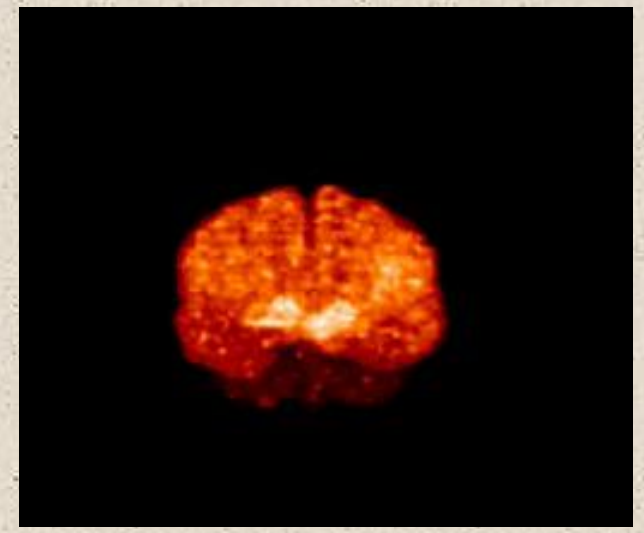
Images of an *Ongoing* Pandemic: Using PET to Understand Addiction



David Matuskey, M.D.
Medical Director, Yale PET Center
Assistant Professor of Radiology and Biomedical Imaging, Psychiatry and Neurology at Yale University School of Medicine

Carte de jour

- Introduction
- A brief history of time (or least PET imaging in addiction)
- The Dark Side
- It’s good to be the king
- Discussion and future musings

Where it all begins…

Patent Medicines

Am. J. Ph.] 7 [December, 1901

BAYER Pharmaceutical Products

HEROIN—HYDROCHLORIDE

is pre-eminently adapted for the manufacture of cough elixirs, cough balsams, cough drops, cough lozenges, and cough medicines of any kind. Price in 1 oz. packages, $4.85 per ounce; less in larger quantities. The efficient dose being very small (1-48 to 1-24 gr.), it is

The Cheapest Specific for the Relief of Coughs

(In bronchitis, phthisis, whooping cough, etc., etc.)

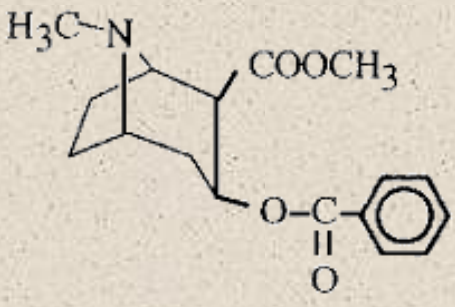
WRITE FOR LITERATURE TO

FARBENFABRIKEN OF ELBERFELD COMPANY

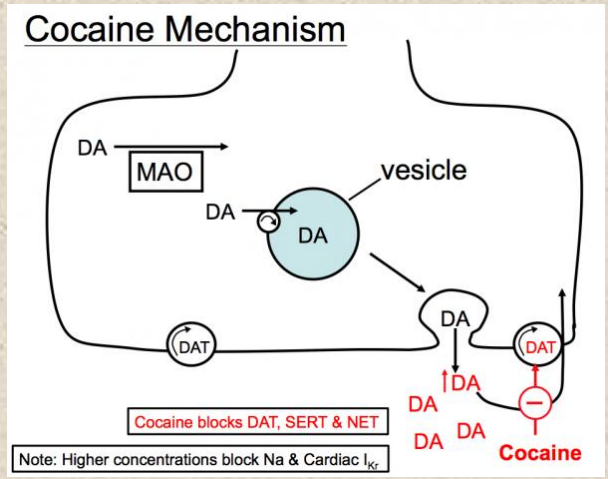
SELLING AGENTS

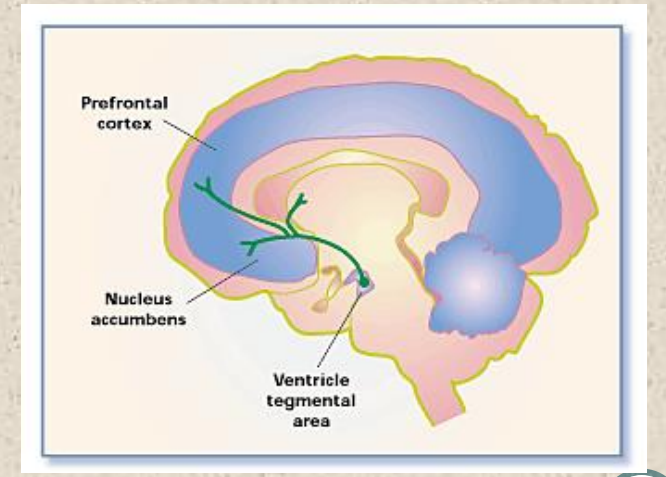
P. O. Box 2160 40 Stone Street, NEW YORK

Basic Cocaine Physiology

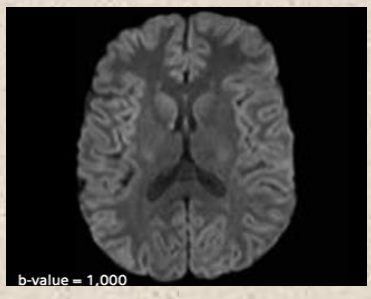


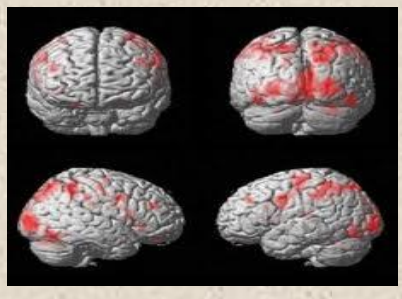
Structure 1. Cocaine

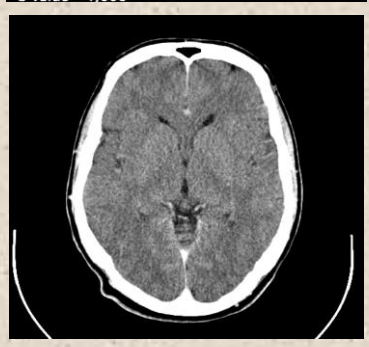


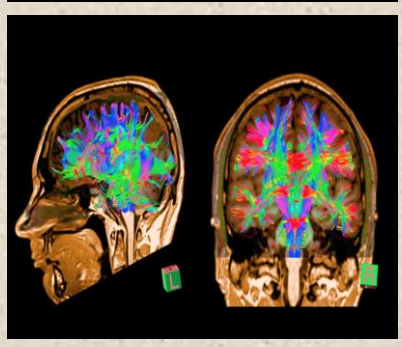


Medical Imaging

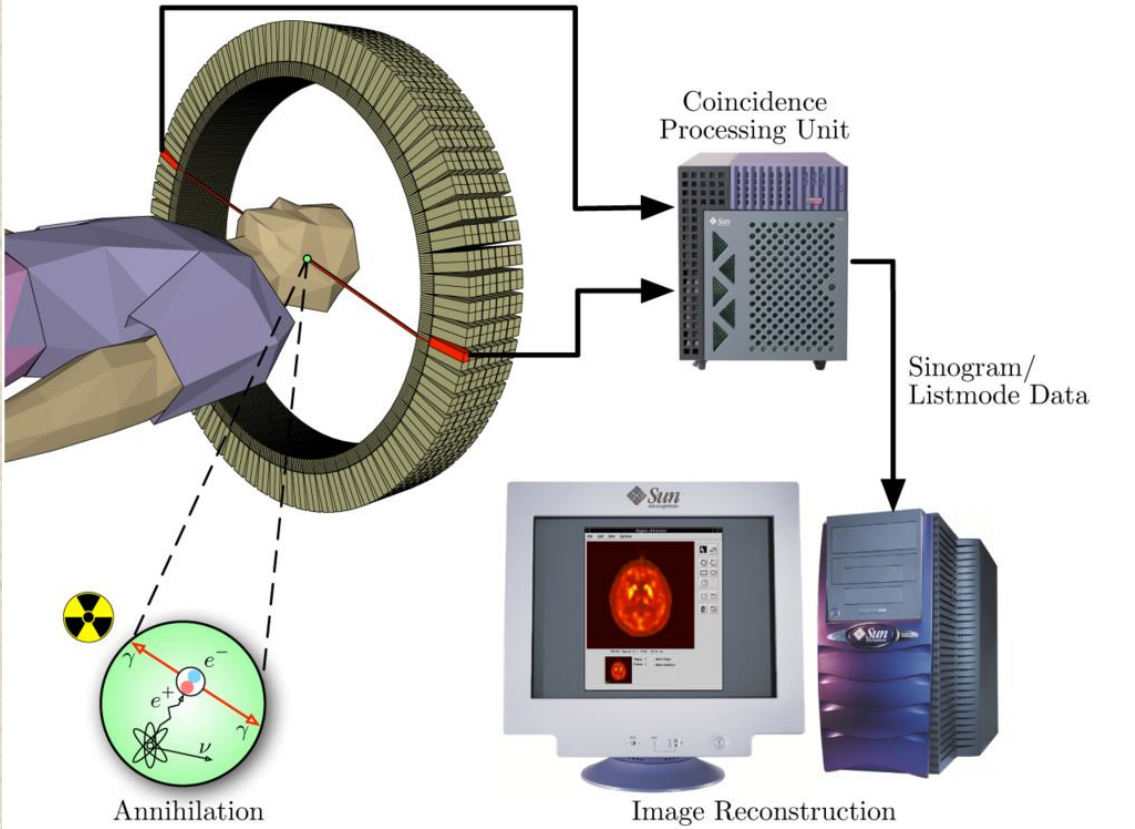






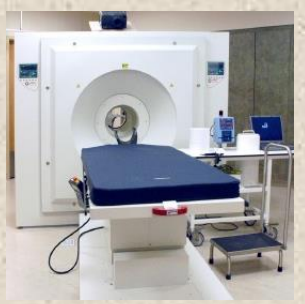


Positron Emission Tomography

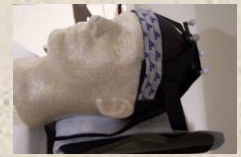


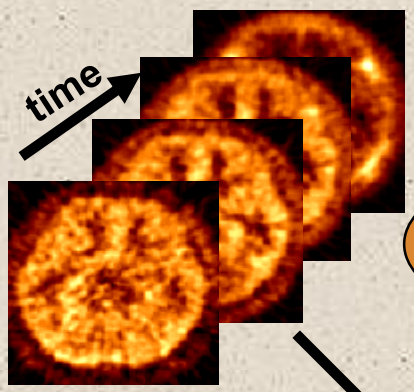
PET Processing

Tissue Radioactivity

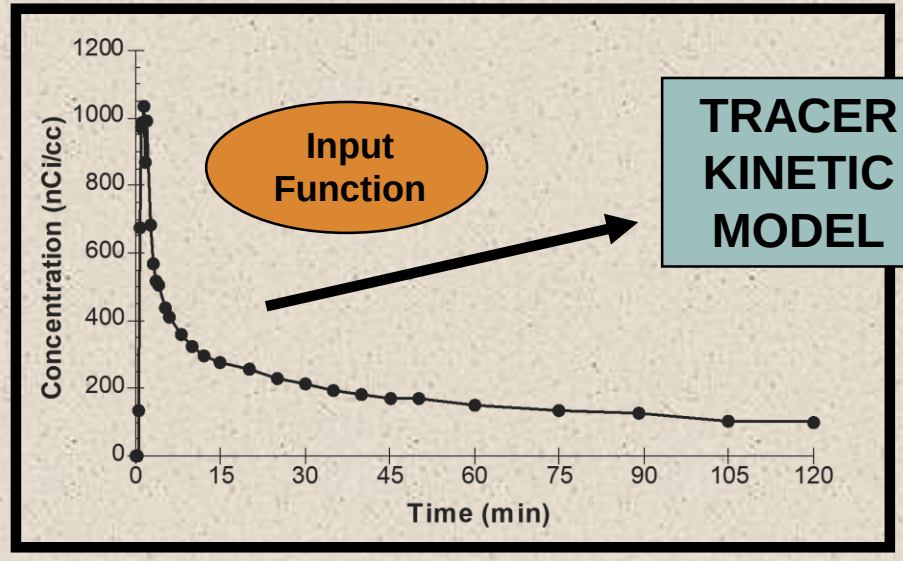


Motion Correction



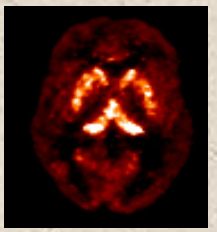


Quantitative Physiological Images

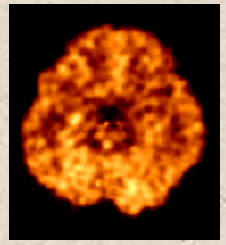


Input Function

TRACER KINETIC MODEL



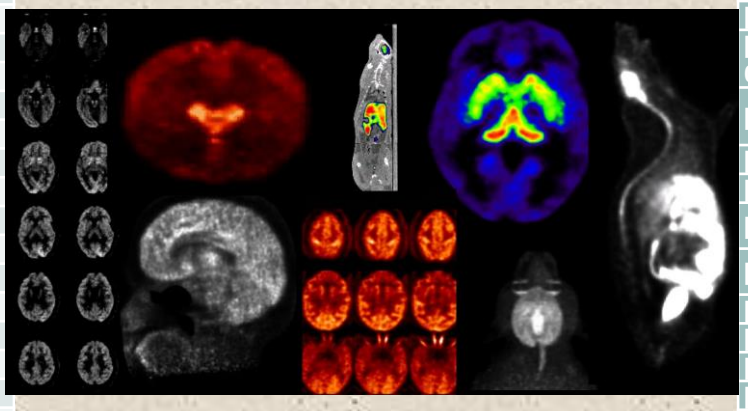
Binding Potential



Delivery (Flow)

Yale PET Menu

Radiotracer	YPC Name	Target
[^{11}C]ABP688	ABP	mGluR5
[^{11}C]AFM	AFM	SERT
[^{11}C]AMI000646	AM646	LPA1 receptors
[C-11]TASP0410699	APM699	V1B receptors
[C-11]UCB-J	APP311	SV2A
[F-18]ASEM	ASEM	alpha-7 antagonist
[18F]AV1451	AV1451	Tau
[F-18]Florbetaben	BPIB	Amyloid
[^{11}C]GSK189254	CBAN	H3
[^{11}C]Carfentanil	CFN	mu agonist
[^{18}F]MK6577	CFPYPB	GlyT1
[^{11}C]CUMI-101	CUMI	5HT1A agonist
[^{11}C]DASB	DASB	SERT
[11C]EKAP	EKAP	Kappa agonist
[C-11]EMO	EMO	M1 receptors
[^{11}C]erlotinib	ERLO	EGFR
[^{18}F]FDG	FDG	Glucose met
[11C]FEKAP	FEKAP	Kappa agonist
[C-11]FLB457	FLB	D2-extrastriatal
[F-18]AV45	FLOR	Amyloid
[F-18]Flutametamol	FLUT	Amyloid
[F-18]LMI11195	FMIBG	Cardiac sympathetic
[F-18]FMISO	FMISO	Hypoxia
[F-18]AS2471907-CL	FMOZAT	11-beta-HSD1
[^{11}C]Flumazenil	FMZ	Benzodiazepine



[^{18}F](+)FP-DTBZ	FPDTBZ	VMAT2
[^{18}F]FPEB	FPEB	mGluR5
[^{11}C]MDL100907	MDL	$5HT_{2A}$
[^{11}C]Methionine	MET	Tumor uptake
[^{18}F](-)FP-DTBZ	MFPDTBZ	VMAT2 inactive enant.
[^{11}C]GR103545	MKAP	Kappa agonist
[C-11]AS2471907-CL	MOZAT	11-beta-HSD1
[^{11}C]MRB	MRB	NET
[^{18}F]NCFHEB	NCFHEB	Nicotinic a4b2 receptors
[C-11]OMAR	OMAR	CB1 receptor
[C-11]PF-06427878	P7878	DGAT2
[^{11}C]PF06809247	P247	MAG Lipase Inhibitor
[^{11}C]P943	P943	5HT1B
[C-11]PBR28	PBR28	TSPO (microglia)
[F-18]BMS986192	PDL192	PD-L1
[F-18]BMS986229	PDL229	PD-L1
[^{11}C]PE2I	PE2I	DAT
[^{11}C]PHNO	PHNO	D_2/D_3
[^{11}C]PIB	PIB	Amyloid
[^{11}C]LY2795050	PKAB	kappa antagonist
[F-18]PF-05270430	PTA	PDE2
[^{11}C]GSK-215083	QUICS	5HT6
[^{11}C]Raclopride	Rac	D_2/D_3
Rb-82	Rb	MBF
[^{11}C]SB-207145	SURF	5-HT4
[^{15}O]water	Water	Blood Flow

A brief history of PET imaging in addiction

Psychopharmacology (1987) 92:241–246

Psychopharmacology

Effects of amphetamine on local cerebral metabolism in normal and schizophrenic subjects as determined by positron emission tomography

A. Wolkin[1,2], B. Angrist[1,2], A. Wolf[3], J. Brodie[1], B. Wolkin[2], J. Jaeger[4], R. Cancro[1], and J. Rotrosen[1,2]

[1] Department of Psychiatry, New York University School of Medicine, 550 1st Avenue, New York, NY 10016, USA
[2] Psychiatry Service, New York VA Medical Center, 24th Street and 1st Avenue, New York, NY 10010, USA
[3] Department of Chemistry, Brookhaven National Laboratory, Upton, New York, NY 11973, USA
[4] Manhattan Psychiatric Center, New York, NY, USA

Article

January 1990

Morphine-Induced Metabolic Changes in Human Brain

Studies With Positron Emission Tomography and [Fluorine 18]Fluorodeoxyglucose

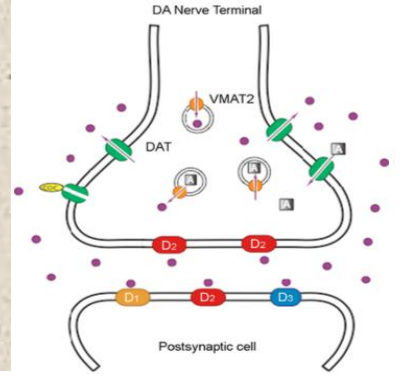
Edythe D. London, PhD; Emmanuel P. M. Broussolle, MD; Jonathan M. Links, PhD; et al

Author Affiliations

From the Addiction Research Center, National Institute on Drug Abuse (Drs London, Broussolle, Cascella, Sano, Herning, and Jaffe, Ms Rippetoe, and Mr Snyder), and Departments of Radiology (Drs Links, Wong, Dannals, and Wagner) and Anesthesiology (Dr Toung), The Johns Hopkins Medical Institutions, Baltimore, Md.

