Striatal dopamine in Dual Diagnosis: Schizophrenia and Addiction

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Outline

Imaging DA release in humans in striatal substructures

Imaging DA release in Schizophrenia

Imaging DA release in Drug Dependence

Imaging DA release in DD: comorbid SCZ and Dependence

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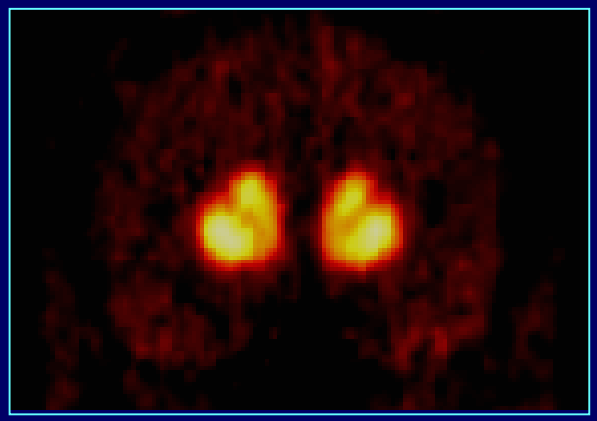
D2/3 with [11C]Raclopride

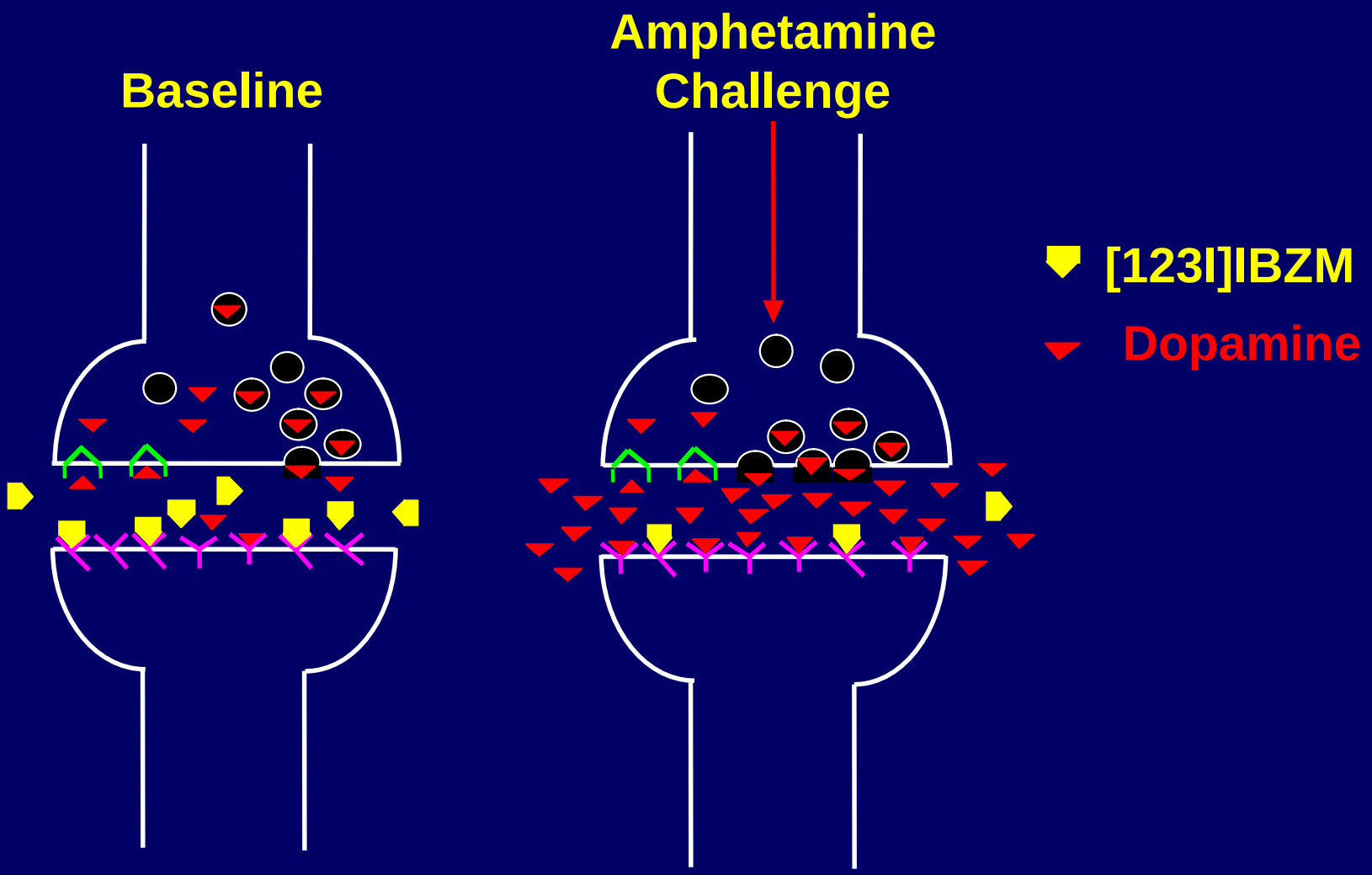


Corresponding D_2 PET Scan

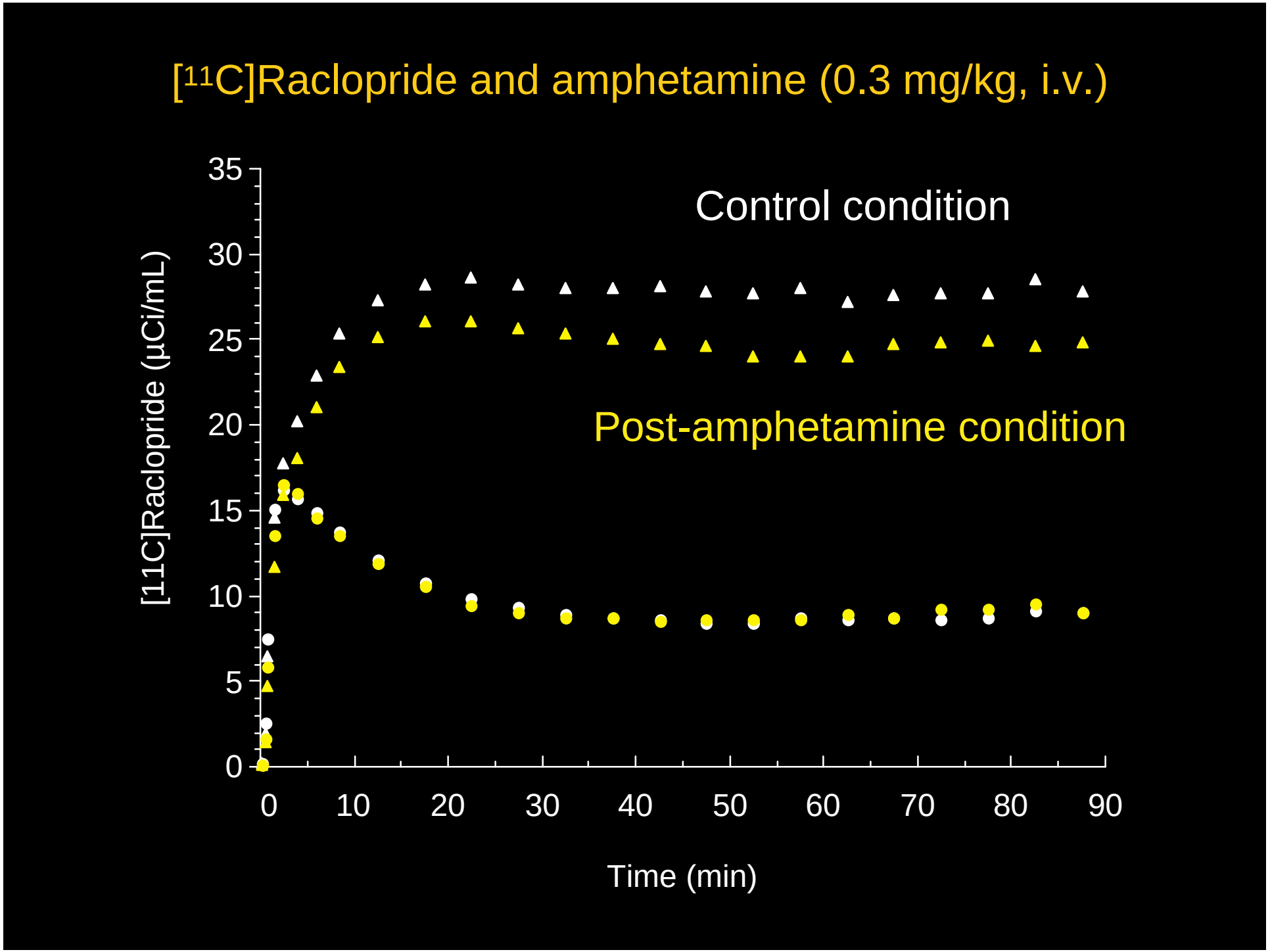
Coronal MRI

Division of Functional Brain Mapping, New York State Psychiatric Institute, Columbia University.

