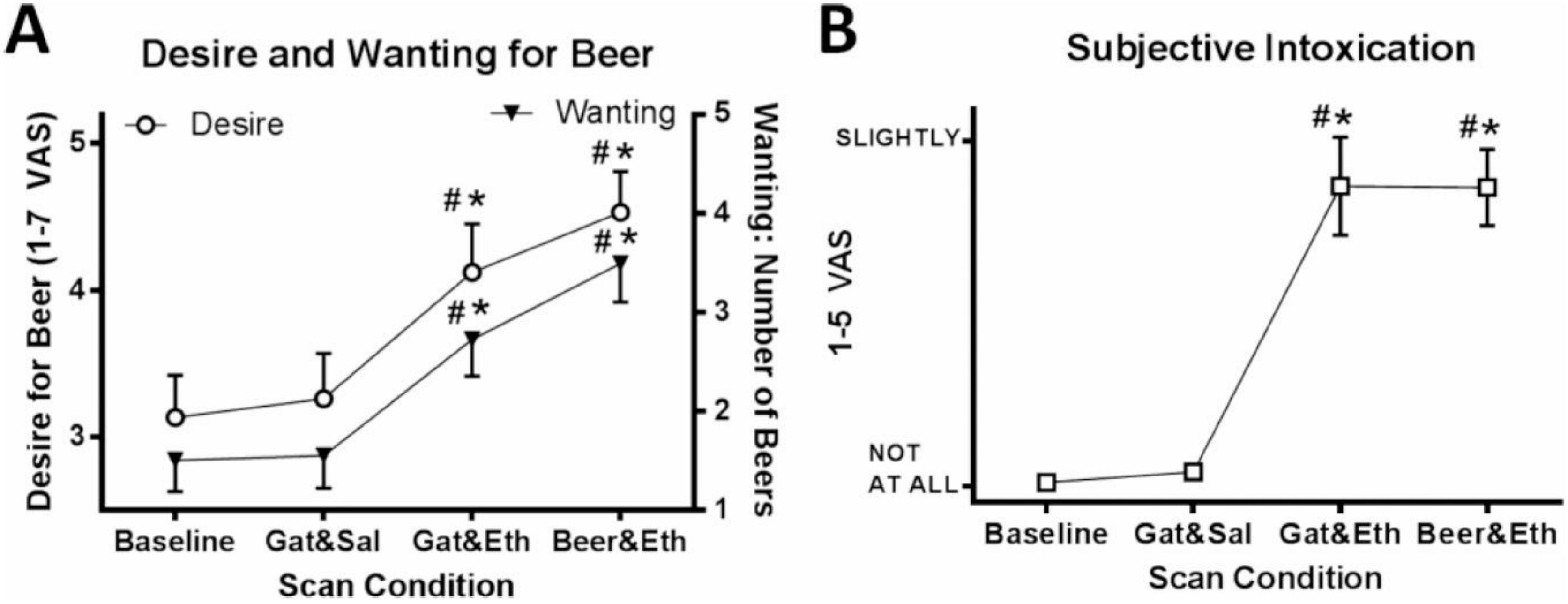
Oberlin et al., *Psychopharmacology* 2015