Arch Gen Psychiatry. 1990;47(1):73-81. doi:10.1001/archpsyc.1990.01810130075010

Cornerstone Study



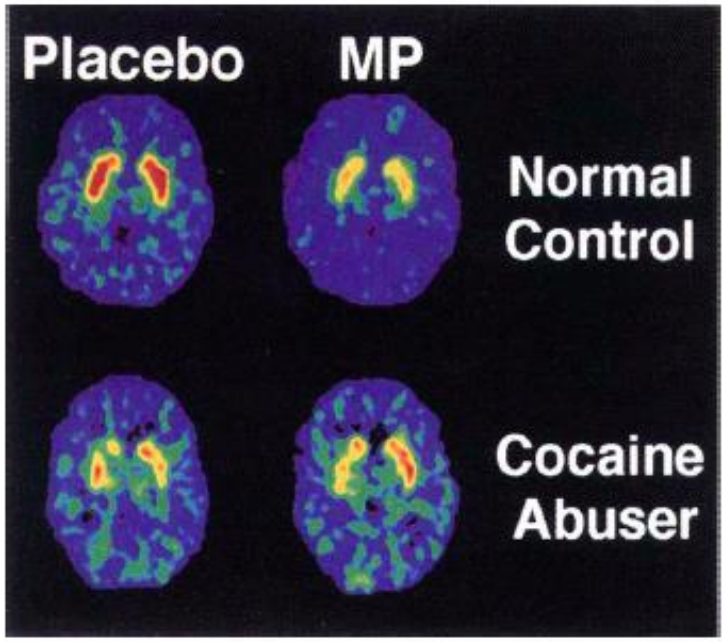


Figure 1 Distribution volume images of [^{11}C]raclopride at the level of the striatum in a normal control and in a cocaine-dependent subject tested after placebo (baseline) and after methylphenidate (MP) administration. Baseline binding for [^{11}C]raclopride in striatum and the reductions in striatal binding with MP were lower in the cocaine-dependent subject than in the control.

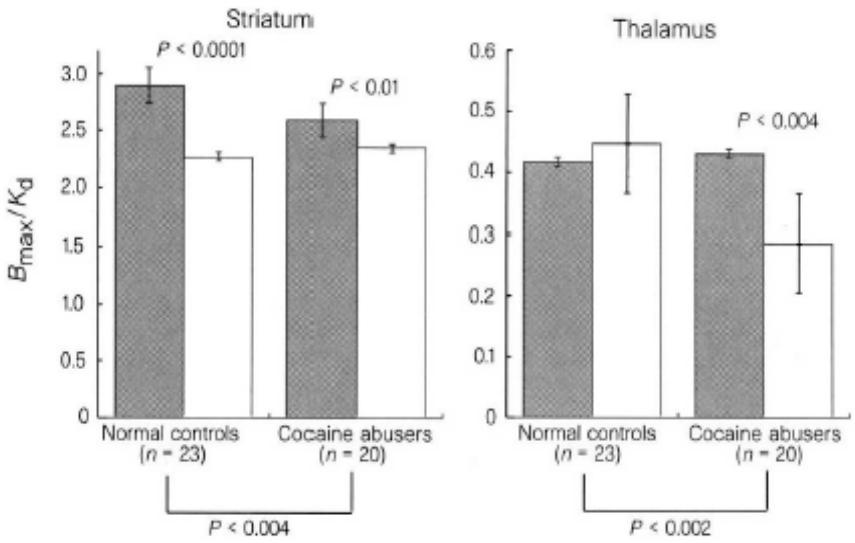


Figure 2 Mean and standard error for the B_{max}/K_d estimates in striatum and in thalamus after placebo (filled bar) and after methylphenidate (MP) administration (empty bar) in normals and in cocaine-dependent subjects. In striatum, results for the ANOVA reveal a significant drug effect ($F = 51$, d.f. 1; $P < 0.0001$) as well as a significant drug by diagnosis interaction effect ($F = 9.3$, d.f. 1,41; $P < 0.004$). Cocaine-dependent subject's response to MP was significantly smaller than that of controls (baseline–MP). In thalamus, MP significantly decrease B_{max}/K_d only in cocaine-dependent subjects ($P < 0.004$). At baseline, B_{max}/K_d in striatum was significantly lower in cocaine-dependent subjects than in controls ($P < 0.01$)

Volkow ND, et al., *Nature* 1997;386 (6627) 830- 833.

More Evidence

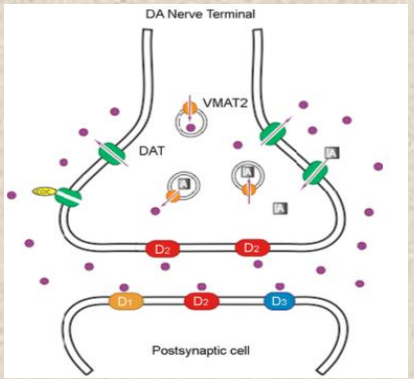
Table 3 Previous Studies with D_2-Like Receptor Tracers in Substance-Dependent Populations

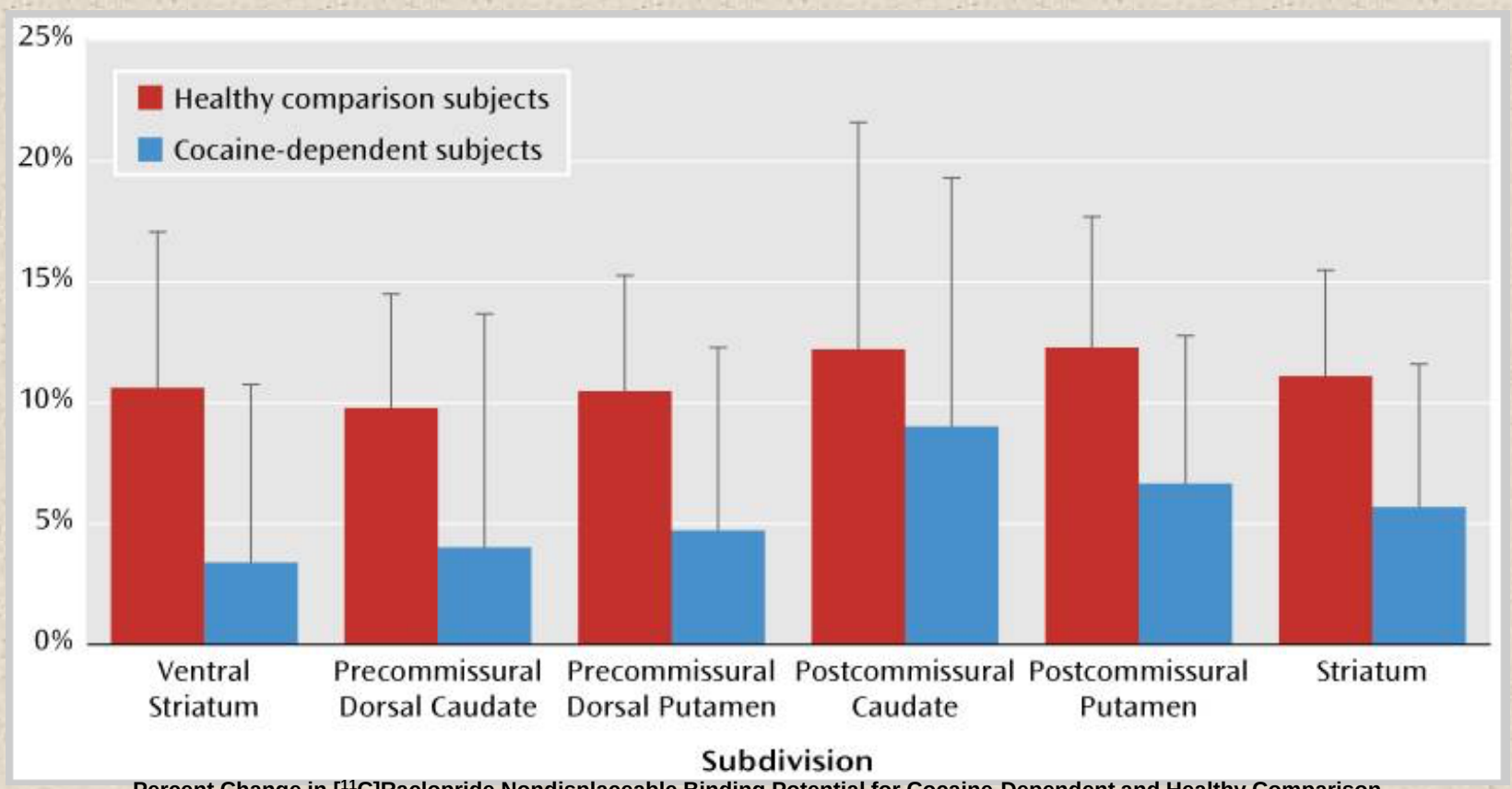
Study	Drug	Tracer	Baseline BP_{ND}	Pharmacological Challenge
Hietala et al. (1994)	ETOH	[^{11}C]raclopride	Down	NA
Volkow et al. (1996)	ETOH	[^{11}C]raclopride	Down	NA
Wang et al. (1997)	Opiates	[^{11}C]raclopride	Down	NA
Volkow et al. (1997)	Cocaine	[^{11}C]raclopride	Down	MP blunted
Volkow et al. (2001)	METH	[^{11}C]raclopride	Down	NA
Martinez et al. (2005)	ETOH	[^{11}C]raclopride	Down	AMPH blunted VST only
Martinez et al. (2007)	Cocaine	[^{11}C]raclopride	Down	AMPH blunted
Volkow et al. (2007)	ETOH	[^{11}C]raclopride	Down VST only	MP
Zijlstra et al. (2008)	Heroin	[^{123}I]IBZM	Down in caudate	Increased in putamen
Fehr et al. (2008)	Nicotine	[^{18}F]fallypride	Down	NA
Lee et al. (2009)	METH	[^{18}F]fallypride	Down	NA
Martinez et al. (2012)	Heroin	[^{11}C]raclopride	Down	MP blunted
Urban et al. (2012)	Cannabis	[^{11}C]raclopride	Normal	AMPH normal

D_2-like imaging studies of drug-dependent subjects. ETOH = alcohol, Opiates = heroin and/or methadone, METH = methamphetamine, NA = not applicable (no stimulant challenge in the study), MP = methylphenidate, AMPH = D-amphetamine.

Mark Slifstein, Eugenii A. Rabiner and Roger N. Gunn, 2014. *Imaging the Human Brain in Health and Disease.*

With or Without Dopamine

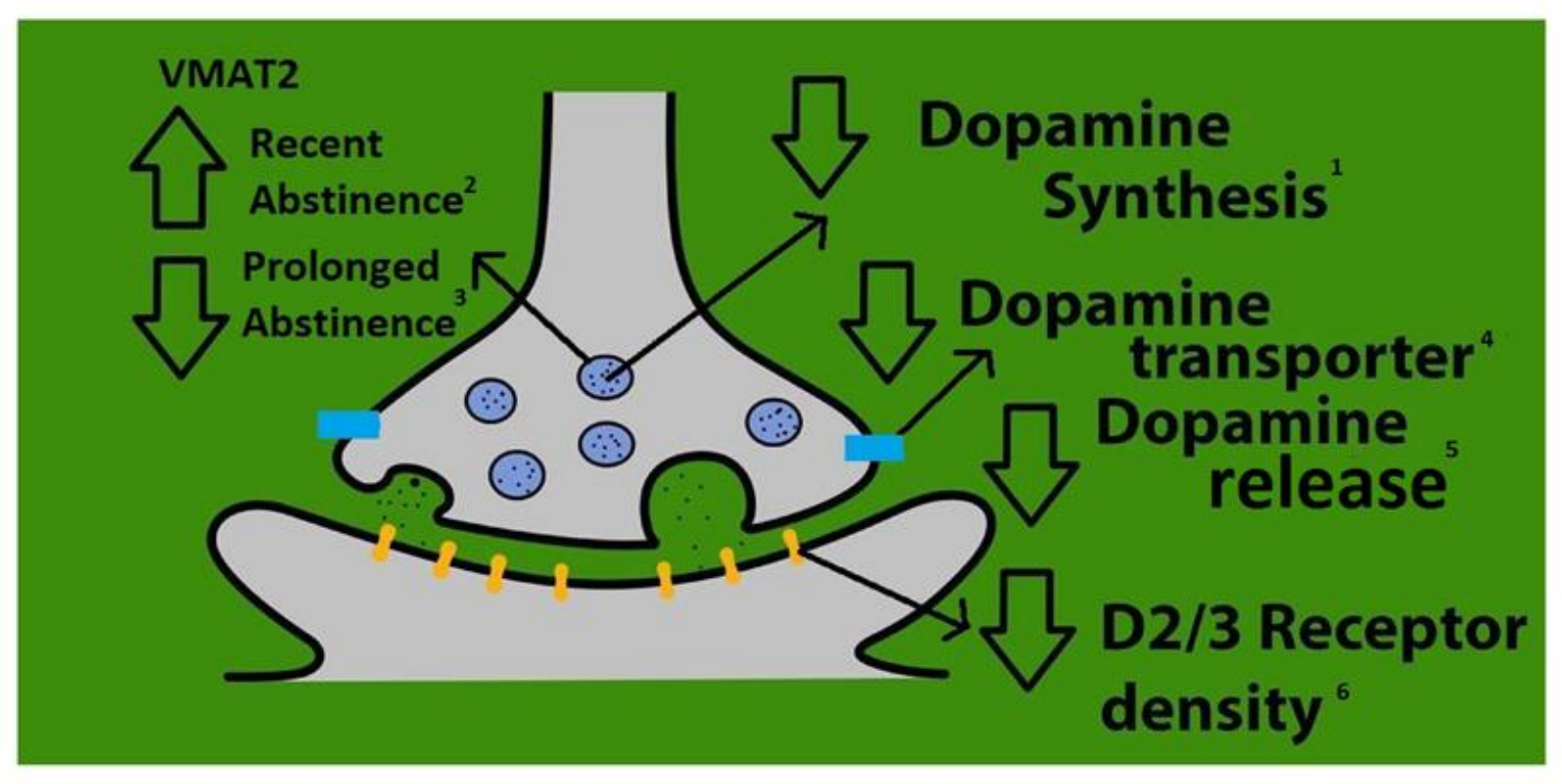




Percent Change in [^{11}C]Raclopride Nondisplaceable Binding Potential for Cocaine-Dependent and Healthy Comparison Subjects Following AMPT Administration. The percent change is significant in each region, with the exception of the posterior caudate.

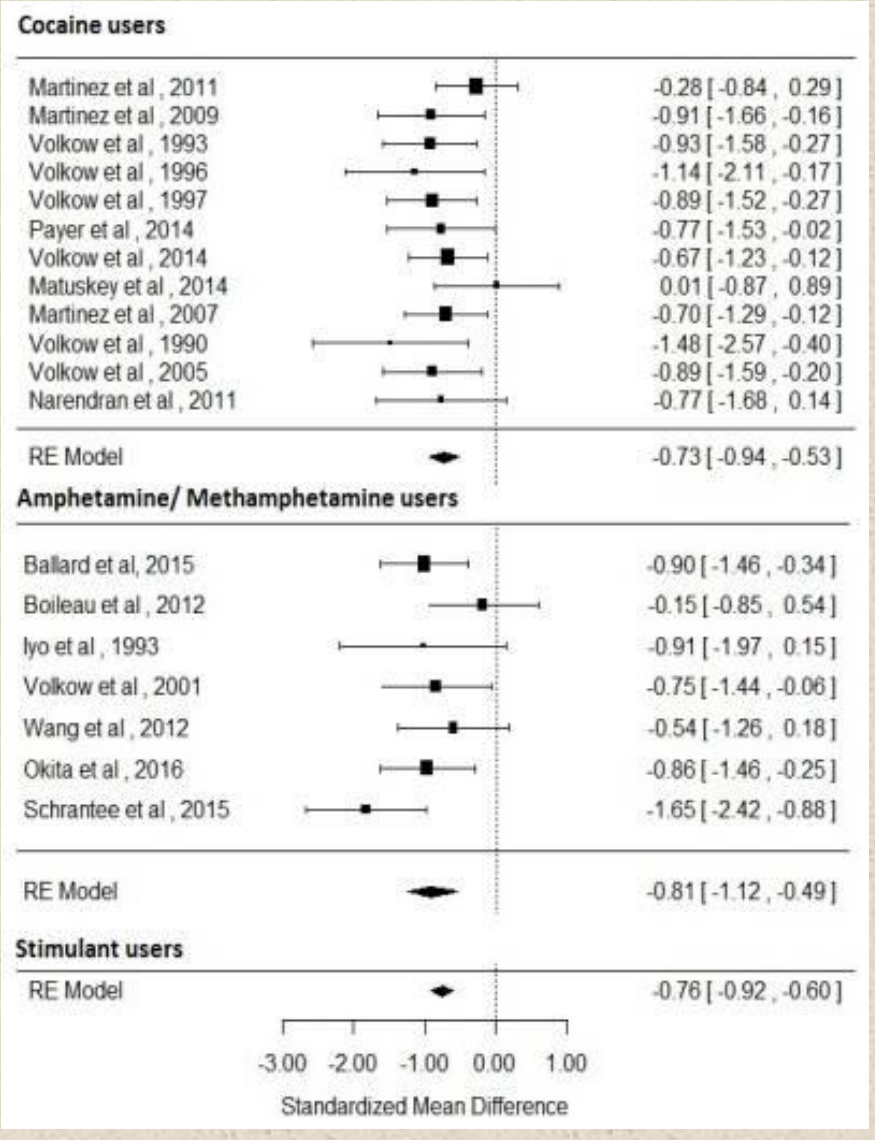
Martinez et al., *AJP*. 2009;166(10):1170-7.