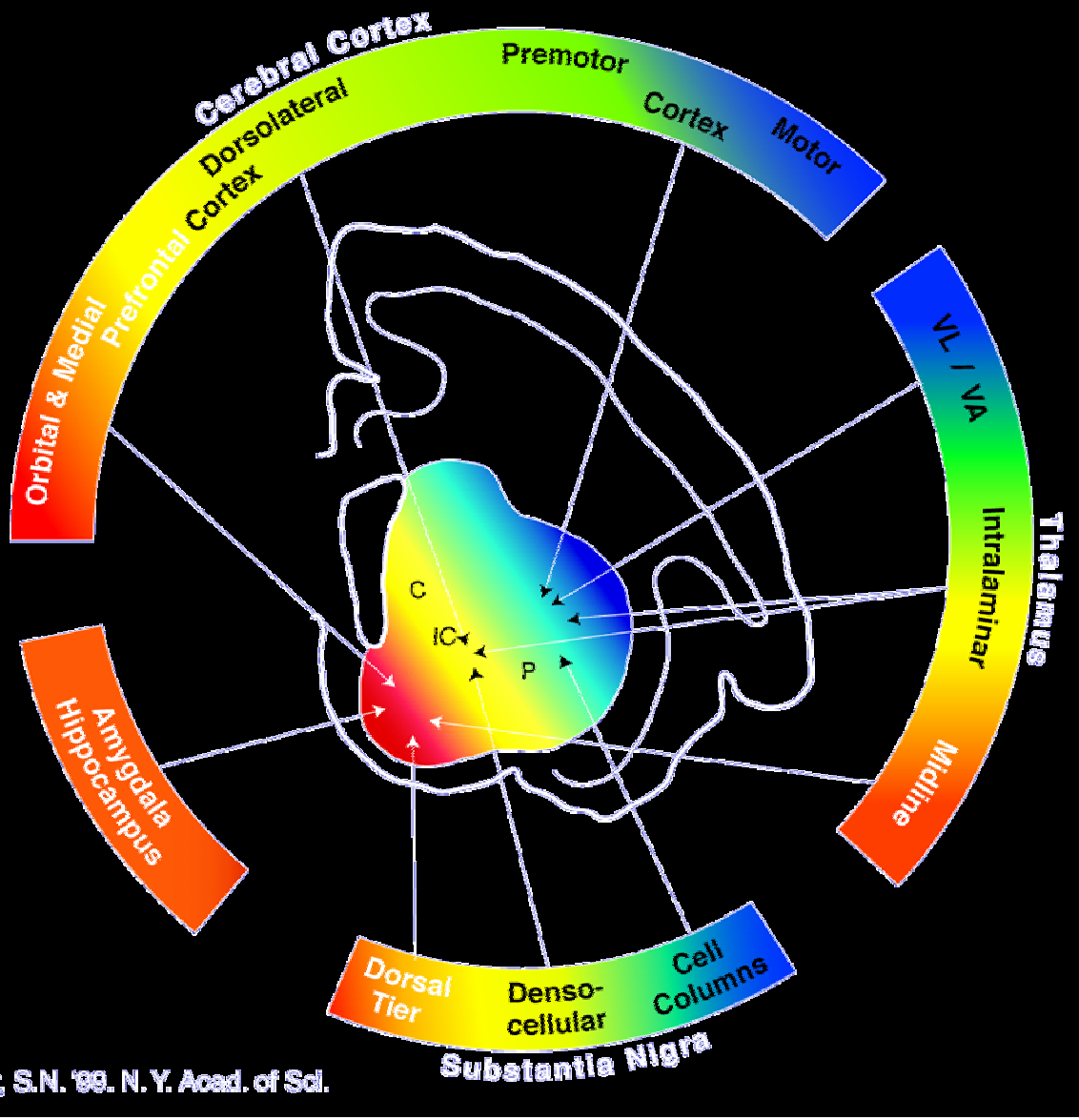
Imaging Intrasynaptic Dopamine Release



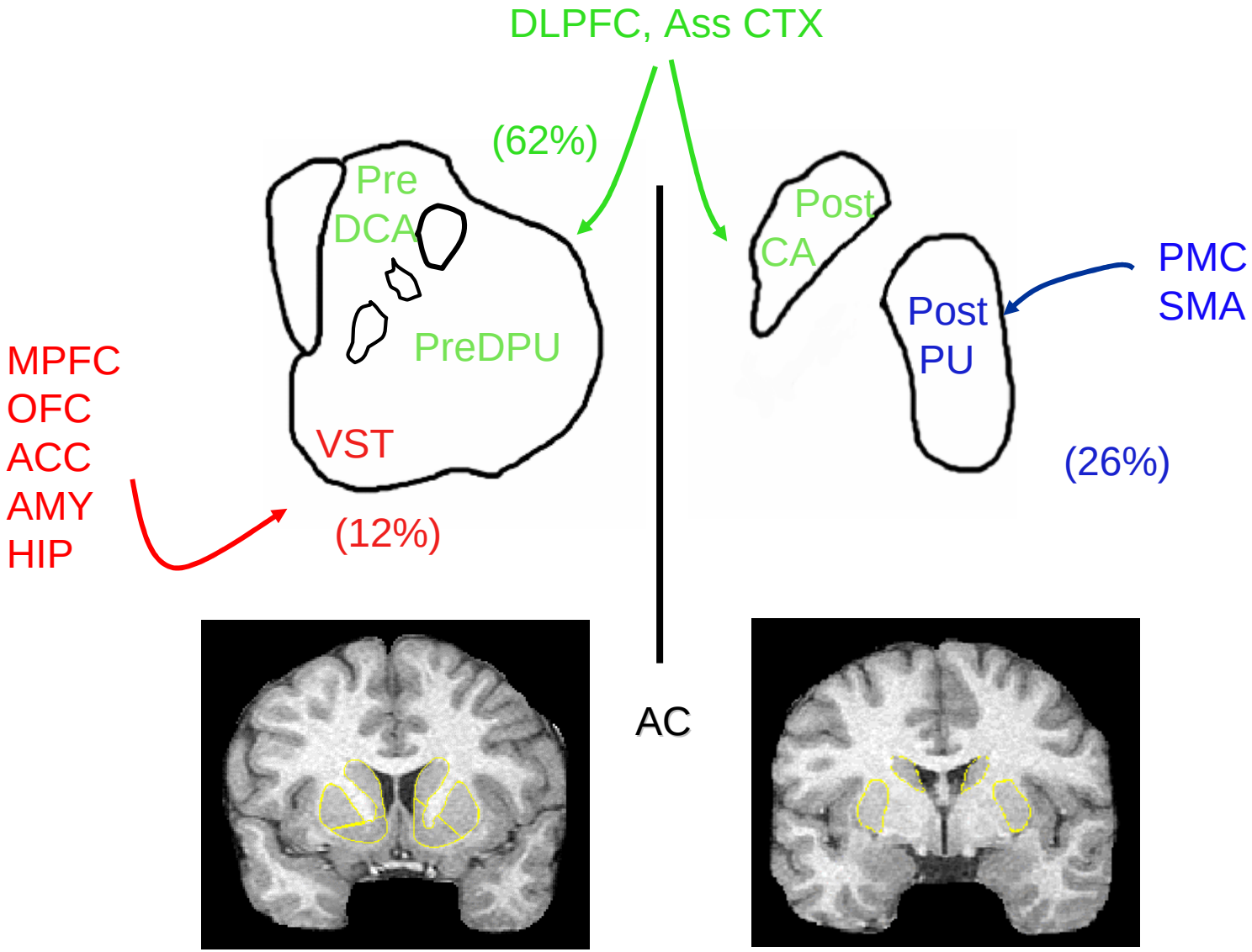
Laruelle M. *Proc Natl Acad Sci USA*. 1996;93:9235-9240.


[11C]Raclopride and amphetamine (0.3 mg/kg, i.v.)
Control condition
Post-amphetamine condition
[11C]Raclopride (µCi/mL)
Time (min)
0
5
10
15
20
25
30
35
0
10
20
30
40
50
60
70
80
90

The striatum is a complex structure, processing information from multiple cortical inputs