26 males heavy beer drinkers

3 ^{11}C-raclopride PET scans

Baseline; flavor favorite beer/Gatorade; by infusion alcohol (3 U) or saline

Oberlin et al., *Psychopharmacology* 2015



Oberlin et al., *Psychopharmacology* 2015

Lef
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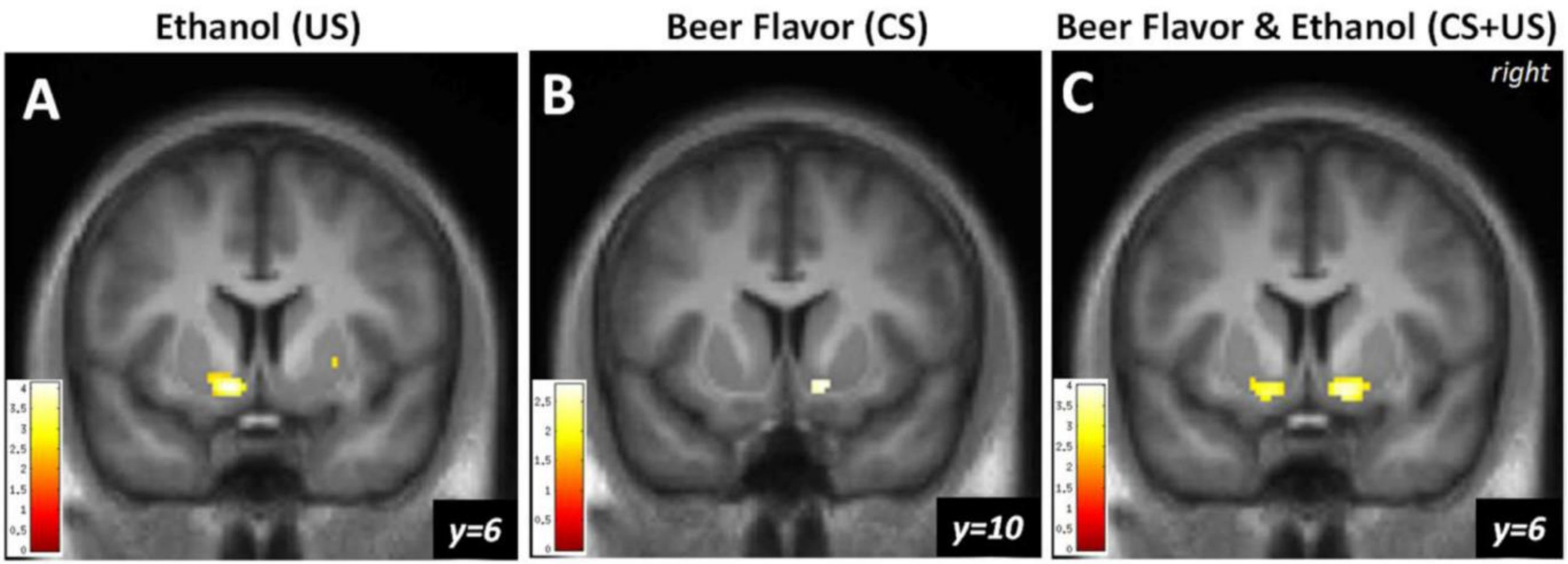
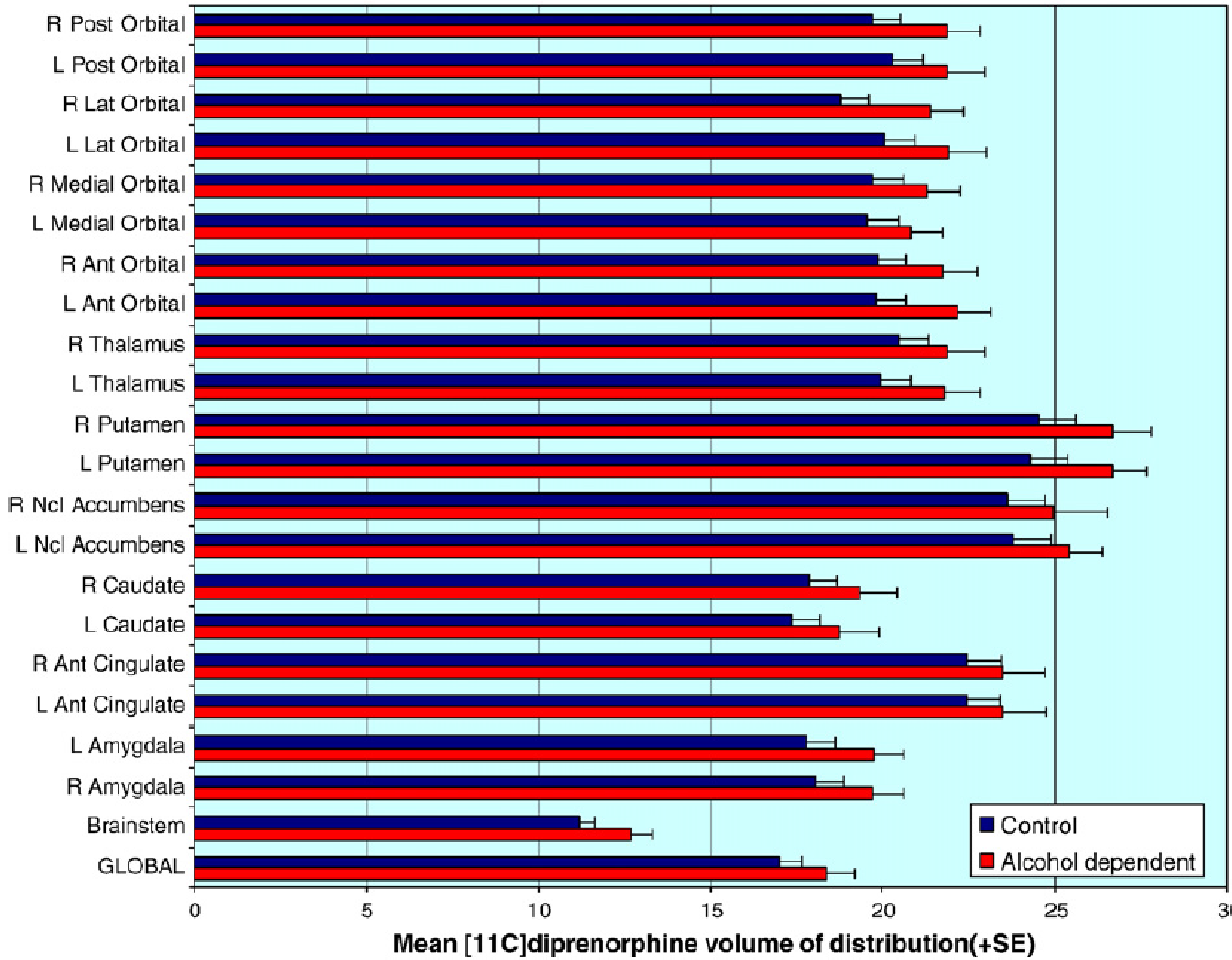
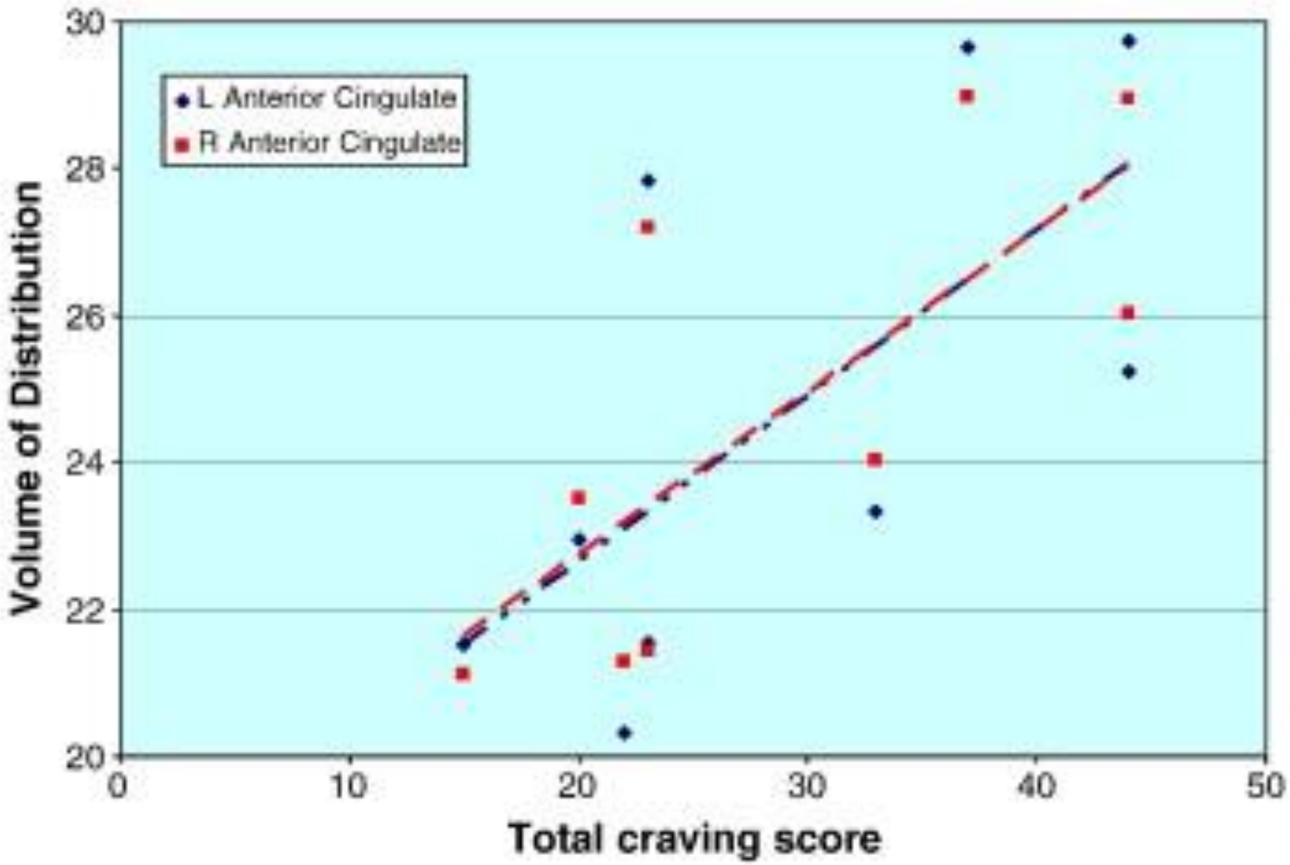