Meta



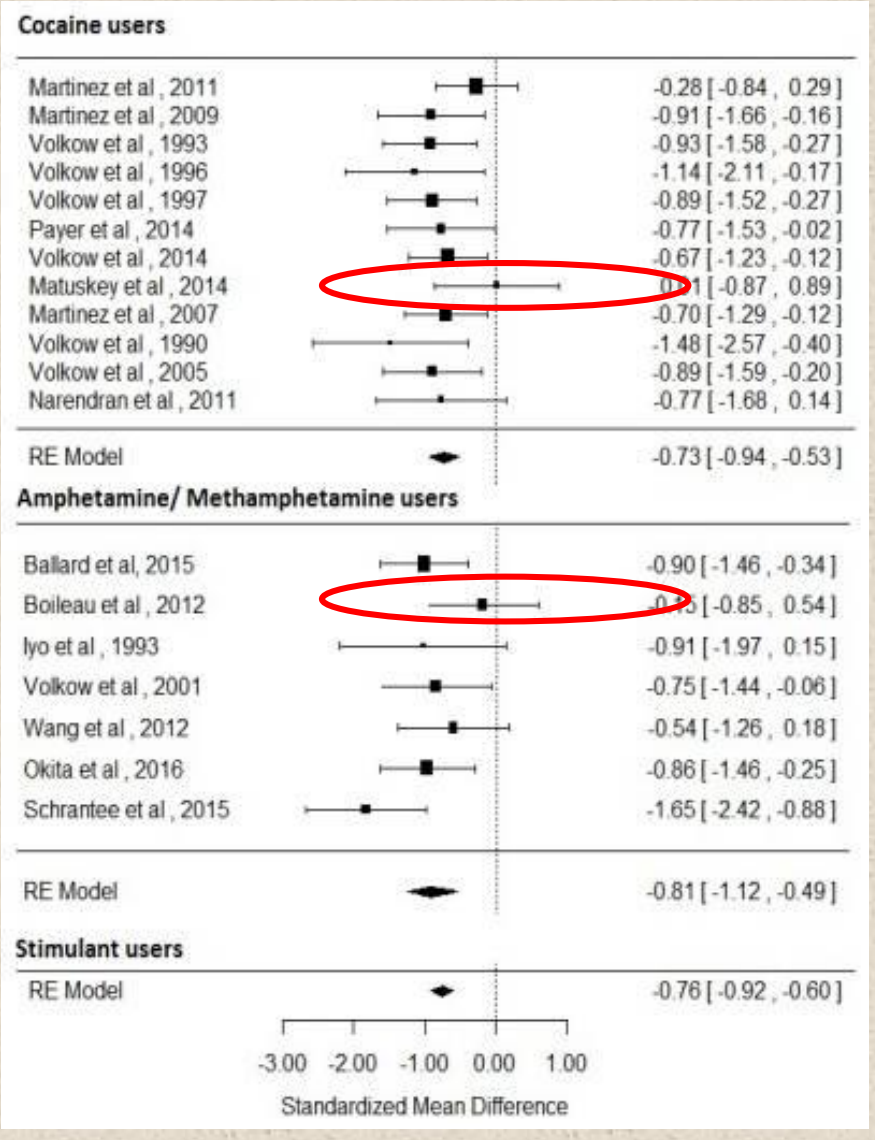
Ashok et al., *JAMA Psychiatry*. 2017;74(5):511-519.

More Meta

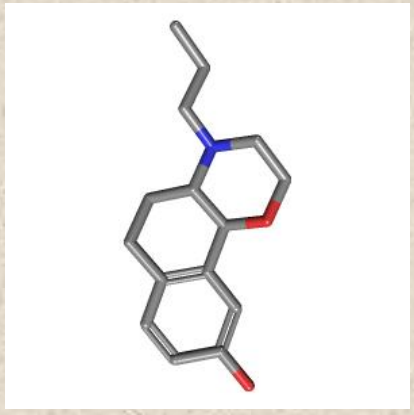


Ashok et al., *JAMA Psychiatry*. 2017;74(5):511-519

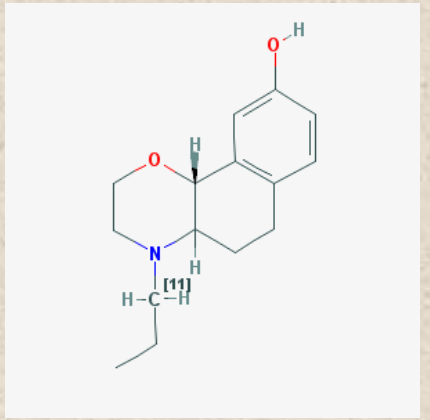
More Meta



Ashok et al., *JAMA Psychiatry*. 2017;74(5):511-519



PHNO



- [11C]-()-4-propyl-3,4,4a,5,6,10 b-hexahydro-2H-naphtho[1,2-*b*] [1,4] oxazine-9-ol ([11C]-(+)-PHNO) is an agonist D2/D3 dopamine receptor radioligand with preferential affinity for the D3 subtype.
- The affinity is 30-53 times higher for D3s than for D2s, and its D3 affinity is intrinsically high (0.16-0.21 nM).
- This high affinity is required to visualize D3 receptors due to their low density, and [11C]-(+)-PHNO is the first radiotracer usable for this application.
- Good test-retest reliability.

D2 vs. D3

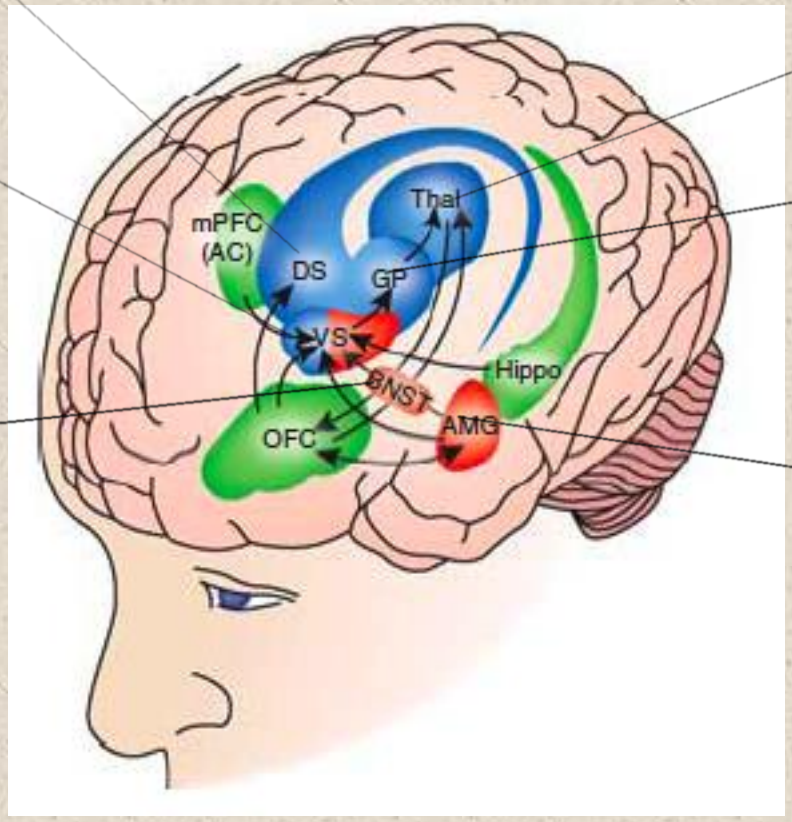
- Anatomically, D_3R is densely present in the mesolimbic system where reward-related learning induced by cocaine occurs (Blaylock and Nader, 2012; Stanwood et al., 2000; Xi and Gardner, 2007)
- D_3R mRNA and protein in these areas show increased expression after exposure to stimulants and other drugs of abuse (Caine and Koob, 1993; Heidbreder and Newman, 2010; Neisewander et al., 2004; Staley and Mash, 1996; Xi and Gardner, 2007)
- Although some apparently inconsistent findings exist, D_3R antagonists and partial agonists inhibit the actions of cocaine in preclinical models (Caine et al., 2012;; Heidbreder et al., 2005; Le Foll et al., 2005; Newman et al., 2012; Xi and Gardner, 2007)

% D3 using PHNO

Putamen =6%

Ventral Striatum=26%

Substantia Nigra =100%



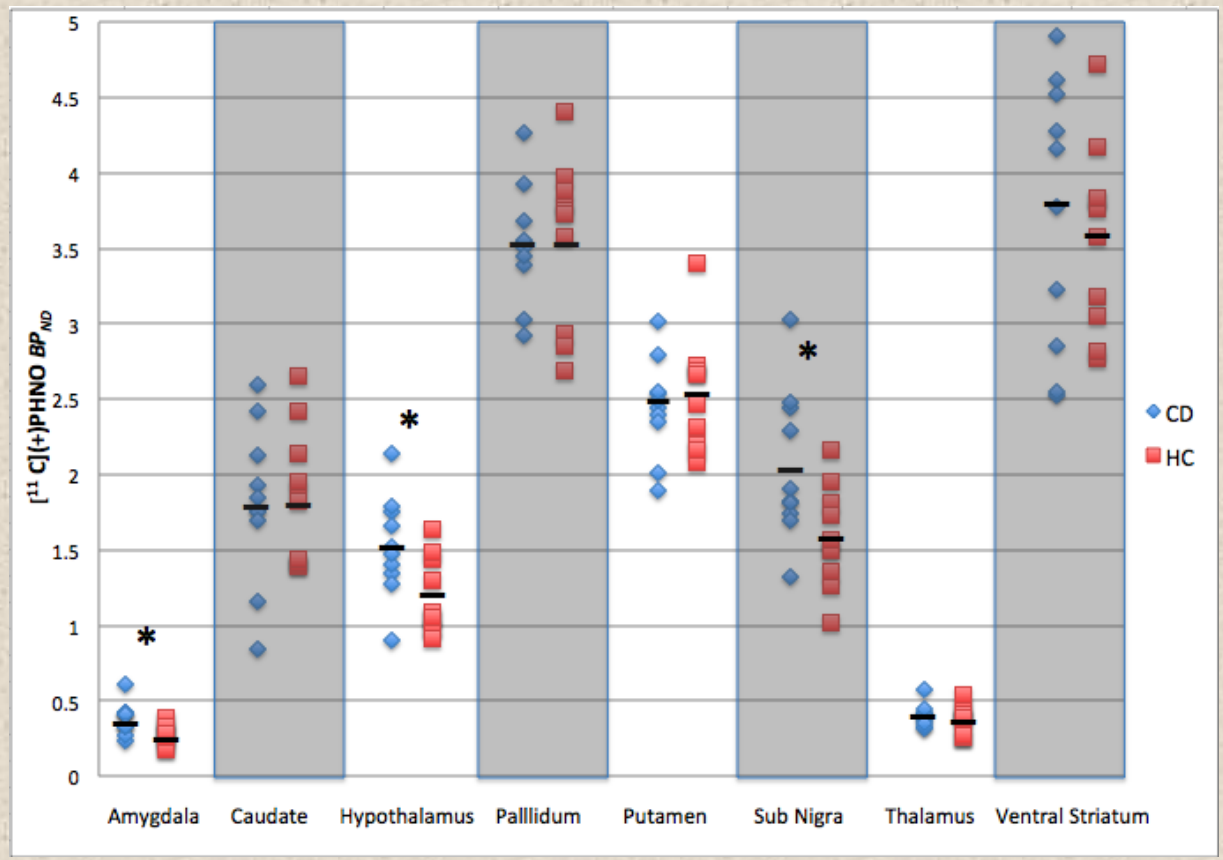
Thalamus =43%

Pallidum =75%

Amygdala =??

Tziortzi et al., 2011. *NeuroImage* 54: 264–277.

Results



Matuskey et al., 2015. Drug and Alcohol Dependence 139; 100–105

Results

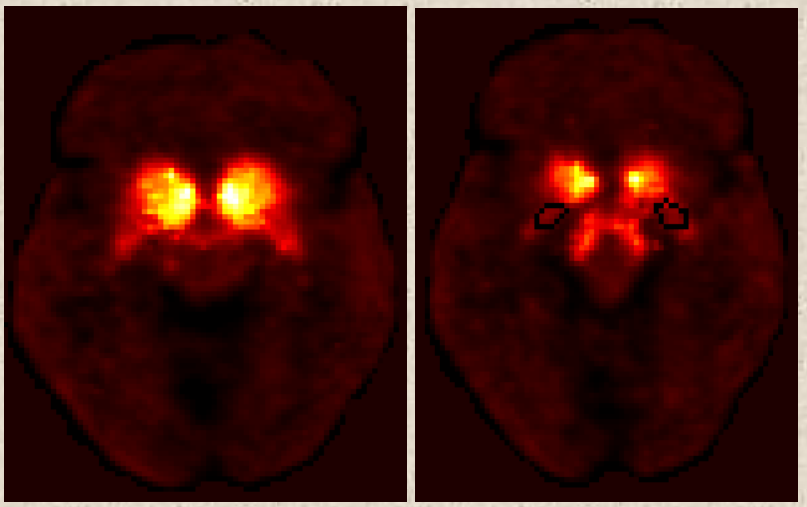
BP_{ND} Mean (S.D.)	CD	HC	ΔCD	P Value
Amygdala	**0.38 (0.11)**	**0.28 (0.28)**	**+35 %**	**0.03**
Caudate	1.81 (0.53)	1.86 (0.45)	-2 %	0.85
Hypothalamus	**1.52 (0.33)**	**1.19 (0.25)**	**+28 %**	**0.02**
Pallidum	3.53 (0.39)	3.56 (0.55)	-1 %	0.88
Putamen	2.45 (0.33)	2.54 (0.39)	-4 %	0.58
Substantia Nigra	**2.05 (0.50)**	**1.59 (0.34)**	**+29 %**	**0.03**
Thalamus	0.40 (0.07)	0.38 (0.09)	+6 %	0.55
Ventral Striatum	3.74 (0.89)	3.57 (0.63)	+5 %	0.63

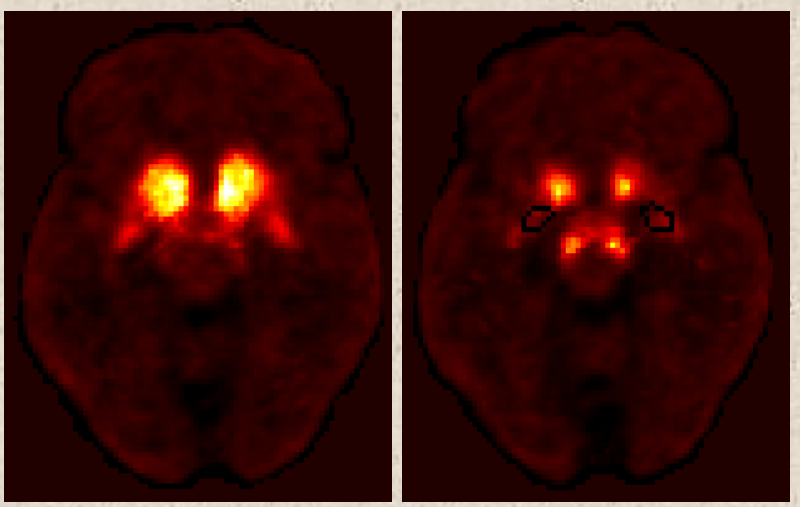
Mean BP_{ND} values (with standard deviation) for each ROI.
Percent difference between CD and HC subjects is tabulated.

Matuskey et al., 2015. Drug and Alcohol Dependence 139; 100–105

Images

Left Figures: representative CD subject displaying striatal (left) and amygdala involvement (outlined on right)



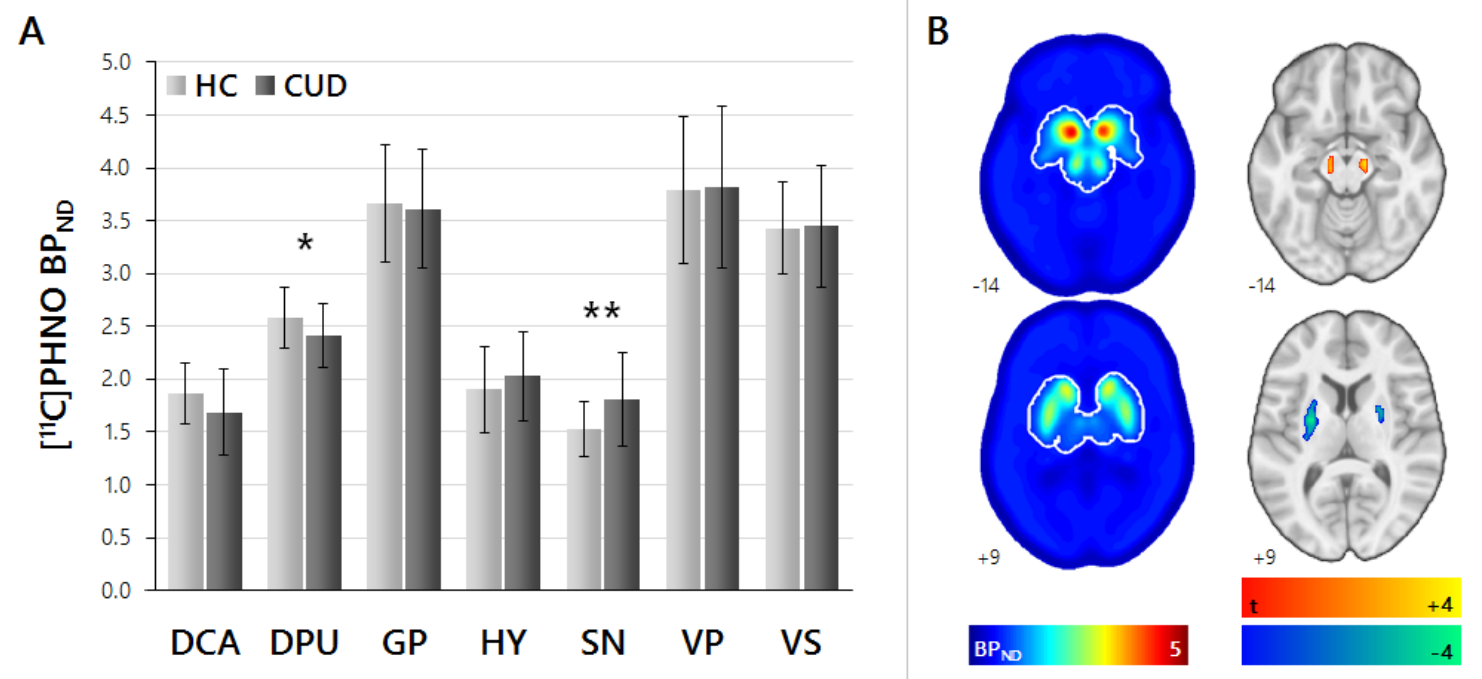


Right Figures: representative HC subject displaying striatal (left) and amygdala involvement (outlined on right)

Matuskey et al., 2015. Drug and Alcohol Dependence 139; 100–105

Bigger, Better

ROI AND WHOLE-BRAIN ANALYSIS

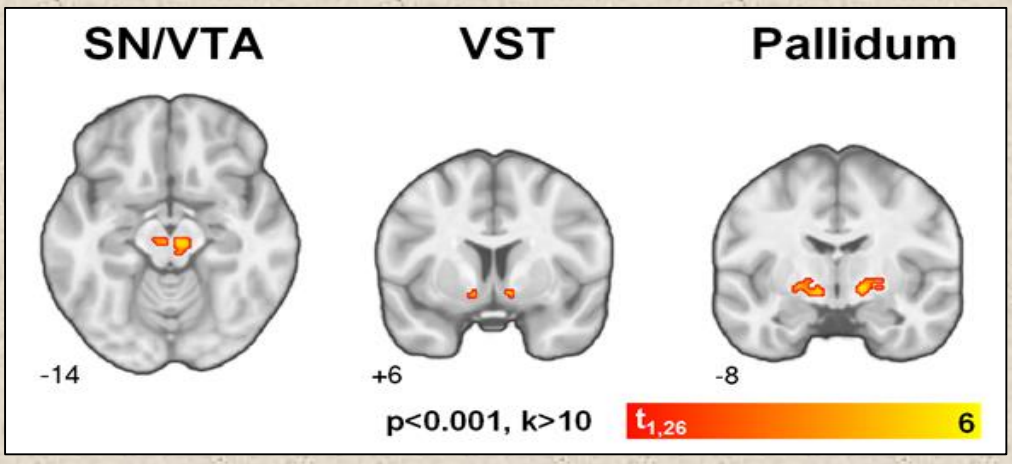


Worhunsky et al., 2017 *NeuroImage* Mar 1;148:343-351

What about other addictions?