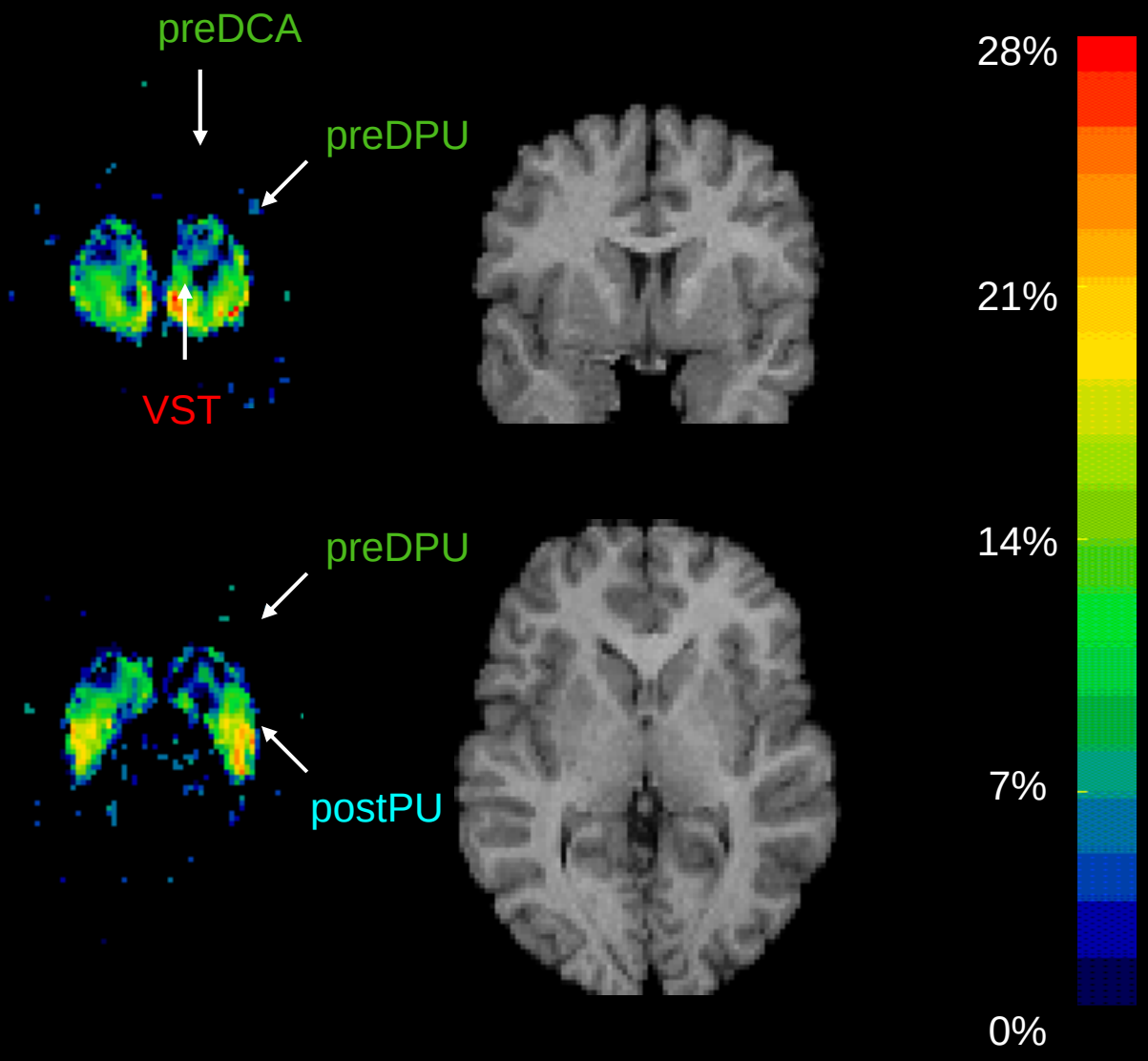


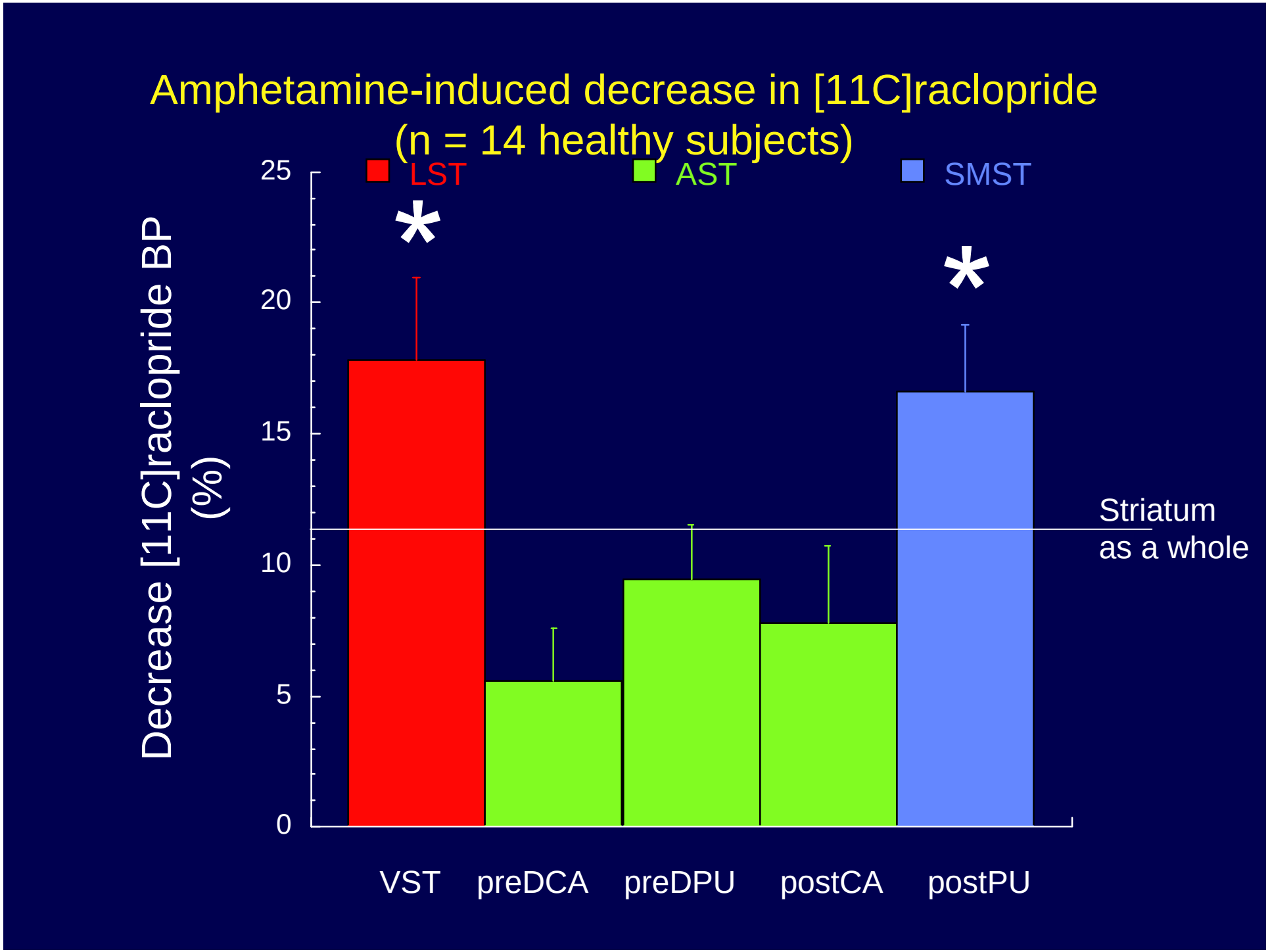
PET imaging of Limbic, associative, and sensorimotor divisions of the striatum with ECAT HR+ (4 mm resolution)



Mawlawi et al.,JCBFM, 2001, Martinez et al. JCBFM, 2003

Dopamine Release Amplitude Maps
(% decrease [11C]raclopride, n = 14 healthy subjects)




Amphetamine-induced decrease in [11C]raclopride
(n = 14 healthy subjects)
LST
AST
SMST
Decrease [11C]raclopride BP (%)
25
20
15
10
5
0
*
*
Striatum as a whole
VST
preDCA
preDPU
postCA
postPU