Williams et al., *ENPP* 2009

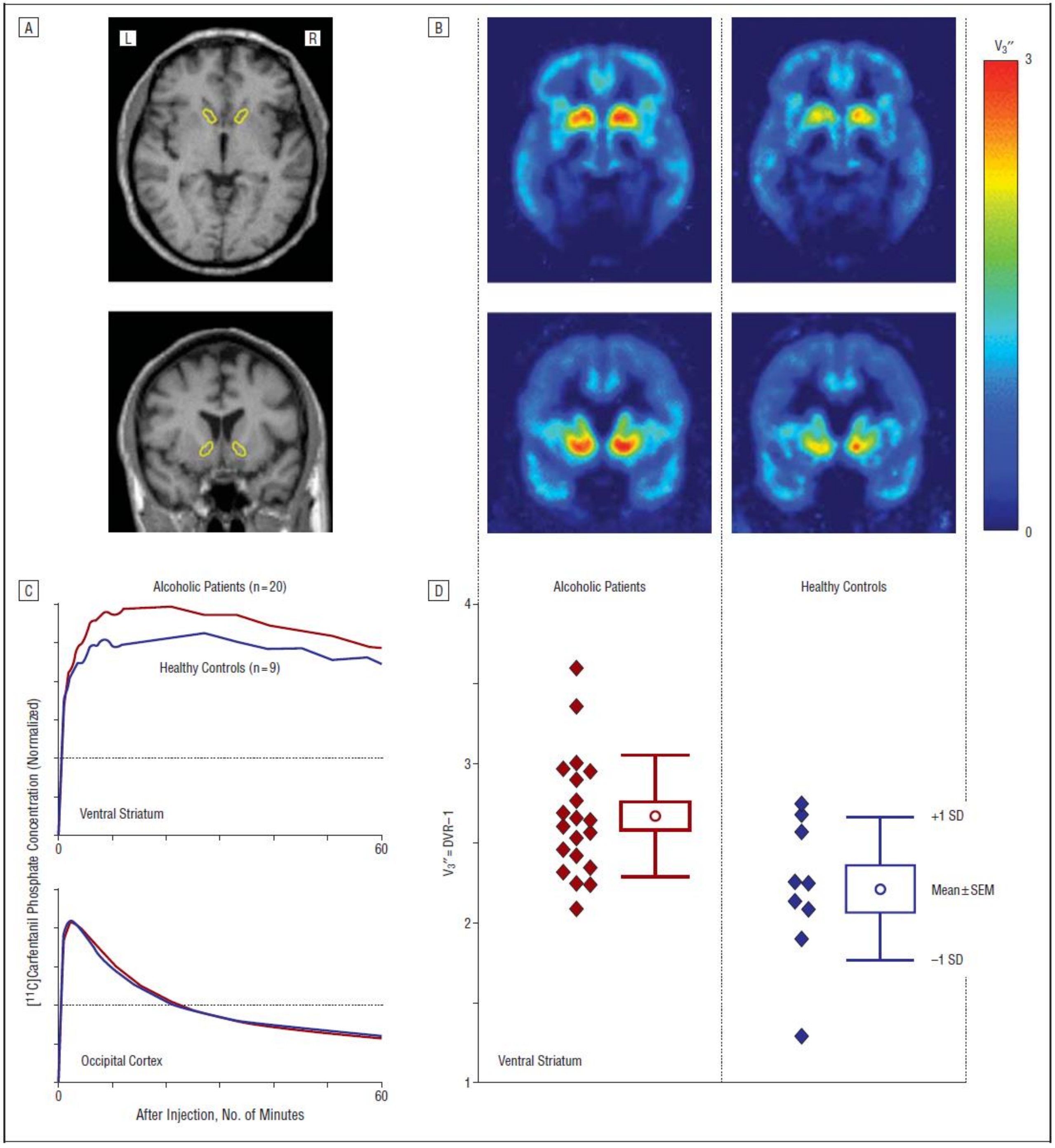
13 controls and 11 early abstinent alcohol dependent patients