Obesity

	Amygdala	Caudate	Hypothalamus	**Pallidum**	Putamen	**SN/VTA**	Thalamus	**VST**
NW (n = 14)	0.27 (0.08)	1.88 (0.32)	1.24 (0.42)	**3.37 (0.39)**	2.52 (0.35)	**1.85 (0.36)**	0.35 (0.09)	**4.12 (0.52)**
OB (n = 14)	0.30 (0.07)	1.98 (0.42)	1.27 (0.24)	**3.73 (0.47)**	2.73 (0.41)	**2.21 (0.42)**	0.37 (0.07)	**4.73 (0.58)**
ΔOB %	+13	+5	+2	**+11**	+8	**+20**	+6	**+14**
p value	0.22	0.47	0.81	**0.02**	0.14	**0.02**	0.54	**< 0.01**

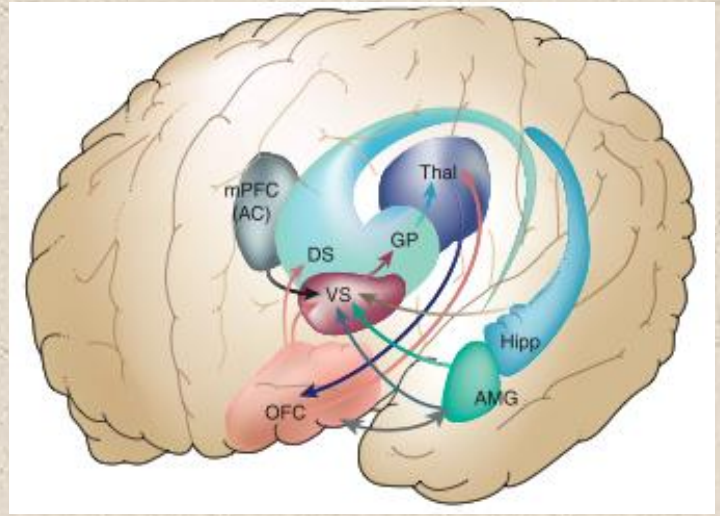


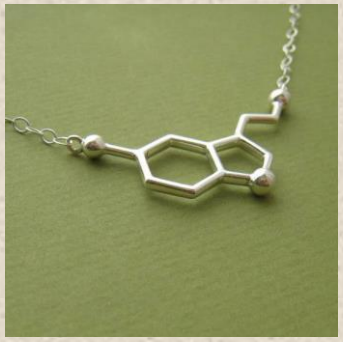
Voxel-wise analyses of OB relative to NW [^{11}C](+)PHNO BP_{ND} in the substantia nigra/ventral tegmental area (SN/VTA), the ventral striatum (VST), and the pallidum. Whole-brain results displayed at uncorrected p <0.001 and k > 10;

Gaiser et al., 2016. Neuropsychopharmacology 41(13):3042-3050.

Limitations of DA Model

- 1.) Complexity of reward system
- 2.) Lack of efficacy of DA treatments
- 3.) Direct and indirect effects on other systems (e.g. opioid, serotonin, NET, sigma, glutamate subtypes)



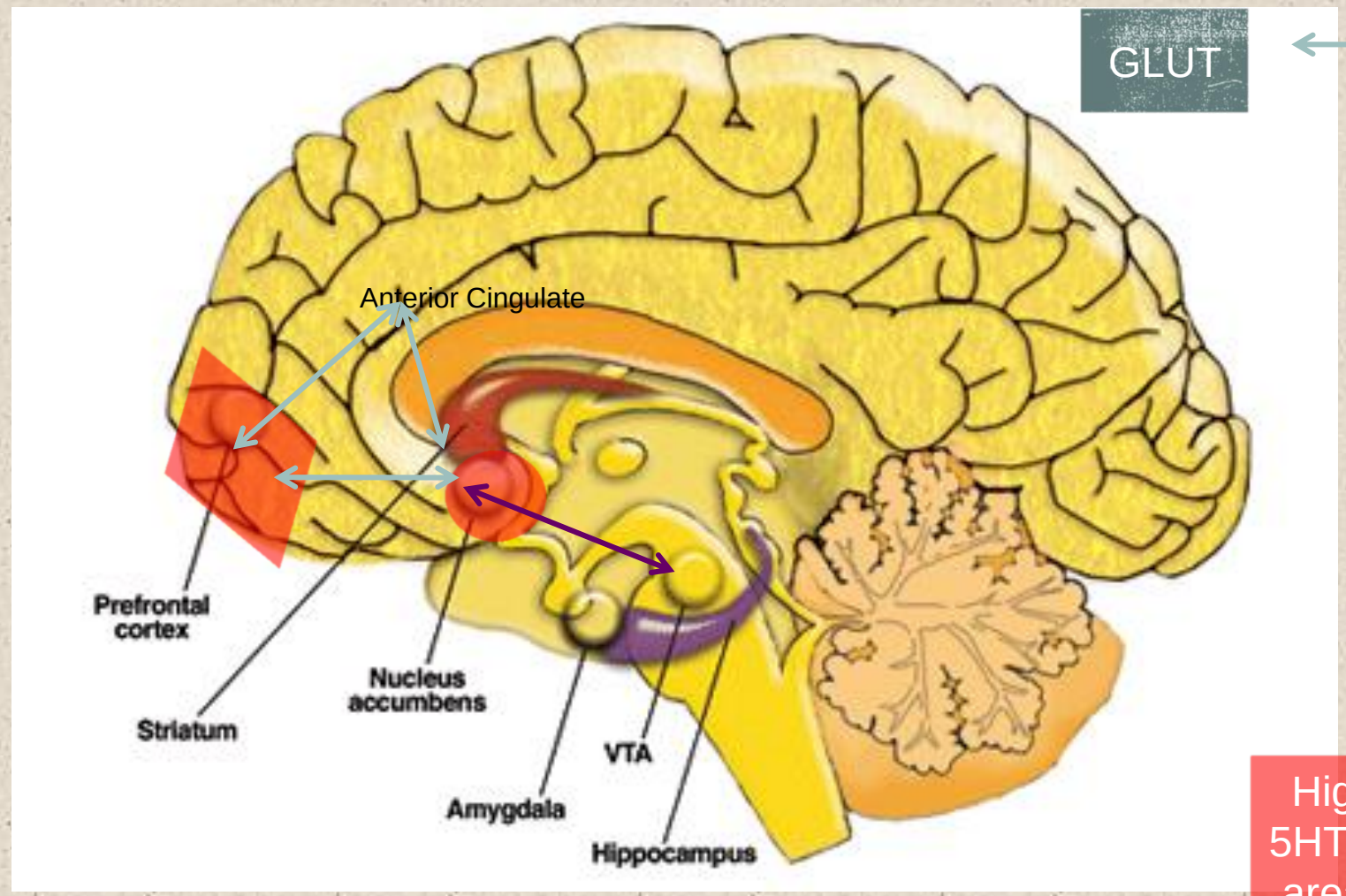


Introducing 5HT1B

- The 5-HT1B receptor is an inhibitory G protein-coupled metabotropic receptor found primarily as a presynaptic terminal auto and heteroreceptors (Pauwels 1997; Hoyer et al. 2002; Hannon and Hoyer 2008)
- In reward, it is thought that 5-HT_{1B} heteroreceptors inhibit GABA release in the VTA, thereby disinhibiting dopaminergic activity and amplifying drug reward mechanisms (Cameron & Williams, 1994, 1995; O'Dell & Parsons, 2004)
- Genetic studies in humans have found associations between 5-HT_{1B} receptor polymorphisms and substance abuse, suggesting that modified 5-HT_{1B} receptor activity may be a contributing factor for increasing susceptibility to addiction (Sun et al., 2002; Huang et al., 2003 ; Proudnikov et al., 2006)

DA

GLUT



High 5HT1B areas

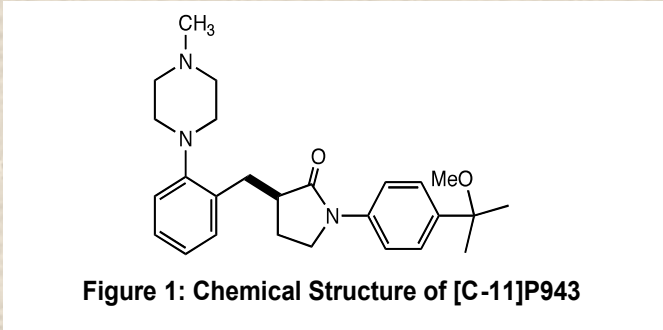
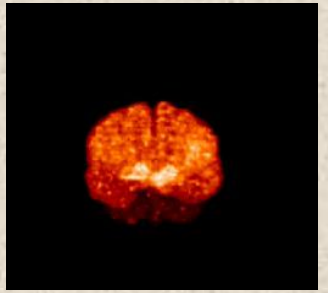


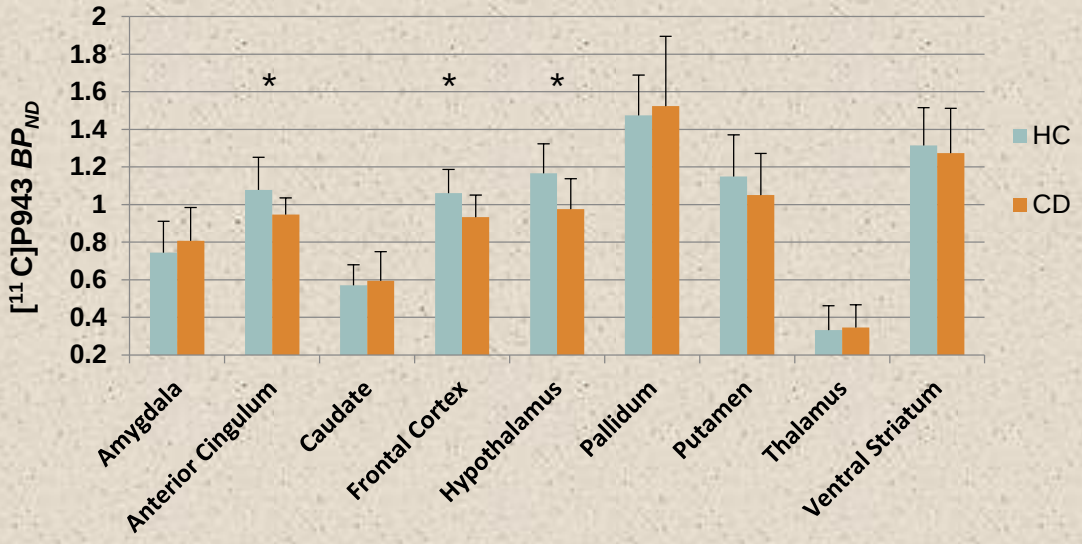
Figure 1: Chemical Structure of [C-11]P943

P943



- P943 (R-1-[4-(2-methoxy-isopropyl)-phenyl]-3-[2-(4-methyl-piperazin-1-yl)benzyl]-pyrrolidin-2-one)
- Potent 5-HT1B antagonist in vitro
- Highly selective ligand. It has 10-fold greater affinity for the 5-HT_{1B} receptor relative to the 5-HT_{1D}
- 1,000-fold higher for 5-HT1B receptors than for 5-HT2A, 5-HT2B, 5-HT2C, and 5-H7 receptors, more than 100 times higher than for 5-HT3 receptors and more than 50 times higher than for 5-HT1A receptors
- Test-retest variation (<10%) in the measure of receptor availability using [^{11}C]P943, with MRTM2 providing the least variability

CD vs. HC



Region of interest analysis after gray matter masking (GMM) and associated mean [^{11}C]P943 BP_{ND} values for HC (blue) and CD (red) subjects. Asterisks are statistically significant at P=0.01 or better. Error bars denote standard deviation.

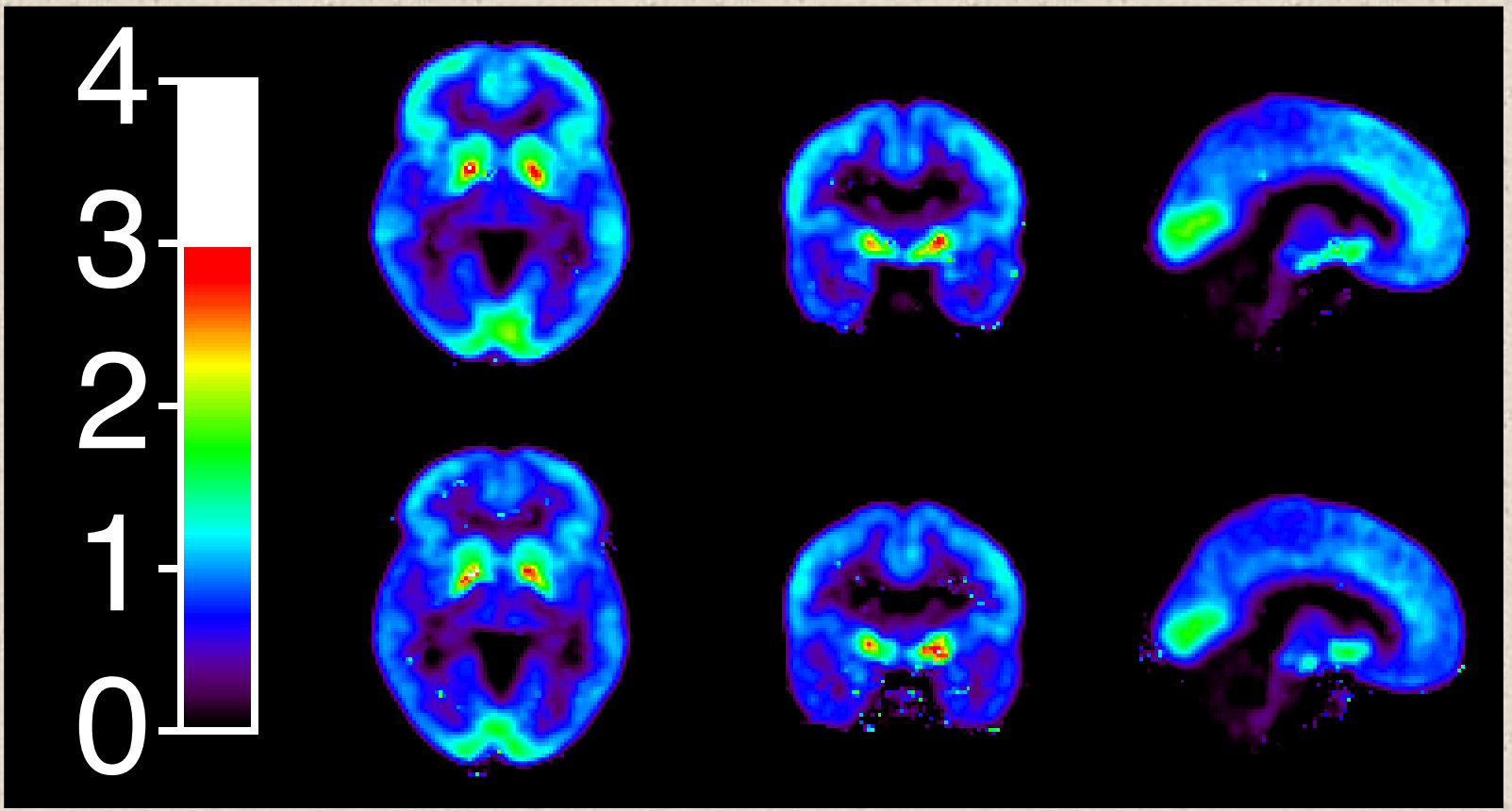
Matuskey et al., 2014. *Biological Psychiatry.* Nov 15; 76(10):816-22.

SPM

Identified brain region	BA	Peak T Value	Mean T Value	Cluster size (voxels)	Peak voxel MNI coordinate (mm)		
					x	y	z
Orbitofrontal Cortex	10,11	5.74	4.05	1454	14	68	0
Superior and Middle Frontal Gyrus	8,9,10	5.03	3.94	523	28	42	36
Cingulate Gyrus	31	4.81	3.90	156	10	-44	34
Temporal and Occipital Gyrus	19,39,22, 40,18	4.60	3.80	1168	-58	-72	26
Cingulate Gyrus/ Precuneus	31	4.13	3.67	128	-14	-56	24
Inferior and Middle Frontal Gyrus	46,45,10	4.06	3.64	174	50	34	14
Inferior and Middle Frontal Gyrus	46,45,6, 8,9	3.81	3.55	238	56	22	22

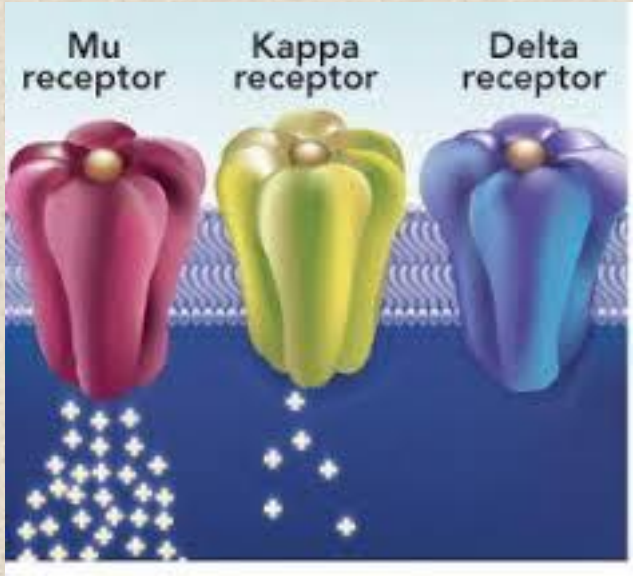
Matuskey et al., 2014. *Biological Psychiatry.* Nov 15; 76(10):816-22.