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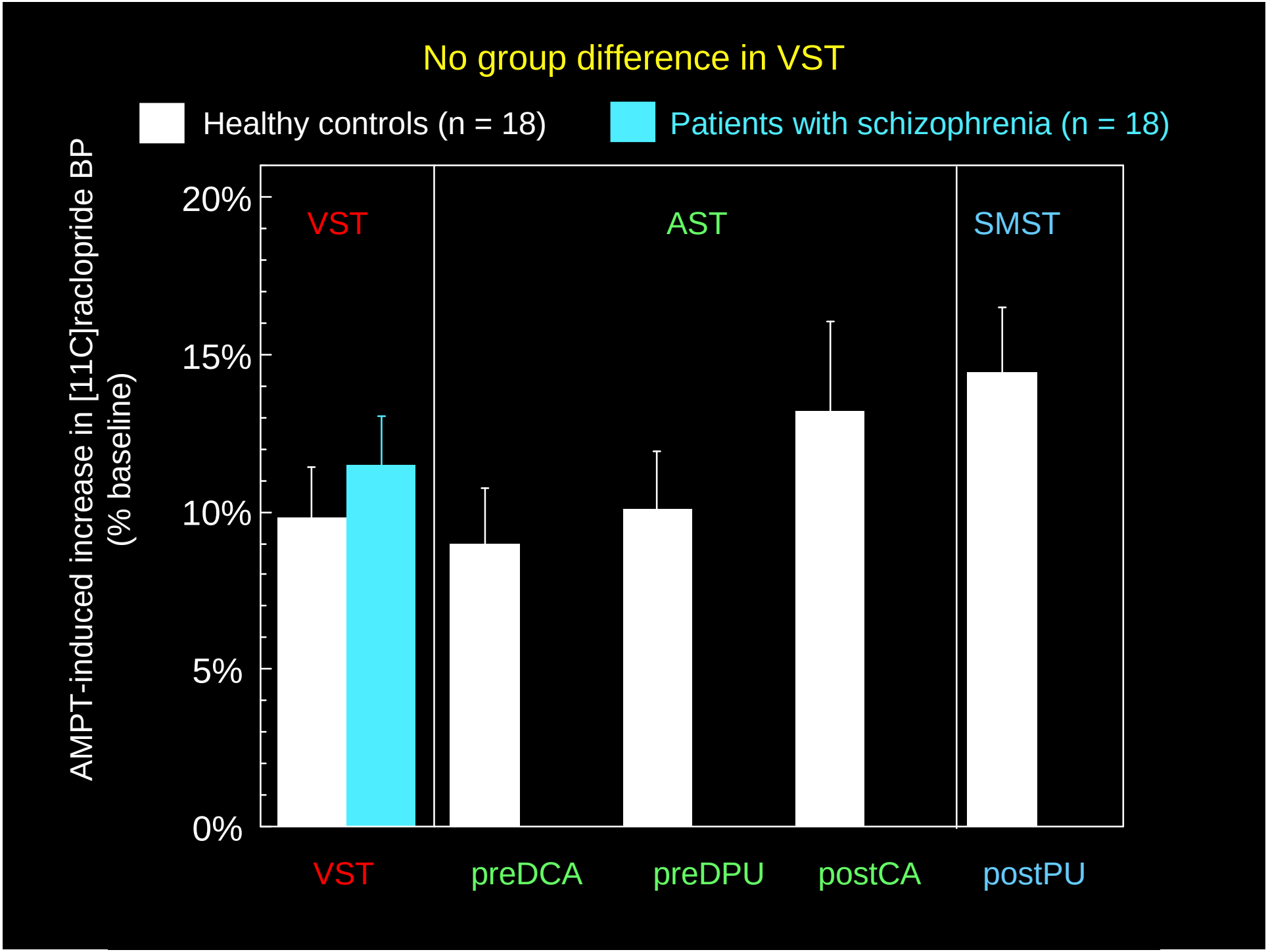
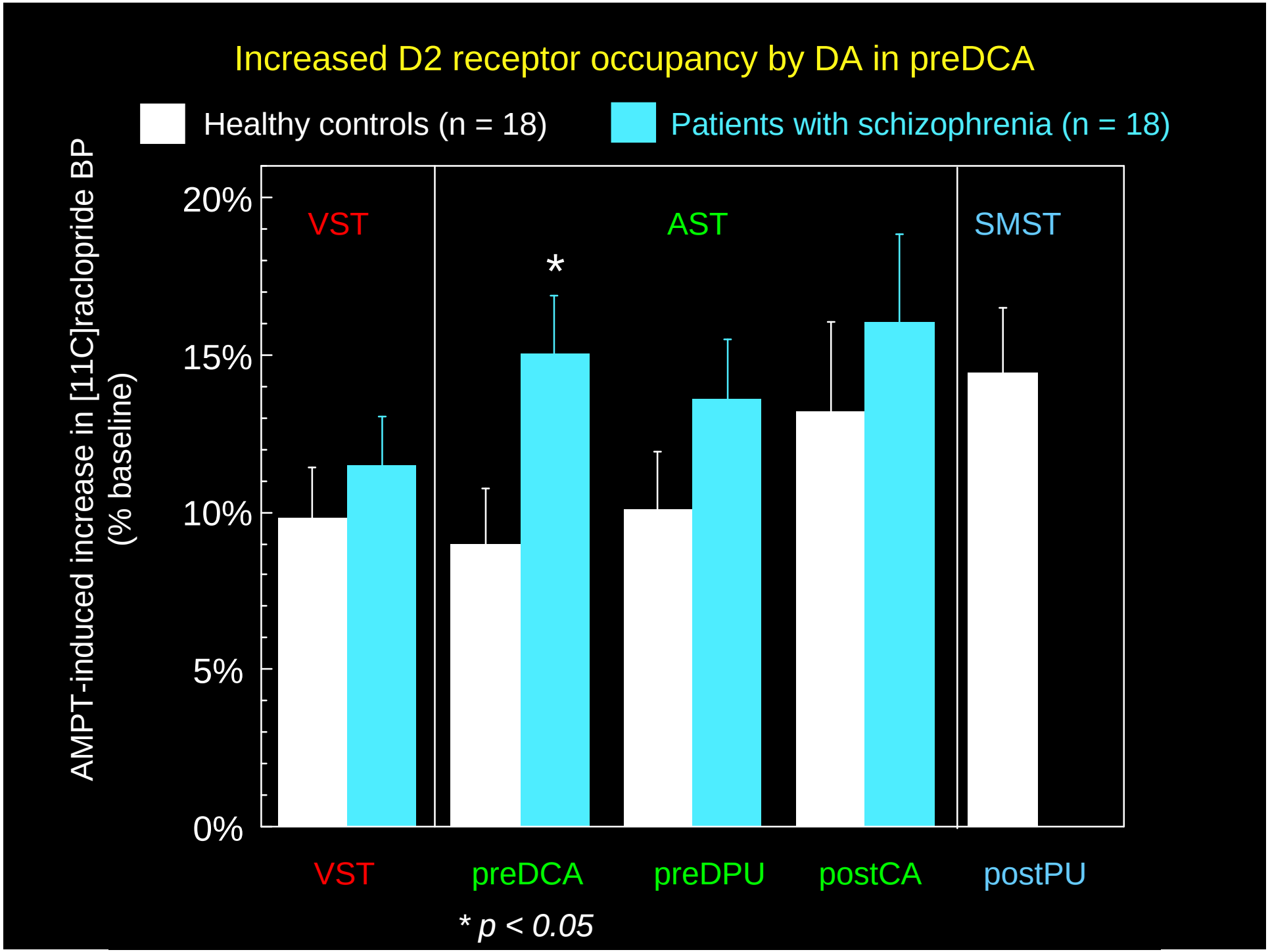
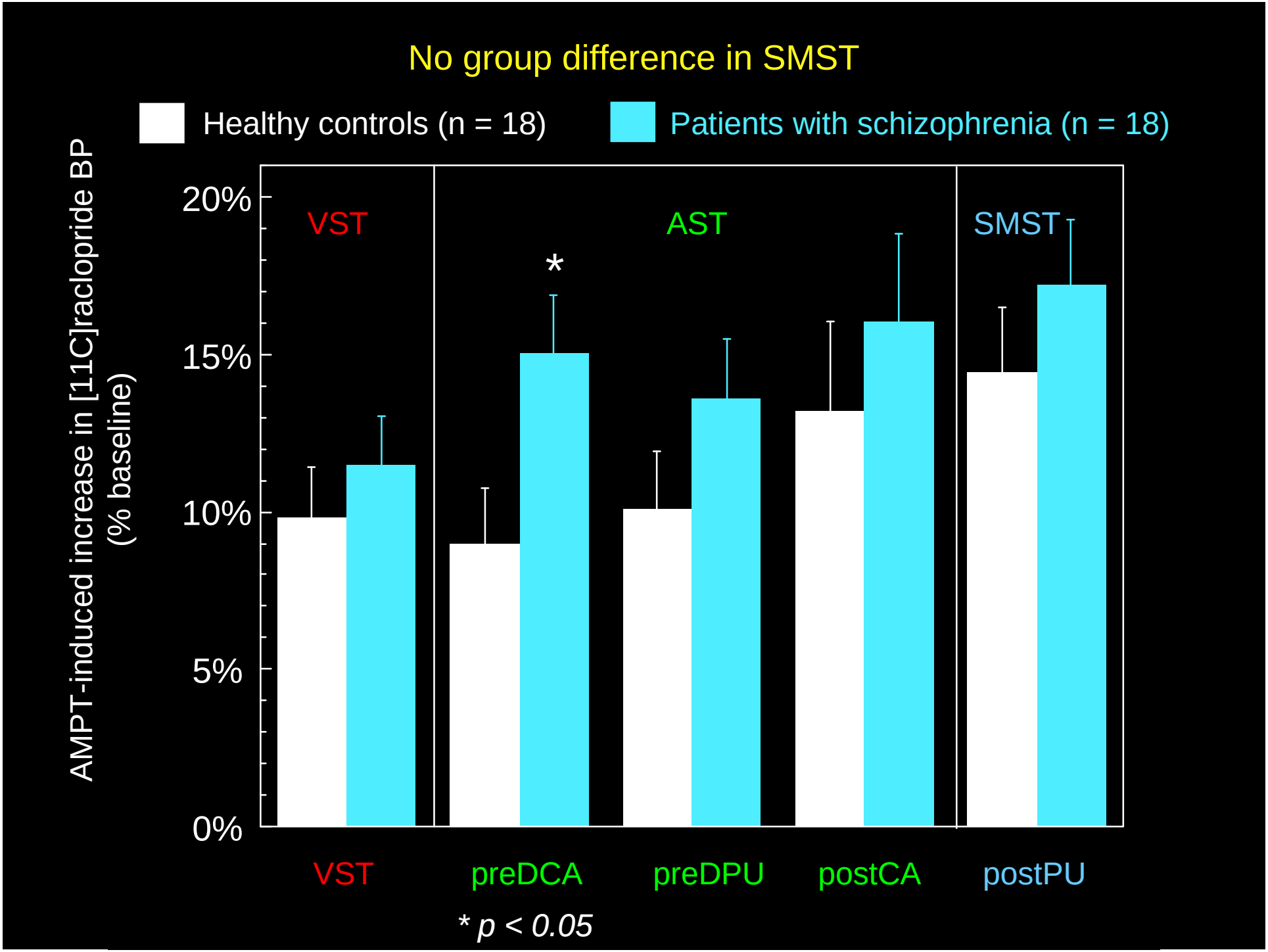
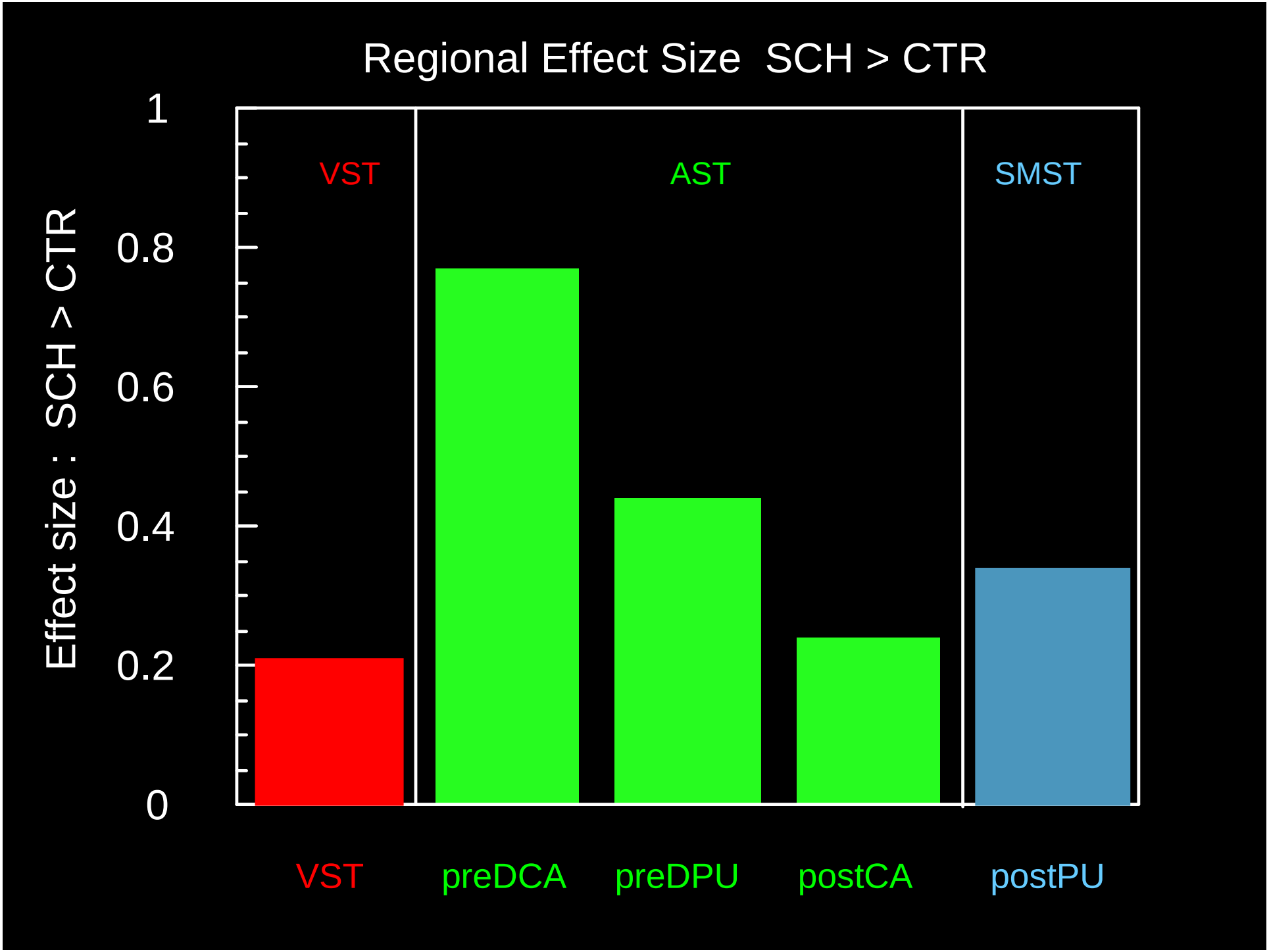
D2 Occupancy by DA in Striatal Subregions in Schizophrenia