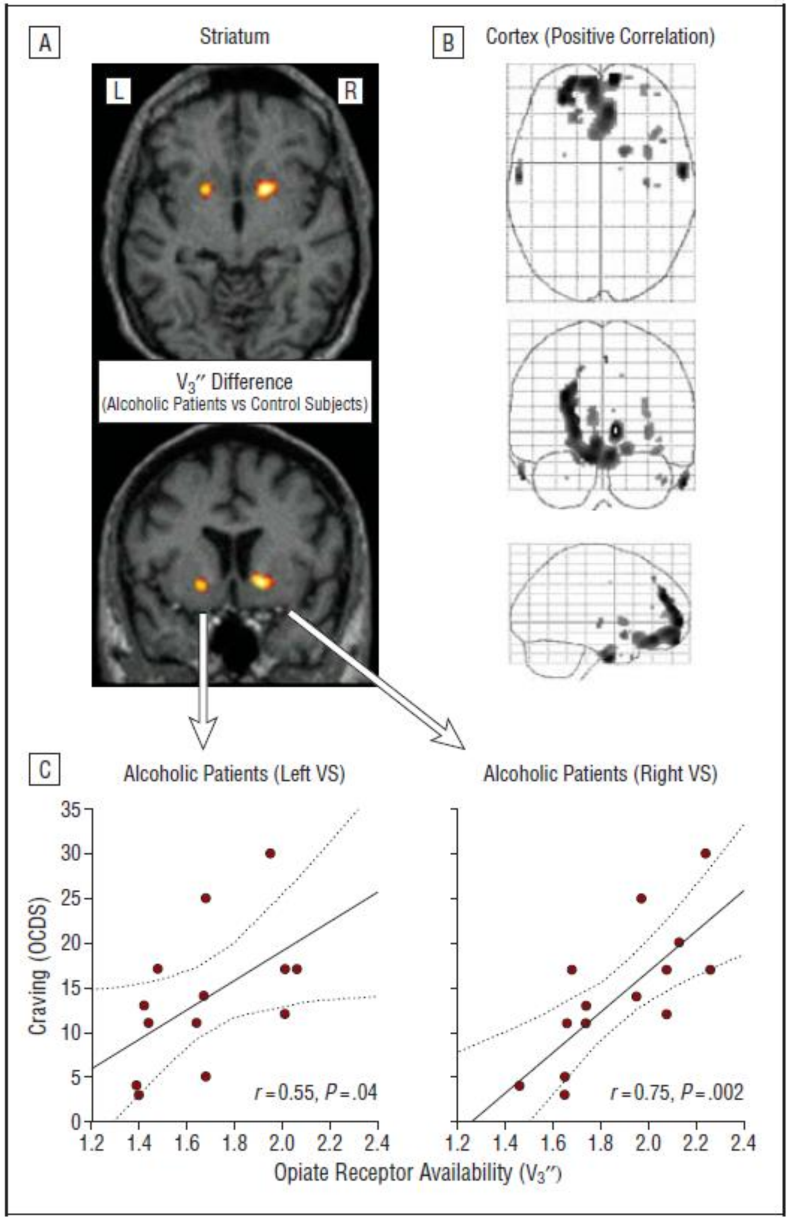
Williams et al., *ENPP* 2009



^{11}C-carfentanil PET



Heinz et al., *Arch Gen Psychiatry* 2005



Heinz et al., *Arch Gen Psychiatry* 2005

Conclusions

PET/SPECT: measure DA $D_{2/3}$ receptors, DA release, DAT, opioid receptors….

Addiction: lower $D_{2/3}$ receptor binding and blunted DA release; association with drug wanting; opioid receptors increased and association with craving

Impulsivity: more DA release, due to lower $D_{2/3}$ binding in SN?

ICD in PD due to DA agonists: impaired processing negative feedback during reward learning

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