Group Images (HC and CD)

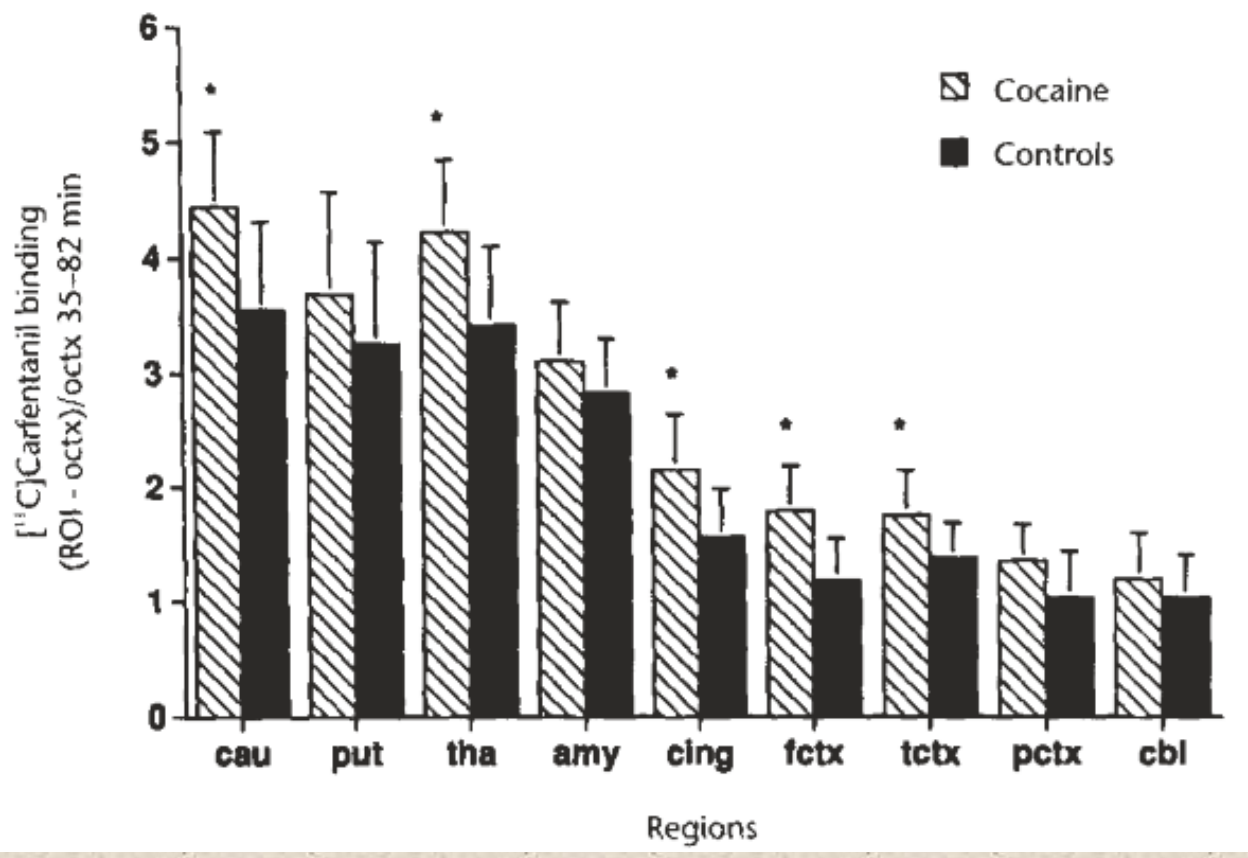


Matuskey et al., 2014. *Biological Psychiatry.* Nov 15; 76(10):816-22.

Opioid System



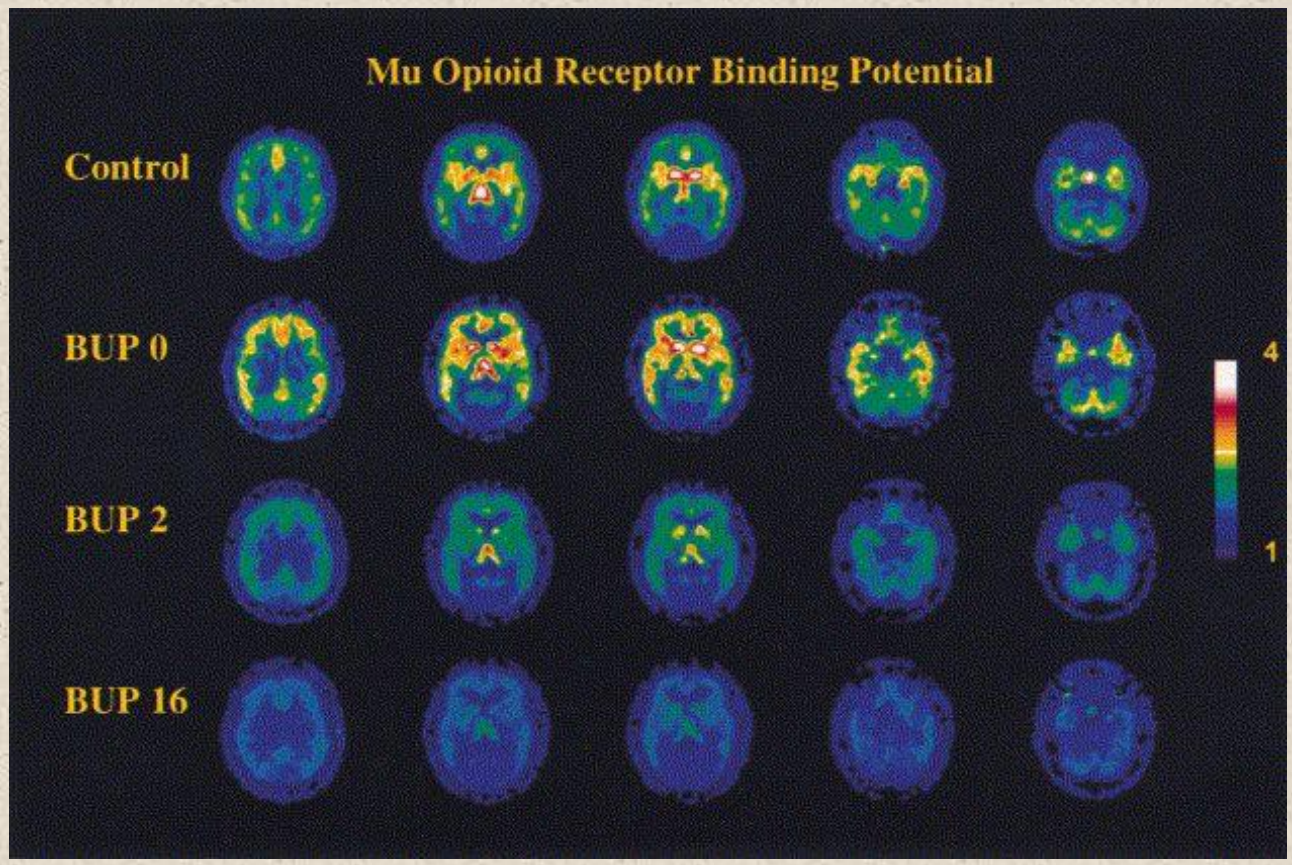
Mu



Mu opioid binding in cocaine-dependent men (*n* = 10) and HC (*n* = 7).

Zubieta et al., 1996. Nature Medicine, v2;11 1225-1229

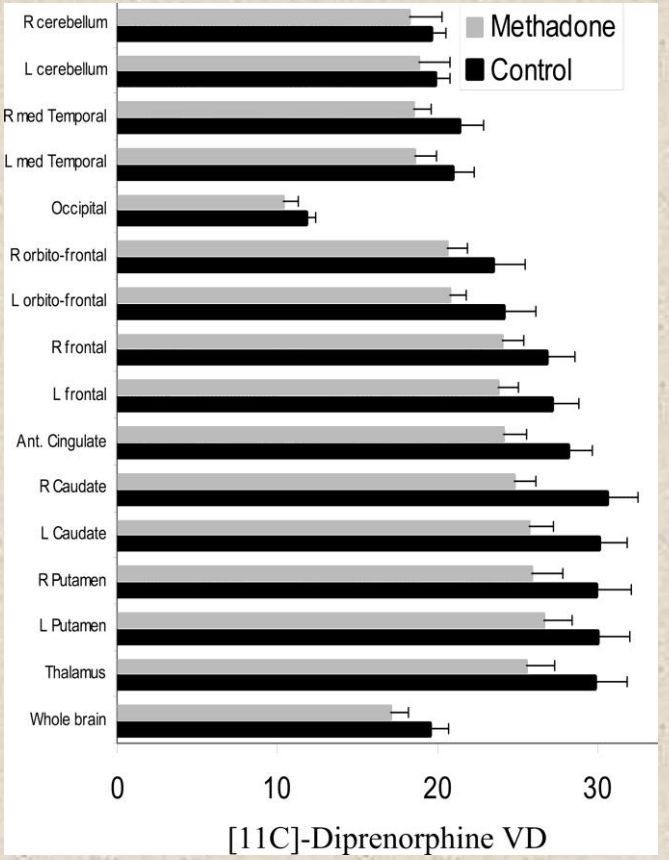
Mu in OUD



Heroin abusers also had greater MOR binding potential in the inferofrontal cortex and anterior cingulate regions compared to matched HCs with [^{11}C]carfentanil. Sublingual buprenorphine 36–50% at 2 mg and 79–95% at 16 mg (N=3).

Zubieta et al., 2000. Neuropsychopharmacology 23:3. 326-334

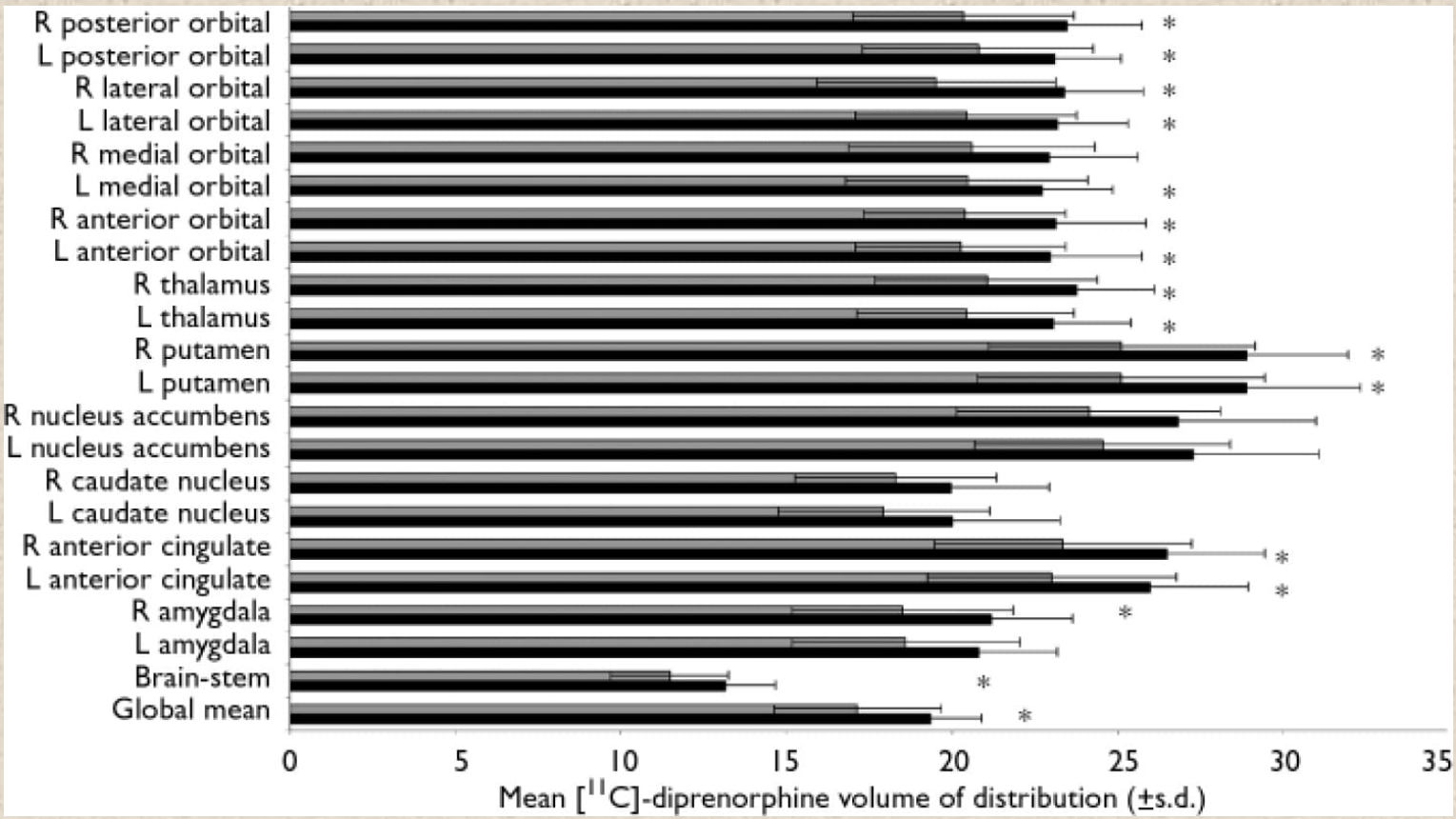
Downregulation?



Graph showing V_D changes in whole brain [^{11}C]diprenorphine binding with opioid use. Note that there is a slight, nonsignificant reduction in binding in the methadone group compared with the normal controls (N=8).

Melichar et al., 2005, Journal of Pharmacology and Experimental Therapeutics

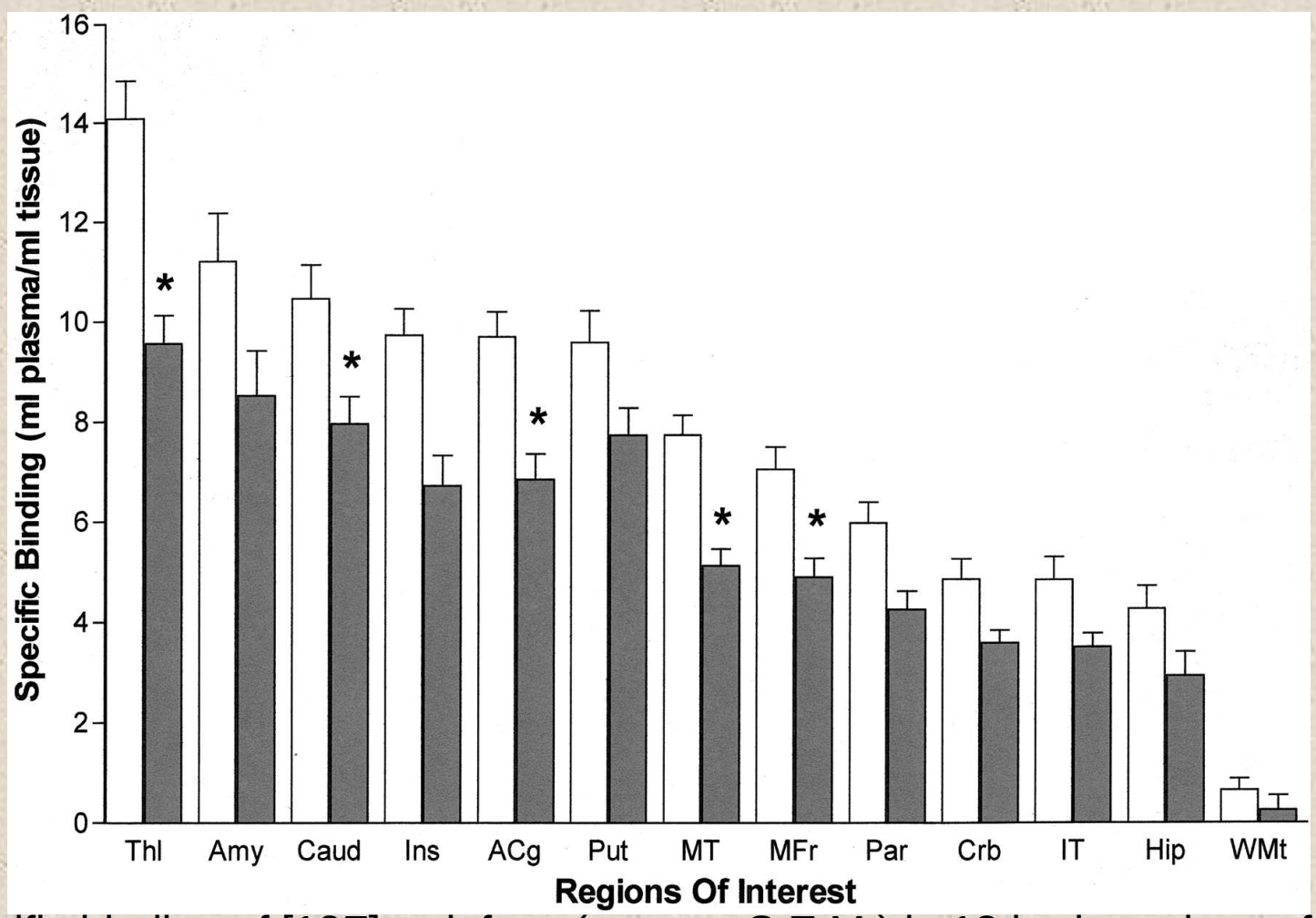
Upregulation?



N=10; Dark bars are Heroin Users; N=20 HC

Williams et al, 2007, British Journal of Psychiatry

Downregulation?



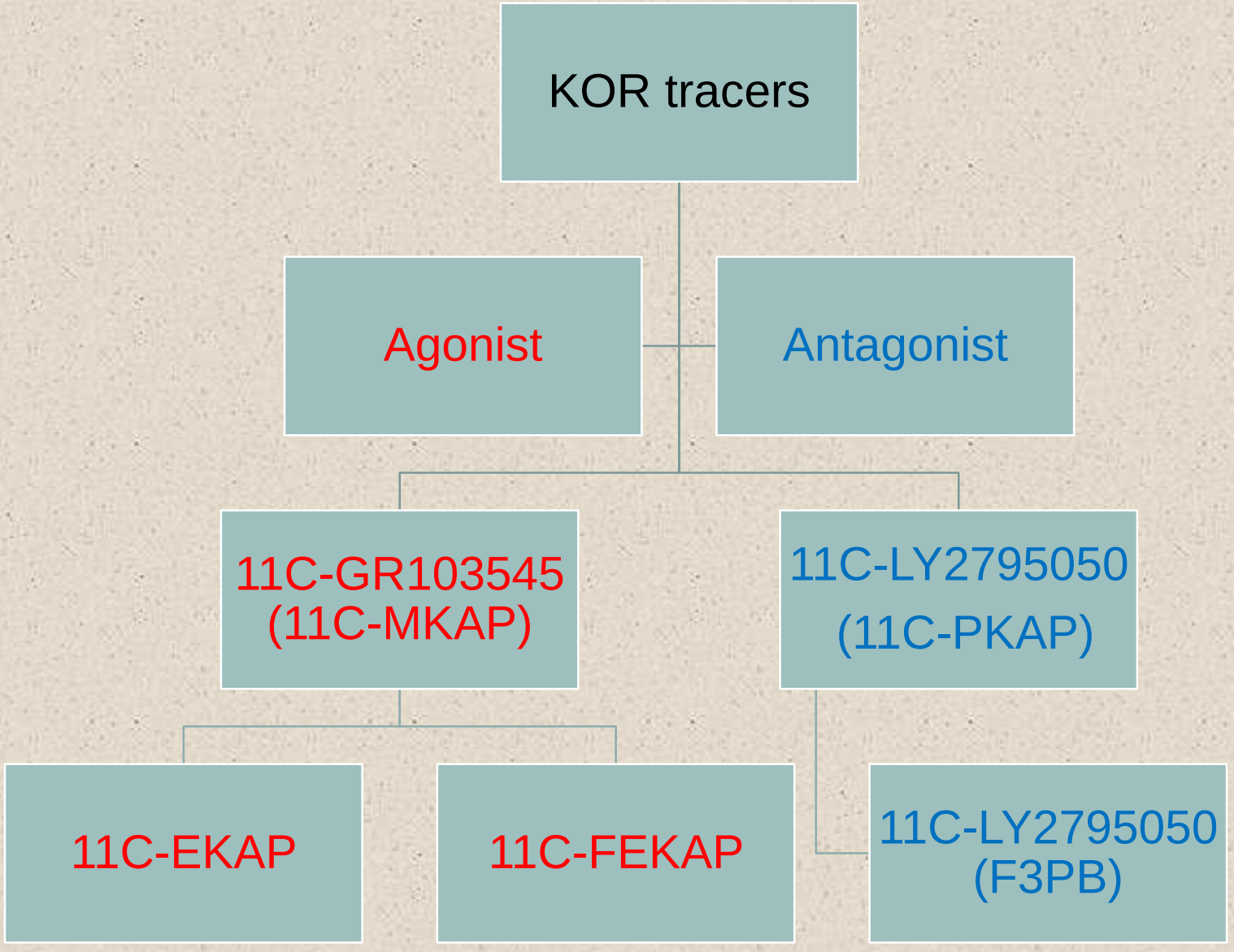
Specific binding of [18F]cyclofoxy (mean + S.E.M.) in 13 brain regions of normal volunteers and long-term, 14 methadone-treated former heroin addicts (dark bar).