Diagnosis	Healthy Controls	Patients with schizophrenia	p
n	18	18	
Age (y)	29 ± 7	29 ± 8	1.00
Gender	13M/5F	13M/5F	-
Ethnicity	7AA/1AS/6C/4H	7AA/1AS/6C/4H	-
Smoker	5Y/13N	4Y/14N	-
Weight (kg)	82 ± 16	84 ± 23	0.74
Drug naïve/Drug free	-	6/12	-
[11C]Raclopride scan at baseline (day 1)			
Dose mCi	11.9 ± 3.2	11.8 ± 4.0	0.99
Dose µg	3.5 ± 1.0	3.5 ± 1.0	1.00
[11C]Raclopride scan in the DA depleted state (day 3)			
Dose mCi	13.4 ± 3.5	11.8 ± 4.3	0.23
Dose µg	3.4 ± 0.9	3.5 ± 1.0	0.75


No group difference in VST
Healthy controls (n = 18)
Patients with schizophrenia (n = 18)
AMPT-induced increase in [11C]raclopride BP
(% baseline)
20%
15%
10%
5%
0%
VST
AST
SMST
VST
preDCA
preDPU
postCA
postPU


Increased D2 receptor occupancy by DA in preDCA
Healthy controls (n = 18)
Patients with schizophrenia (n = 18)
AMPT-induced increase in [11C]raclopride BP
(% baseline)
20%
15%
10%
5%
0%
VST
AST
SMST
*
VST
preDCA
preDPU
postCA
postPU
* p < 0.05


No group difference in SMST
Healthy controls (n = 18)
Patients with schizophrenia (n = 18)
AMPT-induced increase in [11C]raclopride BP
(% baseline)
20%
15%
10%
5%
0%
VST
AST
SMST
*
VST
preDCA
preDPU
postCA
postPU
* p < 0.05


Regional Effect Size SCH > CTR
Effect size : SCH > CTR
1
0.8
0.6
0.4
0.2
0
VST
AST
SMST
VST
preDCA
preDPU
postCA
postPU

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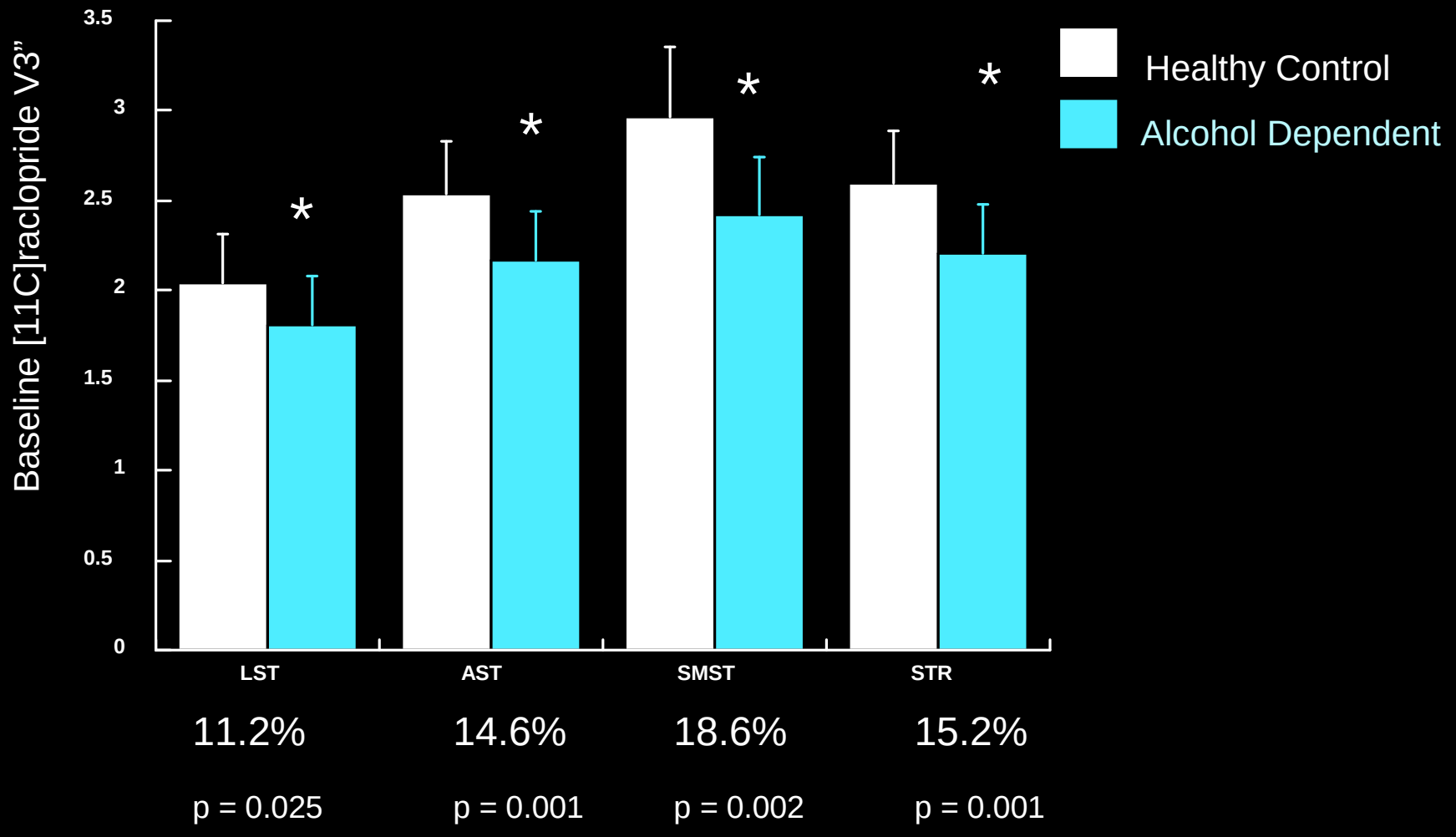
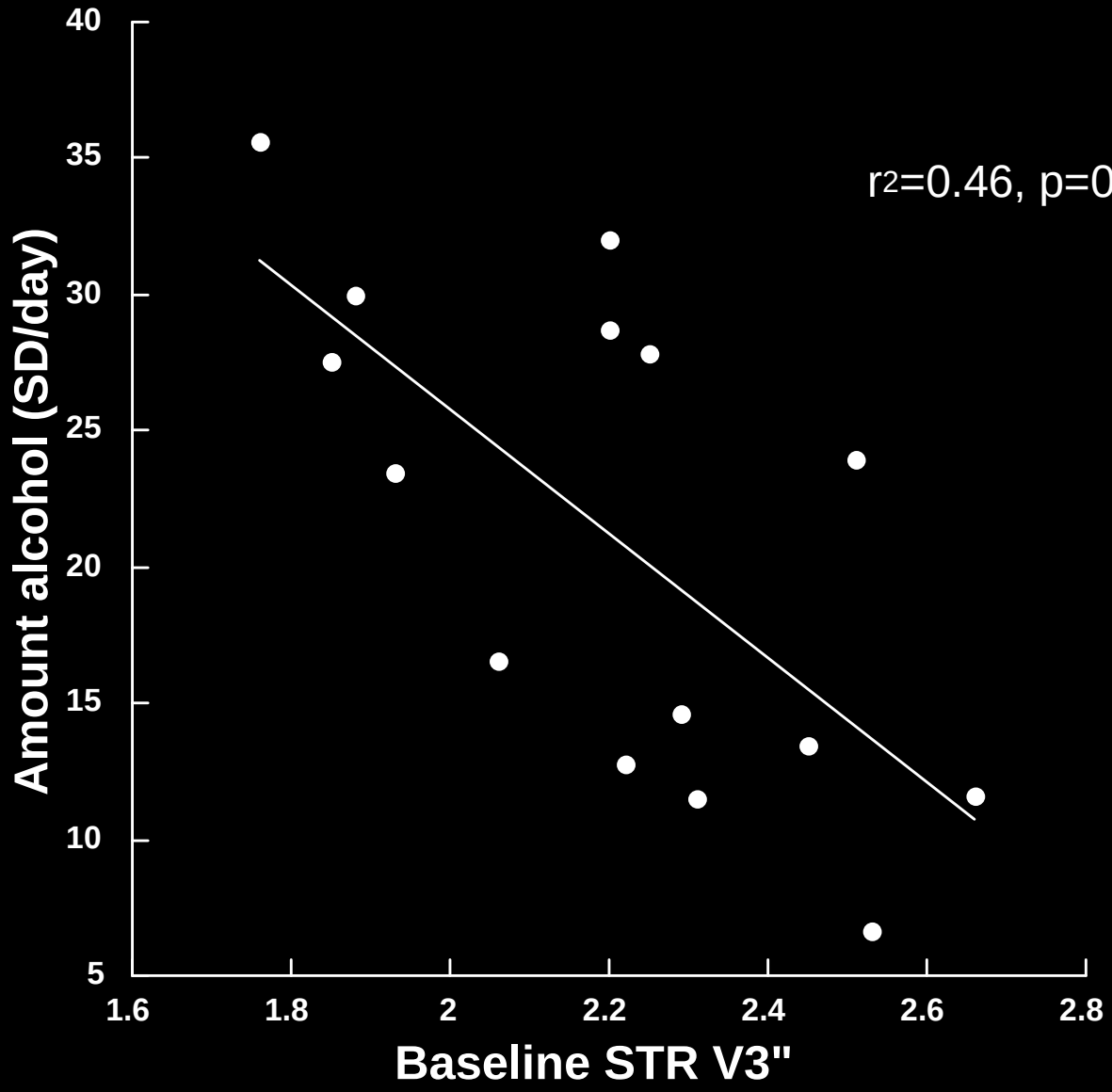
Alcoholism: Baseline D2 receptor availability