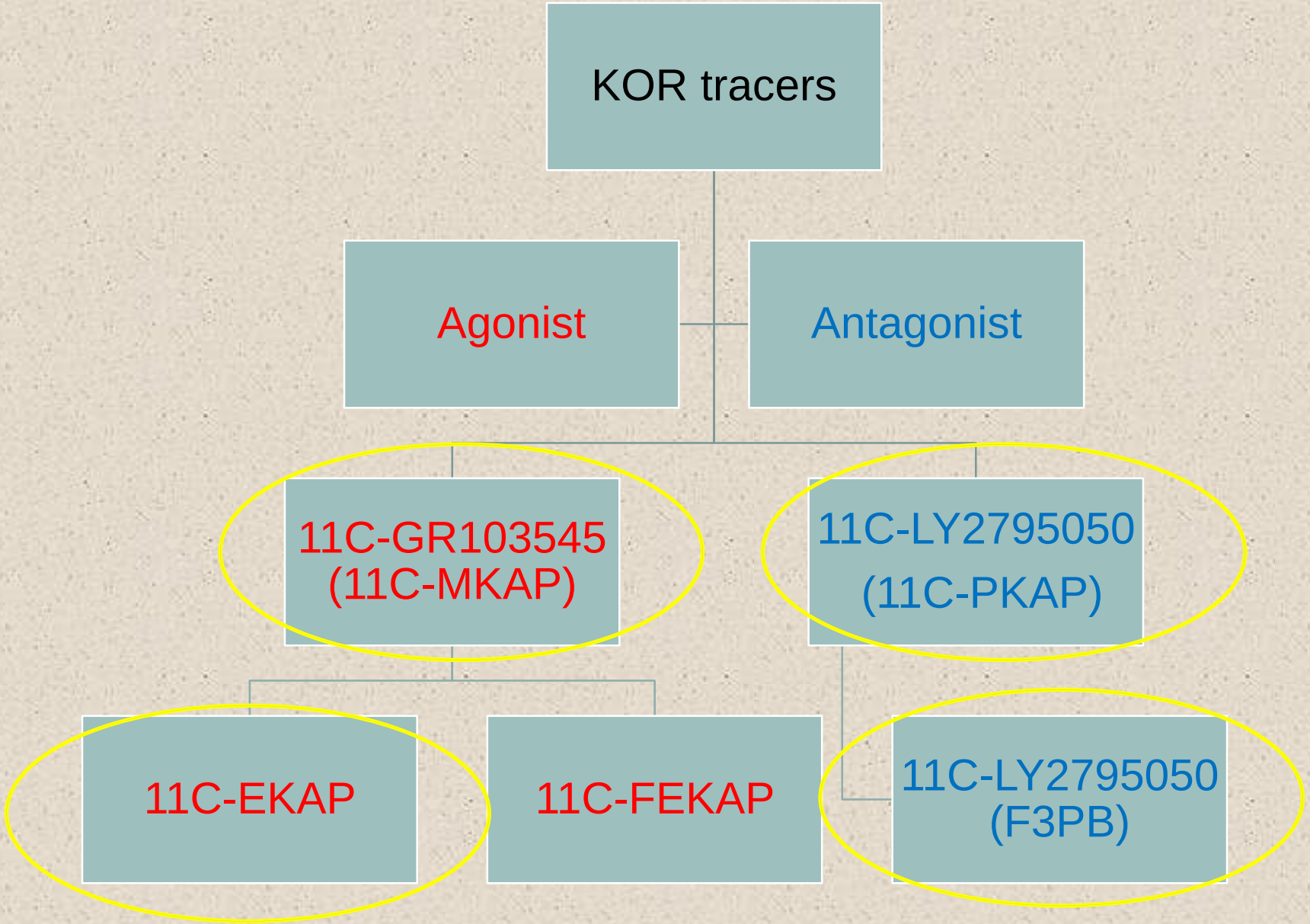
Kling et al. J Pharmacol Exp Ther 2000;295:1070-1076

The Dark Side

The Dark Side

- Dysphoria and aversive effects also play an important role in assessing the value of a reward
- KOR and dynorphin, its endogenous ligand, have thus been characterized as a counterbalance or aversive system to the rewarding dopamine system
- Implicated in drug use and stress induced relapse
- Generally, agonists at KOR are aversive, compared to other opioid receptor agonists such as mu and delta that are rewarding and reinforcing


KOR tracers
Agonist
Antagonist
11C-GR103545
(11C-MKAP)
11C-LY2795050
(11C-PKAP)
11C-EKAP
11C-FEKAP
11C-LY2795050
(F3PB)


KOR tracers
Agonist
Antagonist
11C-GR103545
(11C-MKAP)
11C-LY2795050
(11C-PKAP)
11C-EKAP
11C-FEKAP
11C-LY2795050
(F3PB)

Kappa Agonist Tracers

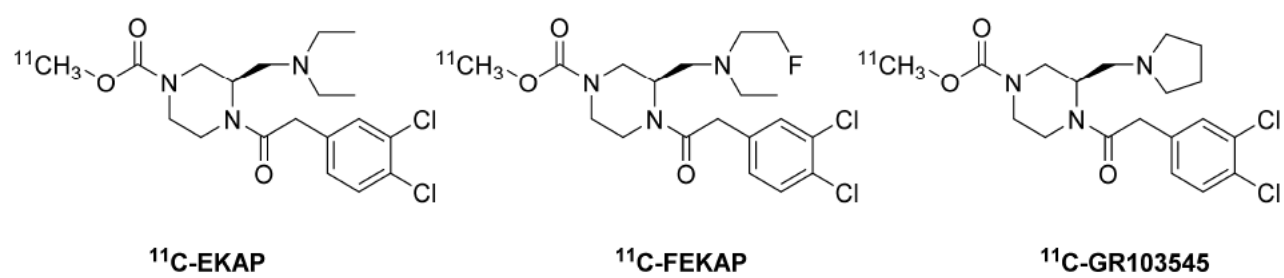


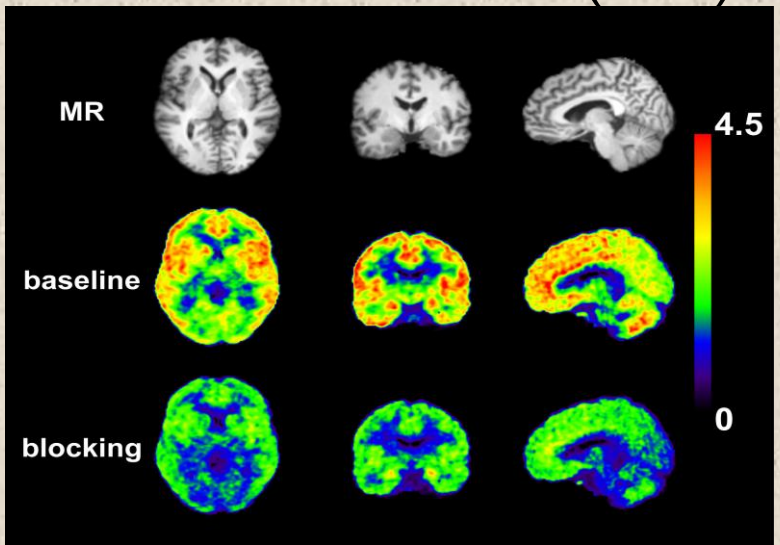
Figure 1: Molecular structures of C-EKAP, ^{11}C-FEKAP, and ^{11}C-GR104545.

- EKAP: in vitro Ki binding affinity: κ=0.28nM, μ=8.6nM, δ=386nM; selectivity of κ/μ over 30 times and κ/δ over 1,300 times
- All have good brain uptake that distribute in a pattern consistent with known KOR rank order in the primate and human brain (i.e., high uptake in cingulate cortex, insula and globus pallidus, intermediate uptake in the caudate, putamen, temporal and frontal cortex, and lower uptake in the thalamus and cerebellum)
- Mean MA1 VT values were highest for 11C-GR103545, followed by 11C-EKAP, then 11C-FEKAP
- Minimum scan time for stable VT measurement: 90min for 11C-EKAP, 110 min for and 11C-FEKAP and 140 min for 11C-GR103545
- 11C-GR103545 is not ideal in high binding areas due to the prolonged scan time
- 11C-EKAP displays faster kinetics, better test-retest variability (~6%) across regions except for the amygdala (17%) and high specific binding signals in vivo

Naganawa et al, *J Nucl Med*. 2020 Mar 13:jnumed.119.227694.

Blocking

- 12 healthy subjects (age: 26-50, gender: 6 M and 6 F) underwent baseline and blocking scans on the same day with EKAP.
- The blocking scan was conducted at 70 min after an oral administration of 150 mg of the nonspecific opioid antagonist naltrexone.
- Distribution volumes decreased in all regions after naltrexone administration, which suggests that there is no ideal reference region for this radiotracer
- The occupancy by 150 mg of naltrexone was 93 ± 6% (n = 6)
- Non-displaceable distribution volume (VND) was 3.5 ± 0.8 mL/cm3



Age

Age	Gender	Race	BMI (kg/m^2)	BSMSS
35 (10); range 20-51	9 M, 9 F	8 C, 6 AA, 3 O,1 H	26 (3); range 20-31	60 (18); range 22-87

ROI	Age	p value	BMI	p value
Amygdala	-0.2975	0.23	-0.5438	0.02
ACC	-0.2478	0.32	-0.4753	0.05
Caudate	-0.4399	0.07	-0.6944	<0.001
Frontal cortex	-0.3904	0.11	-0.7266	<0.001
Hippocampus	-0.3067	0.22	-0.6300	<0.01
Occipital cortex	-0.4074	0.09	-0.7156	<0.001
Pallidum	-0.3485	0.16	-0.6391	<0.01
Parietal cortex	-0.4422	0.07	-0.6986	<0.01
Putamen	-0.4044	0.10	-0.7362	<0.001
Temporal cortex	-0.3854	0.11	-0.7400	<0.001
Thalamus	-0.4137	0.09	-0.7055	<0.01
VS	-0.4096	0.09	-0.6607	<0.01

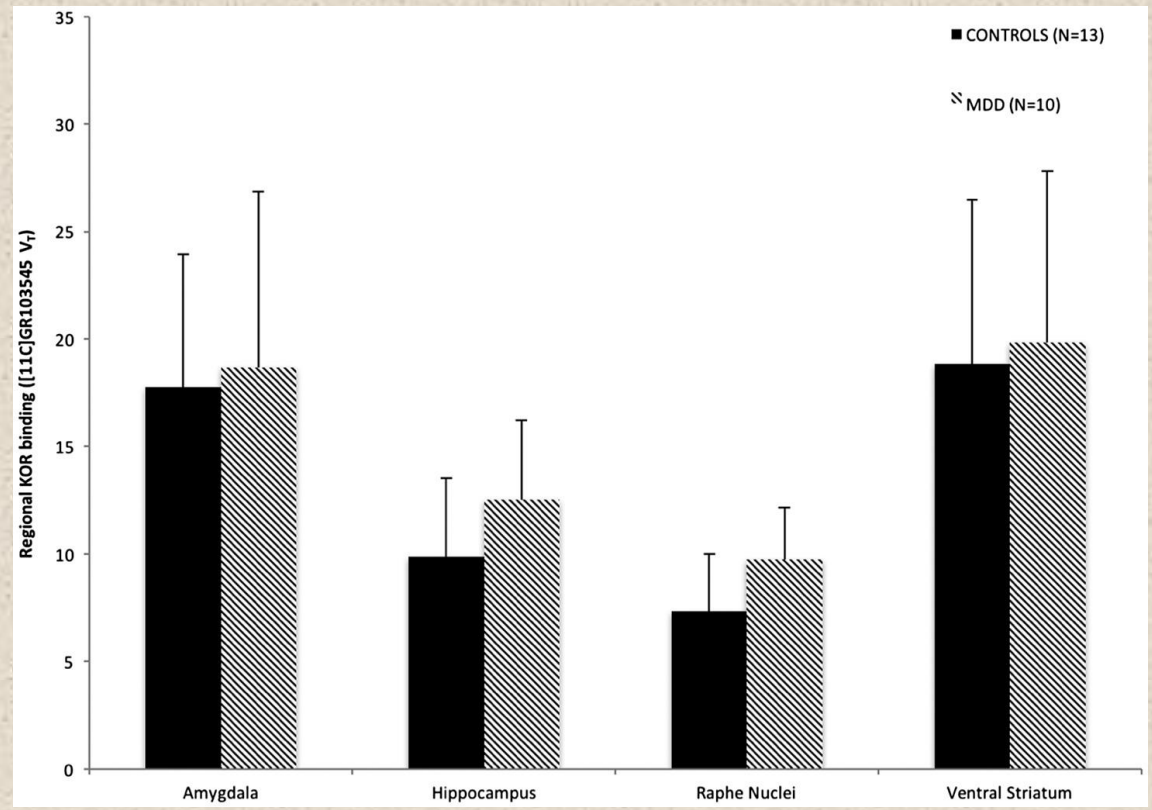
Matuskey et al. 2019. Neuropsychopharmacology

Gender

	Males			Females				
	N	Mean	Std Dev	N	Mean	Std Dev	DF	t Value	Pr > |t|
Amygdala	9	21.2	6.7	9	23.5	5.1	16	-0.86	0.40
ACC	9	13.4	2.6	9	16.0	3.2	16	-1.89	0.08
Caudate	9	6.7	1.5	9	9.2	1.8	16	-3.26	<0.01
Frontal cortex	9	8.6	1.5	9	11.0	1.7	16	-3.26	<0.01
Hippocampus	9	7.8	1.7	9	9.5	2.1	16	-1.89	0.08
Insula	9	13.0	2.6	9	16.9	2.7	16	-3.09	0.01
Occipital cortex	9	7.3	1.3	9	9.3	1.1	16	-3.48	<0.01
Pallidum	9	10.4	2.0	9	14.2	3.3	16	-2.98	0.01
Parietal cortex	9	7.6	1.3	9	9.7	1.3	16	-3.46	<0.01
Putamen	9	8.7	1.4	9	11.4	2.0	16	-3.38	<0.01
Temporal cortex	9	9.3	1.7	9	11.7	1.7	16	-3.12	<0.01
Thalamus	9	4.5	0.7	9	5.8	0.9	16	-3.47	<0.01
VS	9	12.1	2.6	9	15.9	3.0	16	-2.88	0.01

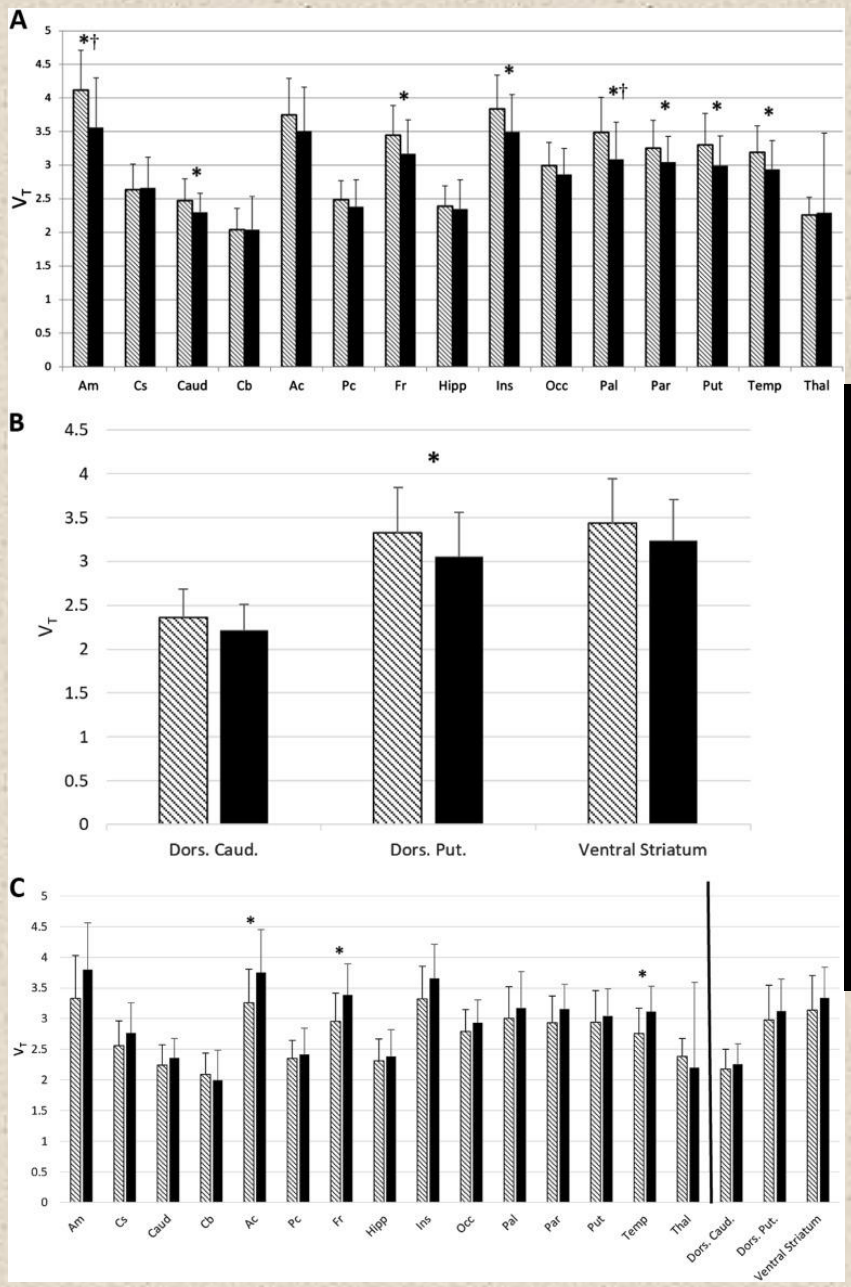
Matuskey et al. 2019. Neuropsychopharmacology