Martinez et al., 2004, 2006

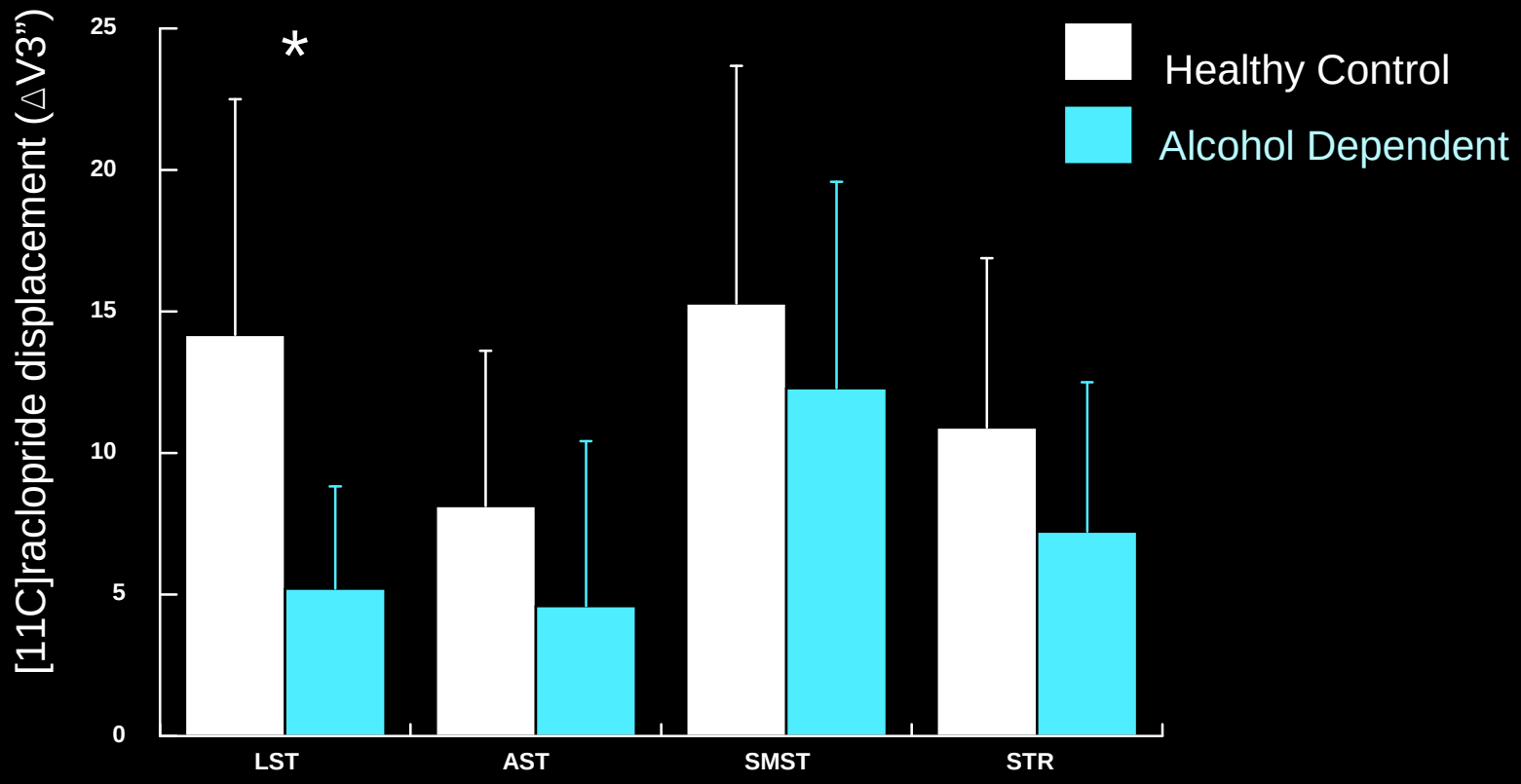
Baseline D2 and clinical measures



LST: r^2=0.41, p=0.011, AST: r^2=0.43, p=0.008, SMST: r^2=0.46, p=0.006

Martinez et al., 2004, 2006

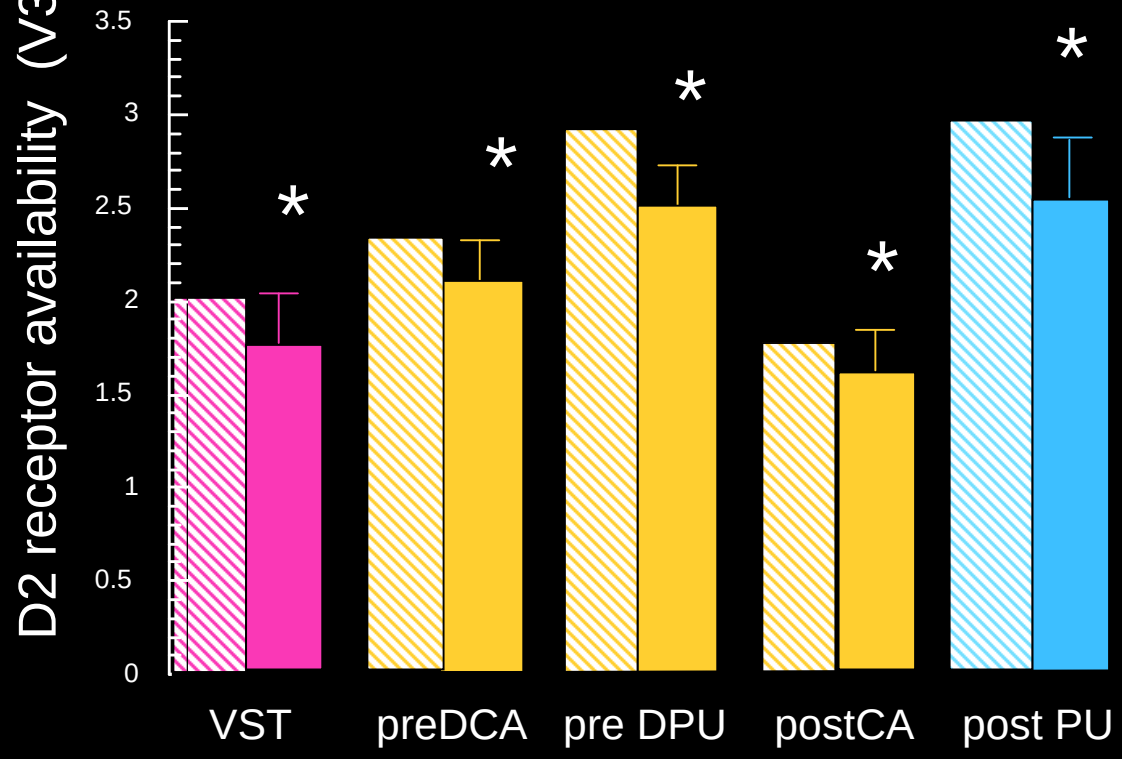
Alcoholism: [^{11}C]Raclopride displacement



	HC	AD	p
LST	-14.2 ± 8.3%	-5.2% ± 3.6%	0.001
AST	-8.1% ± 5.5%	-4.6% ± 5.8%	0.10
SMST	-15.3% ± 8.4%	-12.3% ± 7.3%	0.31

Martinez et al., 2004, 2006

Cocaine dependence: D2 receptor availability



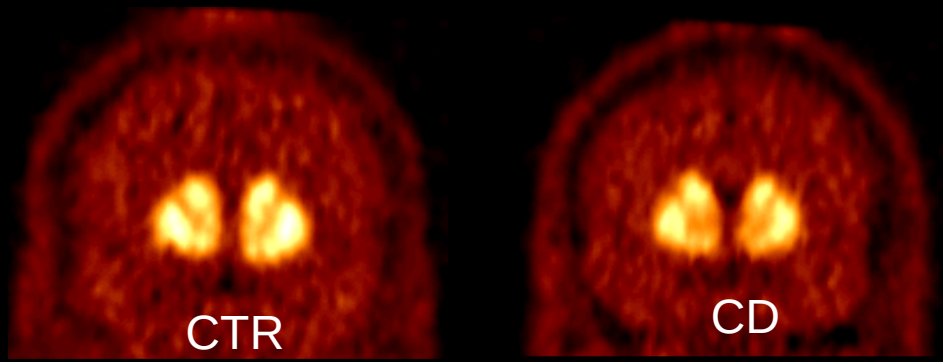
Controls (n =14)

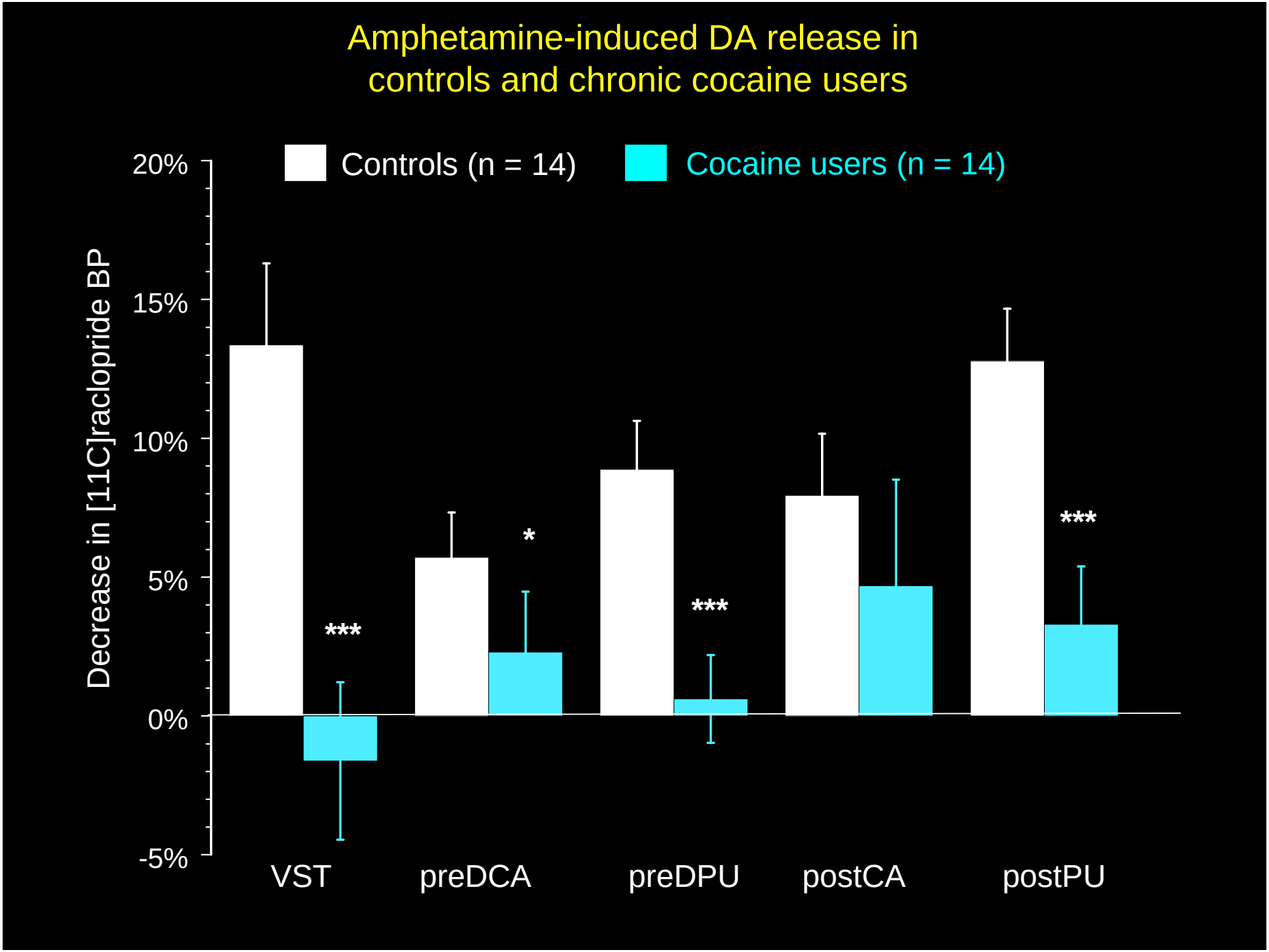
Cocaine (n =14)

Limbic -15%

Assoc -12%

Motor -16%




Amphetamine-induced DA release in
controls and chronic cocaine users
Controls (n = 14)
Cocaine users (n = 14)
Decrease in [11C]raclopride BP
20%
15%
10%
5%
0%
-5%
***
*
***
***
VST
preDCA
preDPU
postCA
postPU

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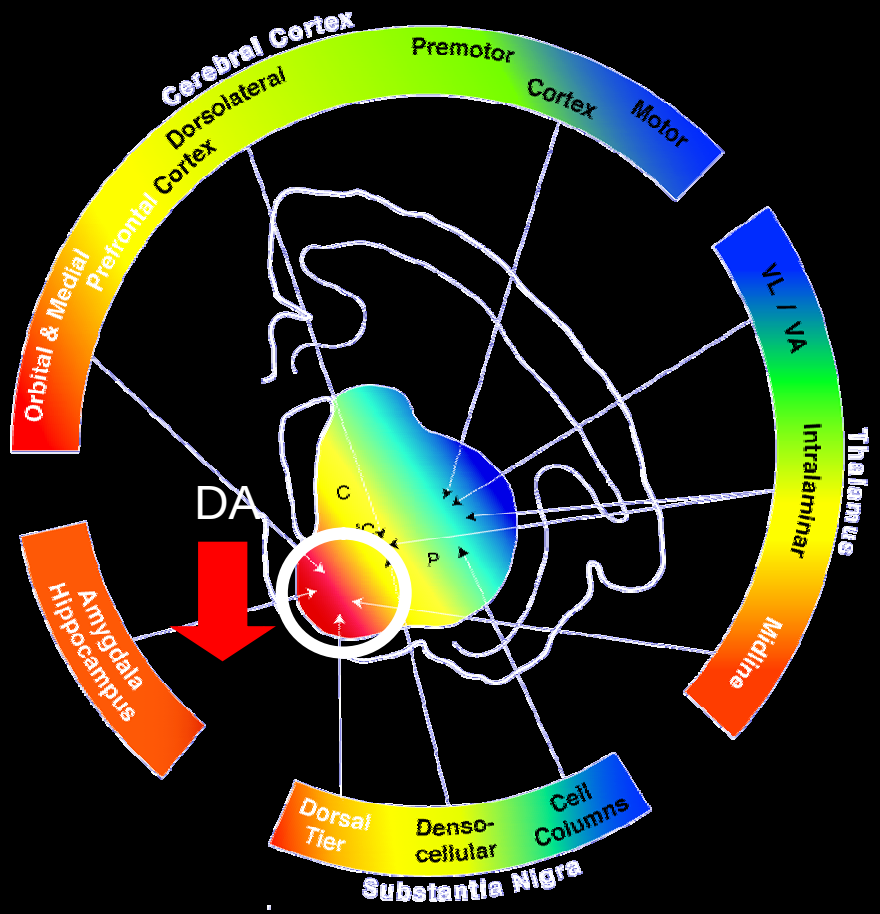
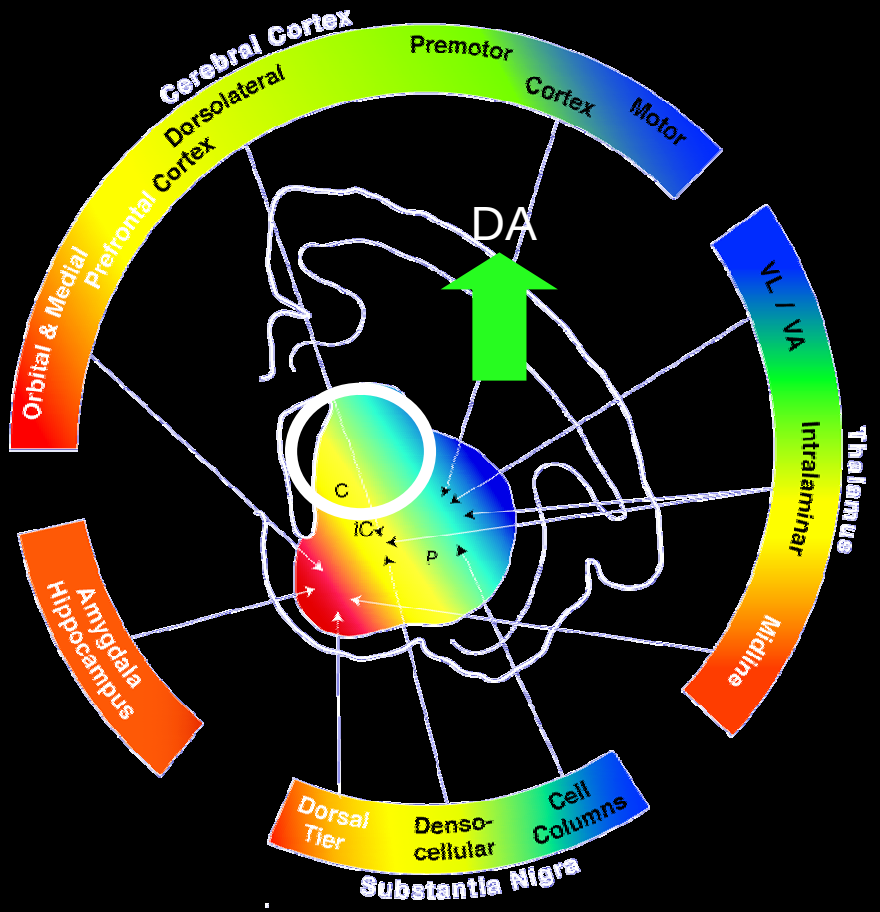
If addiction is associated with decreased DA function in limbic striatum



*

If schizophrenia is associated with increased DA function in associative striatum