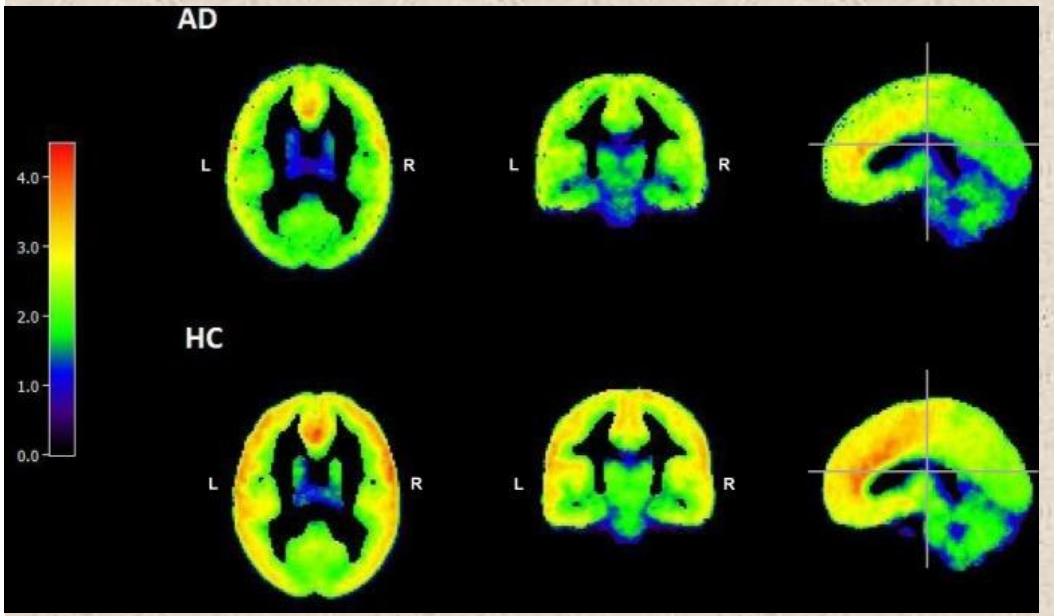
Kappa opioid receptor binding in major depression: A pilot study



Synapse, Volume: 72, Issue: 9, First published: 23 June 2018, DOI: (10.1002/syn.22042)

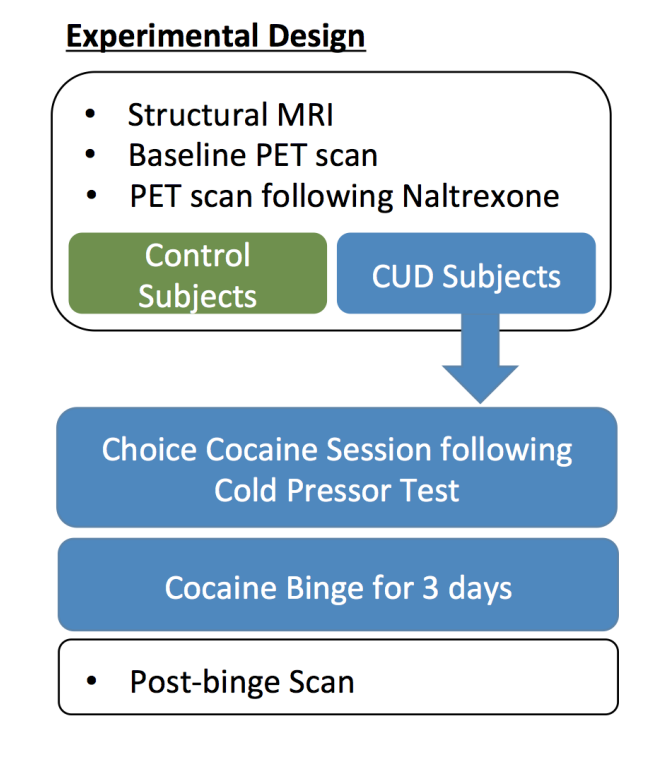
Kappa and ETOH





Vijay et al., Neuropsychopharmacology. 2018 Dec; 43(13): 2539–2547.

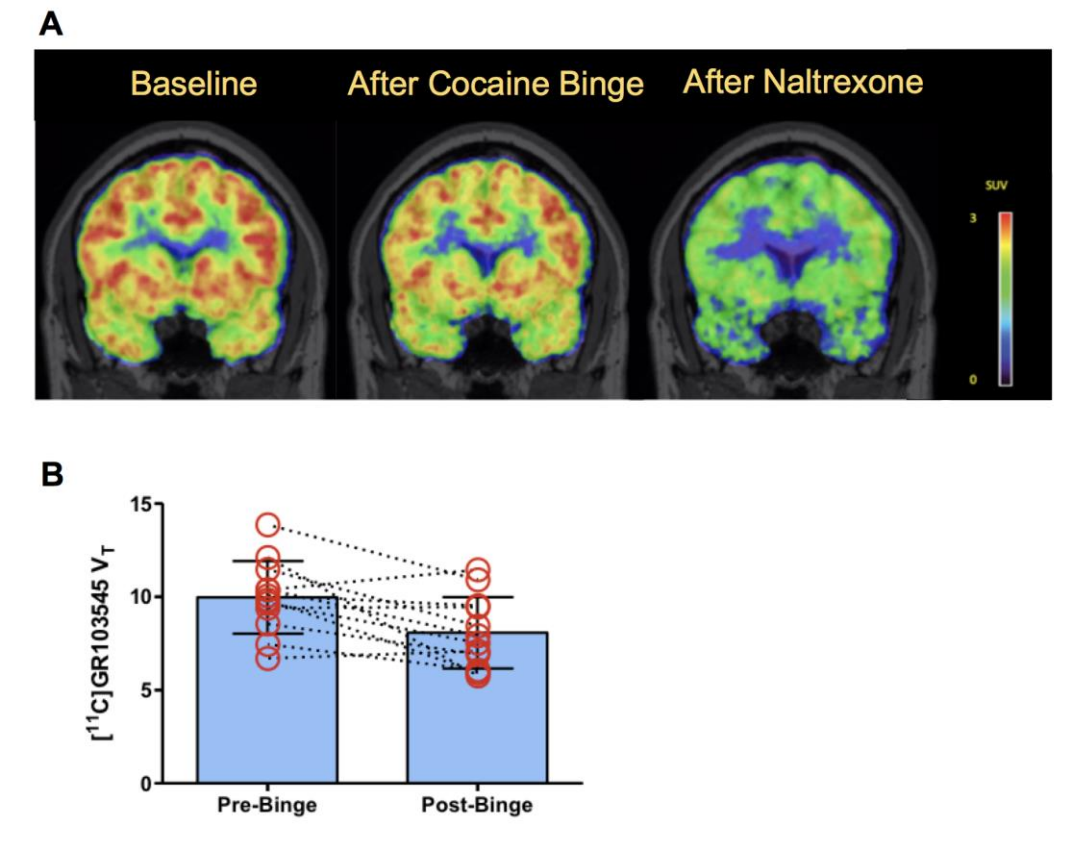
Kappa and Cocaine



- 17 CUD subjects and 14 HCs
- Two types of self-administration sessions in CUD were performed: 1) choice sessions following a cold pressor test, and 2) binge cocaine sessions.
- A significant association between the agonist [^{11}C]GR103545 binding and cocaine self-administration was seen: greater KOR availability was associated with more choices for cocaine.
- Additionally, the three day cocaine binge significantly reduced [^{11}C]GR103545 binding by 18% in the striatum and 14% across brain regions.
- No difference in [^{11}C]GR103545 binding was found between the CUD subjects and controls.

Martinez et al., 2019 *Neuropsychopharmacology*

Kappa in action



Martinez et al., 2019 *Neuropsychopharmacology*

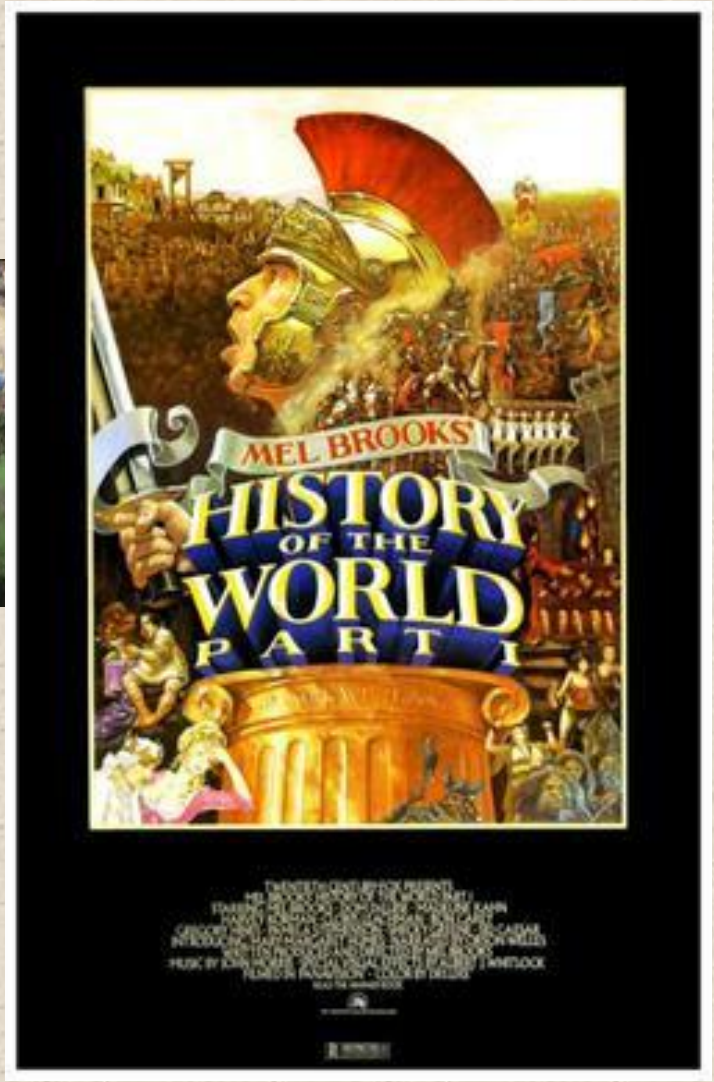
Kappa in OUD

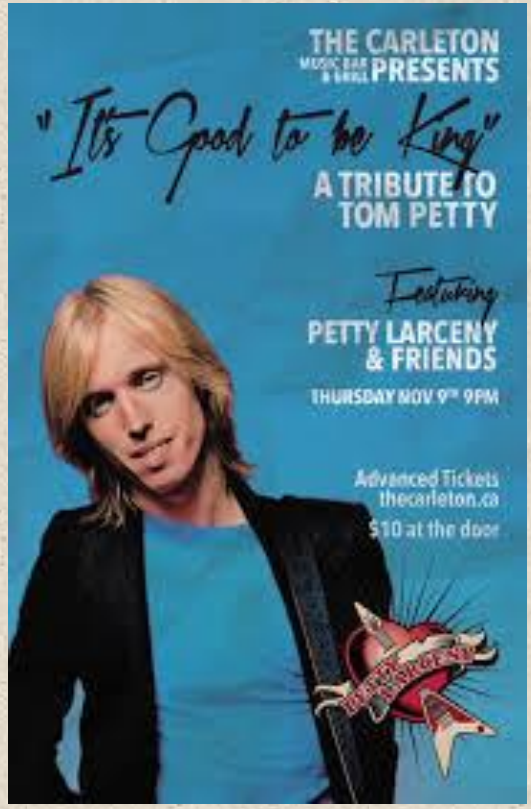
- Opioid use can release dynorphins and engage KORs through its capacity to trigger a stress reaction
- Dynorphins and KORs not only enable the behavioral, emotional, and cognitive response to drug exposure but also decrease dopamine release
- Clinical trials showing that “functional” KOR antagonists (buprenorphine, a MOR agonist/ KOR antagonist, combined with naltrexone) increased effectiveness and retention over naltrexone alone for the treatment of heroin-dependent patients
- *KOR antagonists are now part of “the 10 most wanted” mechanisms proposed by NIDA for developing new and innovative medications to overcome the opioid crisis*

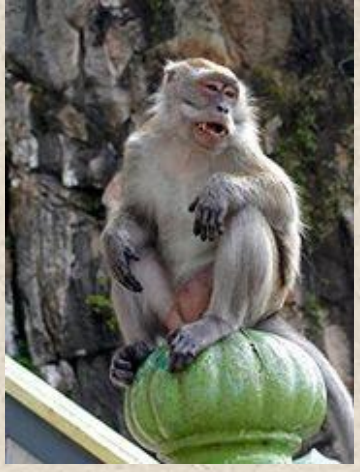
Gerra, G., A. Fantoma, and A. Zaimovic, *Naltrexone and buprenorphine combination in the treatment of opioid dependence.* J Psychopharmacol, 2006. **20**(6): p. 806-14.
Rothman, R.B., et al., *An open-label study of a functional opioid kappa antagonist in the treatment of opioid dependence.* J Subst Abuse Treat, 2000. **18**(3): p. 277-81.
Volkow, N.D., *Medications for opioid use disorder: bridging the gap in care.* Lancet, 2018. **391**(10118): p. 285-287.

Kappa in OUD

It’s good to be the king







Monkey Business

- Twenty experimentally naive adult male cynomolgus monkeys were individually housed for approximately 10 months before the initial PET scans
- Approximately 8 months (range, 5–12 months) after the first PET scan and after at least 3 months of social housing, the second PET scan was conducted
- Monkeys were first trained to respond with food as the reinforcer and then increasing doses of cocaine
- Fixed number of responses on the response lever (for example, a fixed ratio of 30) resulted in presentation of a banana pellet or activation of the infusion pump for 10 seconds

Morgan et al., 2002. Nat Neurosci 5:169–174

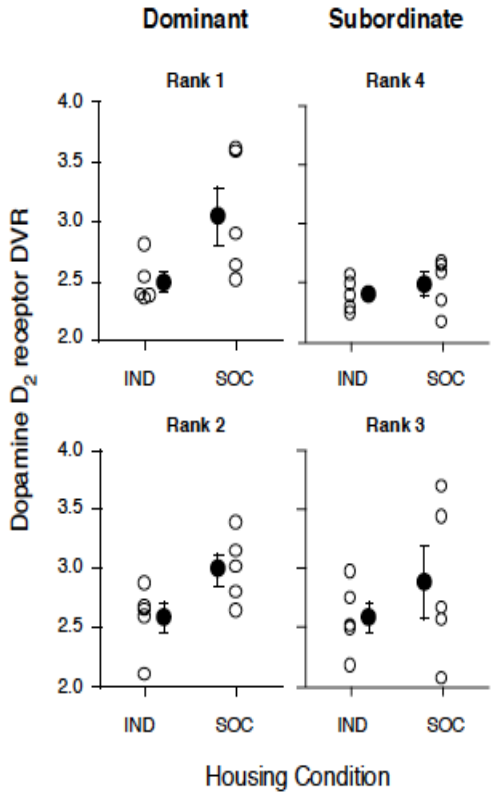


Fig. 2. [^{18}F]FCP binding potential changes as a function of social rank. Panels show the mean and individual [^{18}F]FCP DVR values for monkeys with different social ranks, while they were individually (IND) and socially (SOC) housed.

Table 1. Dopaminergic characteristics of monkeys.

Social rank[a]	[^{18}F]FCP distribution volume ratios		
	Individually housed	Socially housed	Percent change
1	2.49 ± 0.08	3.04 ± 0.23[b,c]	+22.0 ± 8.8
2	2.58 ± 0.13	2.99 ± 0.13	+16.7 ± 6.0
3	2.58 ± 0.13	2.88 ± 0.30	+13.4 ± 15.3
4	2.40 ± 0.06	2.49 ± 0.10	+3.9 ± 5.3

Mean ± s.e.m. [^{18}F]FCP DVR as determined with PET imaging in male cynomolgus monkeys as a function of social rank while individually and socially housed. [a]For individually housed scans, these numbers represent eventual social rank. [b]Significantly higher than individually housed 'dominants.' [c]Significantly higher than socially housed subordinates.