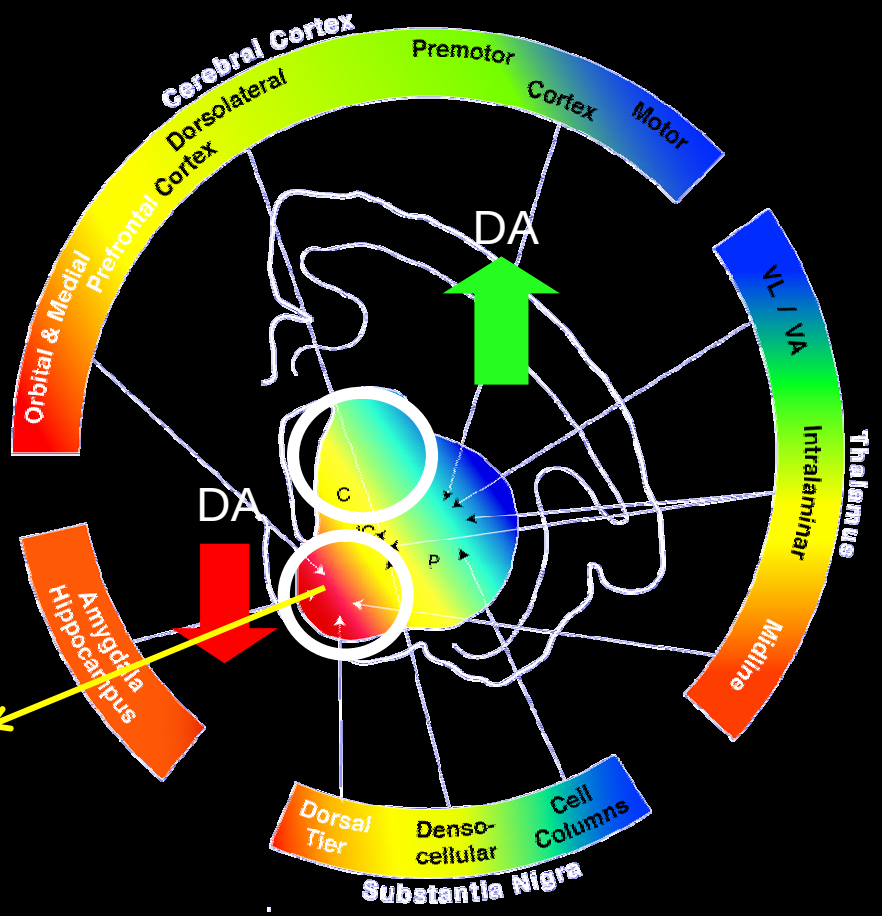


“Dual diagnosis” patients might have both

Worsening of psychosis

ER

D2 blockade by antipsychotic



Drug taking behavior

Worsening drug craving

Antipsychotic discontinuation

Methods: [^{11}C]Raclopride

PET procedures

- ECAT EXACT HR+ in 3D mode/ bolus + constant infusion
- Kbol 105 min.
- Equilibrium analysis on data from 40 - 90 min
- Region of interest analysis: ROI drawn on each subject's MRI
- Five venous samples: for measurement of VND: cer activity/ plasma Css
- BPND = (ROI - CER)/CER = specific/non-specific binding

Procedure repeated 2 min after ampetamine administration (0.3 mg/kg, i.v.)

Delta BPND = (Baseline BPND - Post-amphetamine BPND) / Baseline BPND

Demographics

	DD	HC	p
n	7	10	
Age	28.9 ± 6.9	27.9 ± 6.6	NS
Gender	5 M, 2 F	7 M, 3 F	
Smoker	4 Y, 3 N	10 N	
SES - subject	19.8 ± 4.9	36 ± 15.7	0.01
SES - parental	40.8 ± 15.3	43.6 ± 12	NS
Ethnicity (C,AA,H,As)	2,2,3,0	4,3,2,1	

Clinical Characteristics

Primary diagnosis:	
Schizophrenia	3
Schizoaffective d/o	4
Mean duration of psychotic illness (years) :	6.8 ± 5.8
Psychiatric comorbidities:	
Depression, current (per BDI):	4
OCD	1
Mean time since last medication dose (weeks):	6.3 ± 5
Medication naïve	2
Substance use diagnosis:	
Cannabis dep.	7
Alcohol dep.	5
Alcohol abuse	1
Mean duration substance use (years):	11.6 ± 6
Mean ASI (Addiction severity index, score 0-9)	6 ± 2.4
Mean time since last drug use (weeks):	6.2 ± 5.2

Volumetric measurements: striatal substructures

ROI volume	DD	HC	p
VST vol	2192.36 ± 363.22	2213 ± 432	0.92
AST vol	10890.43 ± 1225.9	11833 ± 1366	0.17
preDCA vol	5260.71 ± 831.16	5589 ± 822	0.43
preDPU vol	3693.43 ± 526.02	4163 ± 576	0.11
postCA vol	1936.29 ± 324.85	4663 ± 882	0.41
postPU vol	4662.86 ± 881.69	4850 ± 450	0.57

	DD (n=7)			HC (n=10)			
PET parameters	***Baseline***	***Post-amph***	***paired t (p)***	***Baseline***	***Post-amph***	***paired t (p)***	***2 group t (p)***
ID (mCi)	**7.17 ± 1.32**	**7.62 ± 1.53**	**0.62**	**8.8 ± 0.94**	**8.29 ± 0.88**	**0.19**	**0.22**
IM (µg)	**4.49 ± 1.69**	**3.36 ± 1.68**	**0.07**	**4.2 ± 1.54**	**2.83 ± 1.27**	**0.02**	**0.91**
SA (Ci/mmol)	**994 ± 516**	**1472 ± 761**	**0.02**	**1291 ± 614**	**1962 ± 1176**	**0.09**	**0.71**
V_{ND}	**0.42 ± 0.06**	**0.41 ± 0.17**	**0.93**	**0.41 ± 0.09**	**0.34 ± 0.08**	**0.001**	**0.22**
fp	**4.3 ± 1.0%**	**3.9 ± 0.5%**	**0.56**	**4.4 ± 0.7%**	**4.1 ± 0.4%**	**0.09**	**0.58**
amph. level (ng/ml)*	**NA**	**36.41 ± 7.8**	**NA**	**NA**	**38.43 ± 5.6**	**NA**	**0.61**

*at 40 min. > injection

Amph. level and $\triangle BP_{ND}$ were not significantly correlated (levels available for 6 HC)

	DD (n=7)			HC (n=10)			
PET parameter	*Baseline*	*Post-amph*	*paired t (p)*	*Baseline*	*Post-amph*	*paired t (p)*	*2 group t (p)*
ID (mCi)	7.17 ± 1.32	7.62 ± 1.53	0.62	8.8 ± 0.94	8.29 ± 0.88	0.19	0.22
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SA (Ci/mmol)	994 ± 516	1472 ± 761	0.02	1291 ± 614	1962 ± 1176	0.09	0.71
V_{ND}	0.41 ± 0.06	0.35 ± 0.04	0.11	0.41 ± 0.09	0.34 ± 0.08	0.001	0.69
fp	4.3 ± 1.0%	3.9 ± 0.5%	0.56	4.4 ± 0.7%	4.1 ± 0.4%	0.09	0.58

*V_{ND} **for DD** without outlier

Baseline D2 and ΔBPND

	DD BP_{ND}			HC BP_{ND}			ΔDD v ΔHC
ROI	baseline	post-amph.	ΔBP_{ND}	baseline	post-amph.	ΔBP_{ND}	p
LST	2.18 ± 0.39	2.02 ± 0.36	-5.7 ± 17.4%	2.19 ± 0.37	1.99 ± 0.41	-8.5 ± 14.4%	0.72
AST	2.46 ± 0.3	2.28 ± 0.25	-7 ± 4.0%	2.65 ± 0.35	2.39 ± 0.4	-9.9 ± 8.0%	0.38
Pre-DCA	2.43 ± 0.28	2.21 ± 0.27	-8.9 ± 5.8%	2.62 ± 0.41	2.36 ± 0.45	-9.9 ± 9.0%	0.79
Pre-DPU	2.82 ± 0.34	2.63 ± 0.3	-6.5 ± 3.5%	3.09 ± 0.35	2.73 ± 0.43	-12.1 ± 6.8%	0.06
Post-CA	1.85 ± 0.38	1.8 ± 0.29	-1.7 ± 10.2%	1.95 ± 0.39	1.81 ± 0.36	-5.9 ± 16.0%	0.55
SMST	3.19 ± 0.36	2.82 ± 0.36	-11.5 ± 6.5%	3.31 ± 0.42	2.71 ± 0.39	-18.1 ± 7.3%	0.08
PUT	3.03 ± 0.34	2.74 ± 0.31	-9.4 ± 4.6%	3.2 ± 0.35	2.72 ± 0.37	-15.1 ± 6.2%	0.05
STR	2.62 ± 0.3	2.4 ± 0.26	-8.3 ± 3.7%	2.75 ± 0.33	2.43 ± 0.36	-11.7 ± 6.3%	0.22

	HC BP_{ND}: Abi-Dargham in prog. n=10, age=28 ± 7 yr			HC BP_{ND} : Martinez et al., 2003 n=14, age=33 ± 7		
ROI	baseline	post-amph.	$^2BP_{ND}$	baseline	post-amph.	$^2BP_{ND}$
LST	2.19 ± 0.37	1.99 ± 0.41	-8.5 ± 14.4%	2.03 ± 0.34	1.71 ± 0.31	−15.3 ± 11.8
AST	2.65 ± 0.35	2.39 ± 0.4	-9.9 ± 8.0%	2.56 ± 0.31	2.34 ± 0.23	−8.1 ± 7.2
Pre-DCA	2.62 ± 0.41	2.36 ± 0.45	-9.9 ± 9.0%	2.44 ± 0.31	2.28 ± 0.25	−6.1 ± 7.6
Pre-DPU	3.09 ± 0.35	2.73 ± 0.43	-12.1 ± 6.8%	3.11 ± 0.35	2.78 ± 0.29	−10.2 ± 7.9
Post-CA	1.95 ± 0.39	1.81 ± 0.36	-5.9 ± 16.0%	1.77 ± 0.33	1.63 ± 0.30	−7.6 ± 11.0
SMST	3.31 ± 0.42	2.71 ± 0.39	-18.1 ± 7.3%	3.14 ± 0.39	2.62 ± 0.34	−16.1 ± 9.6
PUT	3.2 ± 0.35	2.72 ± 0.37	-15.1 ± 6.2%	-	-	-
STR	2.75 ± 0.33	2.43 ± 0.36	-11.7 ± 6.3%	2.53 ± 0.24	2.26 ± 0.24	

Tentative Conclusions

1- DD patients have smaller striatal volume

2- DD patients have lower D2 BP

3- DD patients have lower dopamine release

4- sample is too small for definitive conclusions but suggest that DD is more similar to Dependence than to schizophrenia. AST is least affected, suggesting that patients may have started like SCZ and evolved as in dependence.

5- Implications: psychosis in the absence of increased dopamine, more treatment resistant?

6- longer duration of substance dependence than of schizophrenia may have influenced the results

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NIMH: SCZ