nature *neuroscience* • volume 5 no 2 • february 2002

Morgan et al., 2002. Nat Neurosci 5:169–174

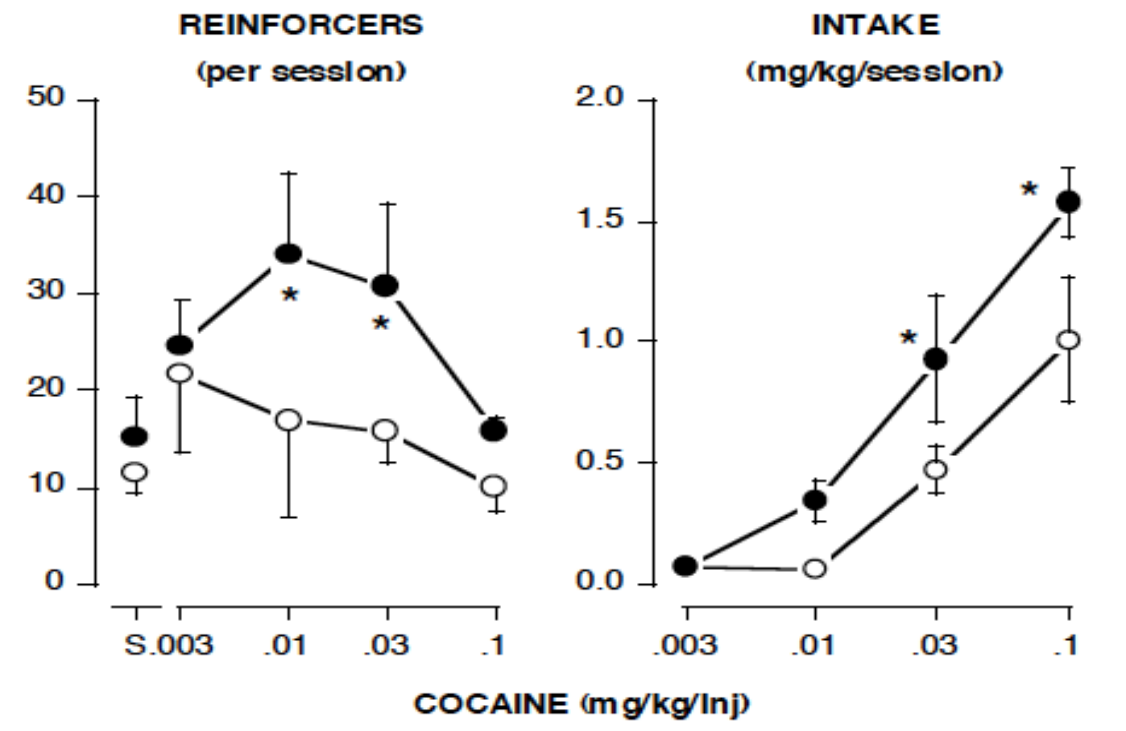
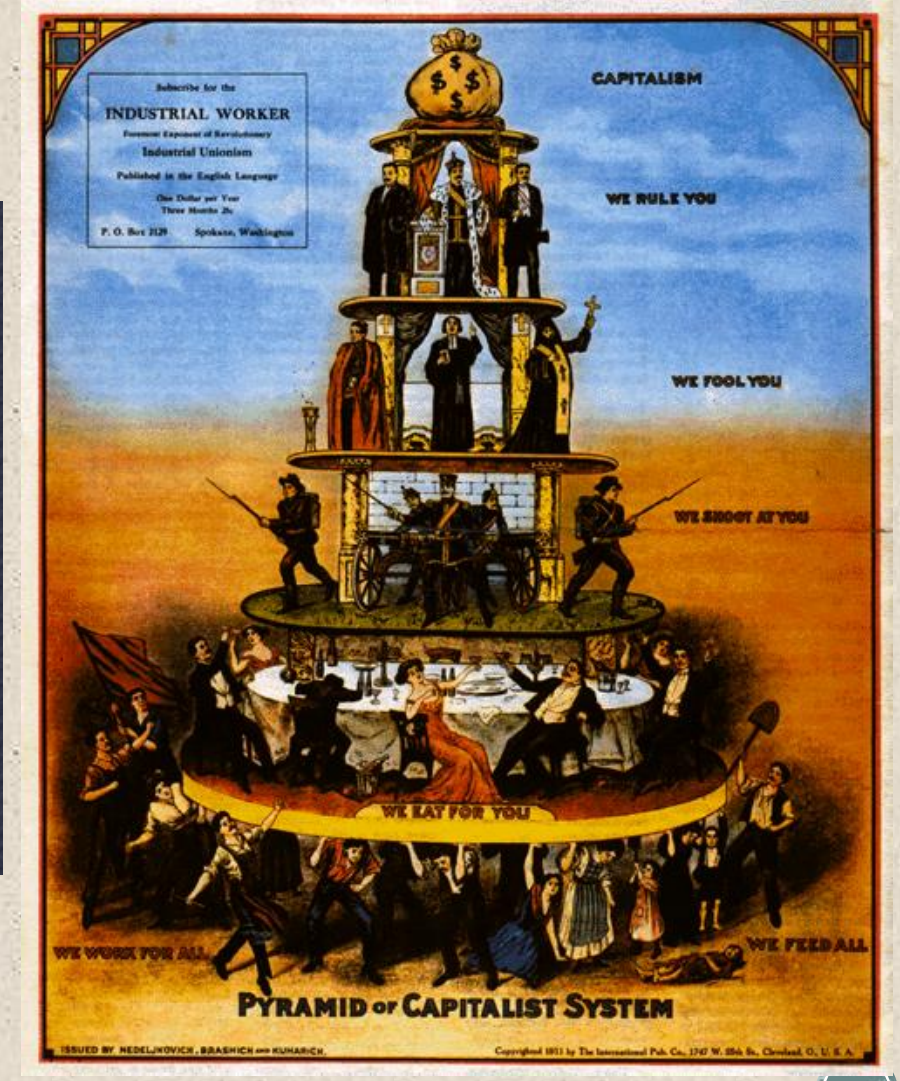


Fig. 4. Reinforcing effects of cocaine are greater in subordinate monkeys compared to dominant animals. Left, mean number of intravenous injections (either saline or various doses of cocaine) per session for 5 dominant (rank 1 and 2, white symbols) and 4 subordinate (rank 3 and 4, black symbols) monkeys. Right, mean intake per session for dominant (white symbols) and subordinate (black symbols) monkeys. Each dose was available for at least 7 sessions and until responding was stable. Data represent the mean of the last 3 days of availability for each animal. Asterisk indicates a statistically significant difference ($p < 0.05$) from dominant monkeys at that particular dose, and from the appropriate saline point.

Morgan et al., 2002. Nat Neurosci 5:169–174


© Original Artist
Reproduction rights obtainable from
www.CartoonStock.com
search ID: jcon721
"BELIEVE IT OR NOT, IN OBEDIENCE SCHOOL, HE WAS THE ALPHA MALE."


Subscribe for the
INDUSTRIAL WORKER
Industrial Unionism
Published in the English Language
P. O. Box 2129 Spokane, Washington
CAPITALISM
WE RULE YOU
WE FOOL YOU
WE SHOOT AT YOU
WE EAT FOR YOU
WE WORK FOR ALL
WE FEED ALL
PYRAMID OF CAPITALIST SYSTEM

Social Status

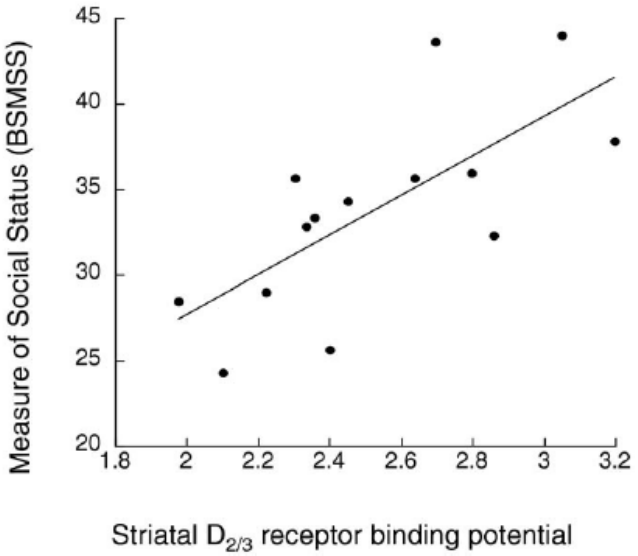


Figure 1. Correlation between [^{11}C]raclopride BP (x axis) and social status, measured with the Barratt Simplified Measure of Social Status (BSMSS). A positive correlation was seen, where higher BP correlated with higher BSMSS ($r = .71$, $p = .004$, age-corrected $p = .007$). BP, binding potential.

Martinez et al, 2010. Biological Psychiatry 275-278

A Dopamine mediated quote?

“Monarchy is the greatest thing on earth. Kings are rightly called gods since just like God they have power of life and death over all their subjects in all things. They are accountable to God only ... so it is a crime for anyone to argue about what a king can do" King James I

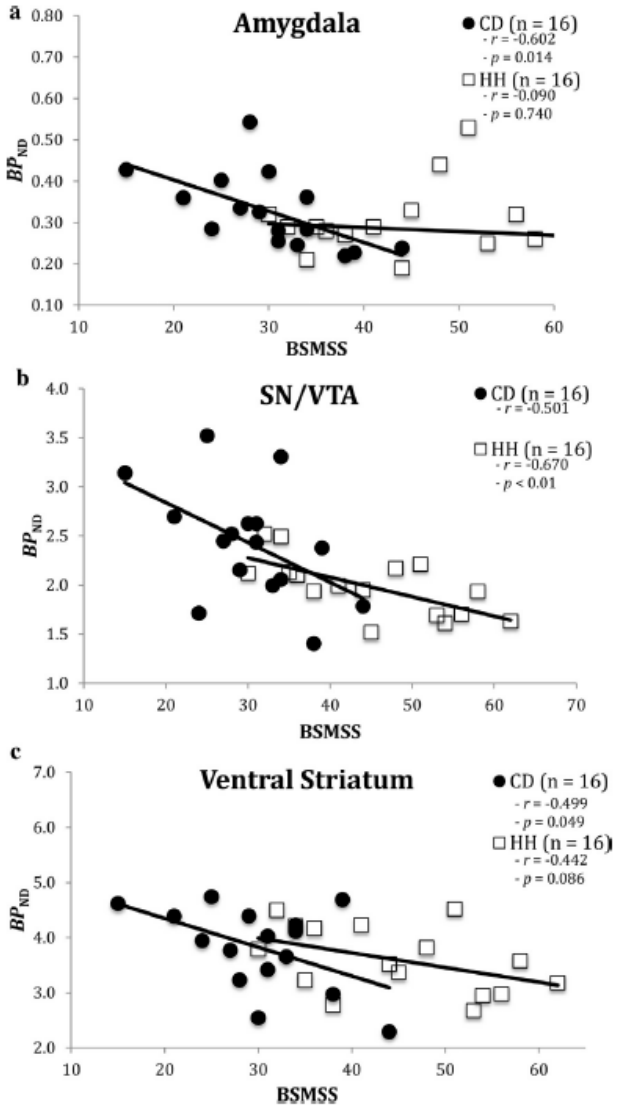


Fig. 1. Correlations between BSMSS and [^{11}C](+)PHNO BP_{ND} in both CD and HH participants for the amygdala (a), the substantia nigra/ventral tegmental (SN/VTA) area (b), and the ventral striatum (c). Correlations shown are not BMI and age-adjusted.

???

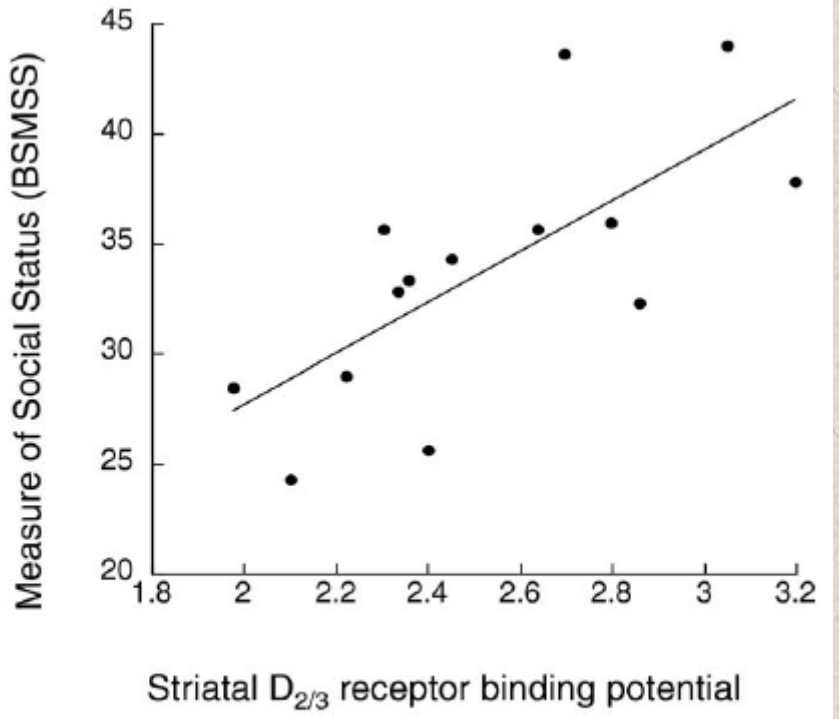


Figure 1. Correlation between [^{11}C]raclopride BP (x axis) and social status, measured with the Barratt Simplified Measure of Social Status (BSMSS). A positive correlation was seen, where higher BP correlated with higher BSMSS ($r = .71$, $p = .004$, age-corrected $p = .007$). BP, binding potential.

≠

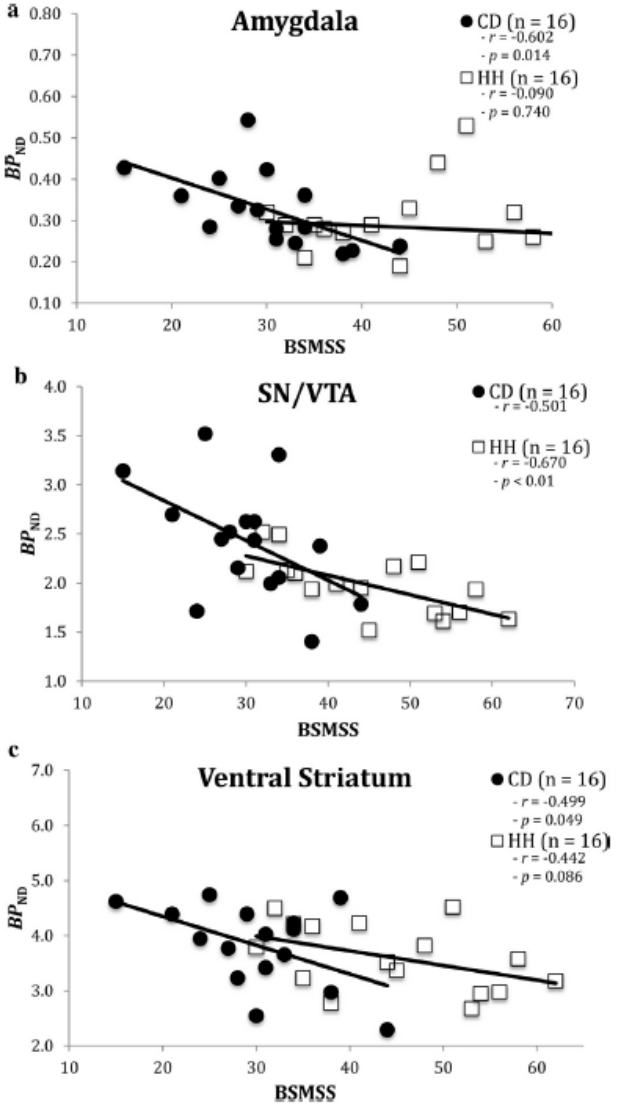
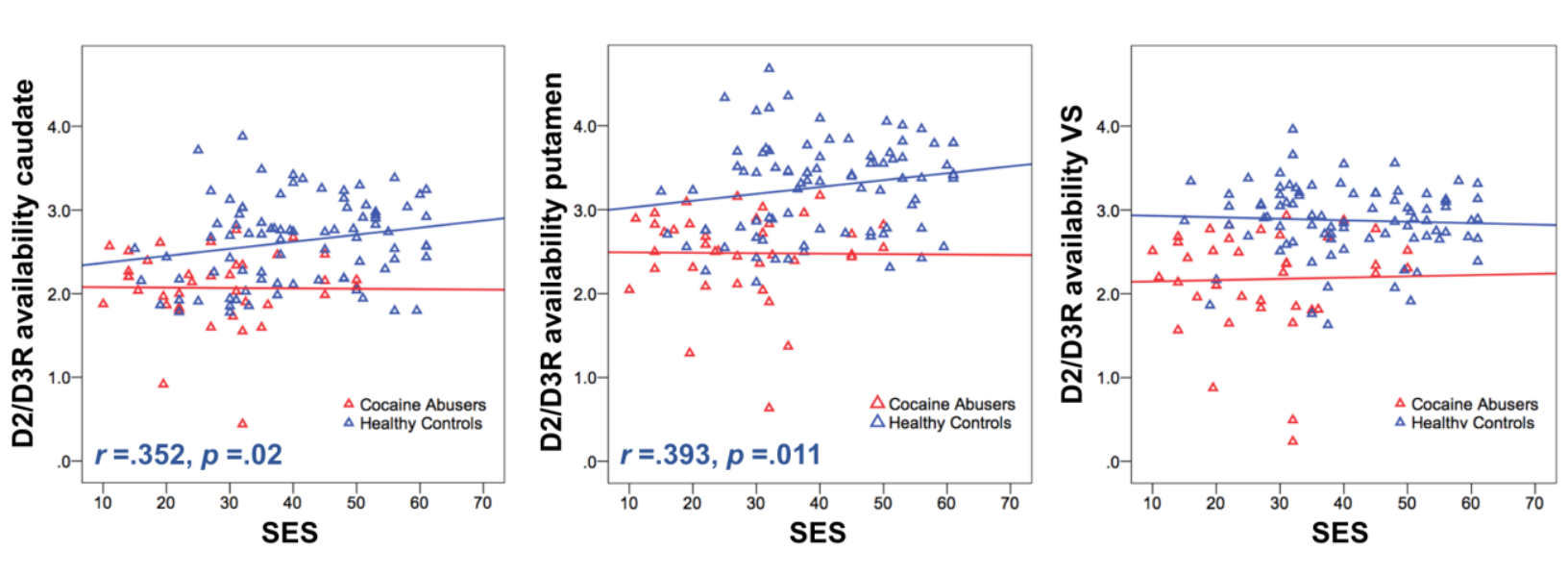


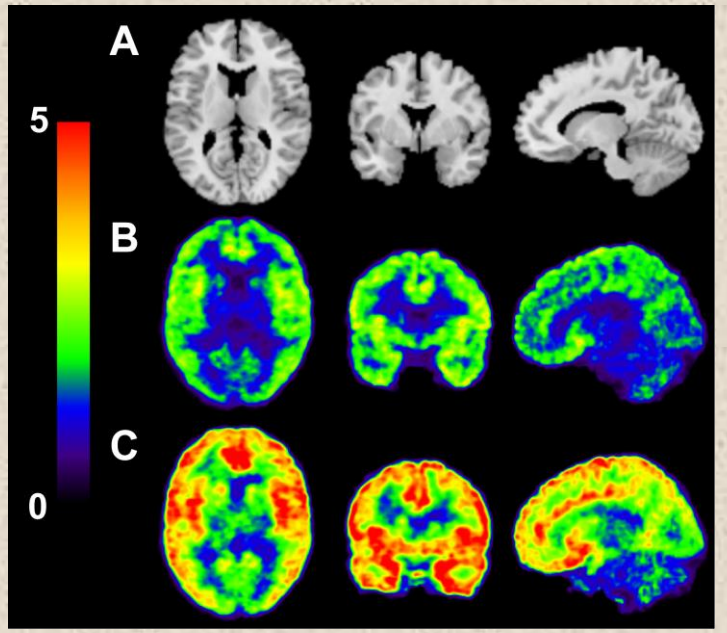
Fig. 1. Correlations between BSMSS and [^{11}C](+)PHNO BP_{ND} in both CD and HH participants for the amygdala (a), the substantia nigra/ventral tegmental (SN/VTA) area (b), and the ventral striatum (c). Correlations shown are not BMI and age-adjusted.



Wiers et al. 2016, Socioeconomic status is associated with striatal dopamine D2/D3 receptors in healthy volunteers but not in cocaine abusers. Neuroscience Letters.

Return of the Sith

Region of Interest (ROI)	V_T Mean (SD)	Pearson R	p value	Slope	p value (Hommel)
Amygdala	22.4 (5.9)	-0.69	<0.01	-0.1963	0.04
ACC	14.7 (3.1)	-0.56	0.02	-0.0892	0.04
Caudate	7.9 (2.1)	-0.66	<0.01	-0.0493	0.03
Frontal	9.8 (2.0)	-0.52	0.04	-0.0353	0.04
Hippocampus	8.7 (2.0)	-0.60	0.01	-0.0579	0.04
Pallidum	12.3 (3.3)	-0.59	0.02	-0.0733	0.04
Putamen	10.1 (2.1)	-0.62	0.01	-0.0432	0.04
VS	14.0 (3.4)	-0.66	<0.01	-0.0817	0.04



Matuskey et al., Social Status and Demographic Effects of the Kappa Opioid Receptor: A PET Imaging Study with a Novel Agonist Radiotracer in Healthy Volunteers

Social Status

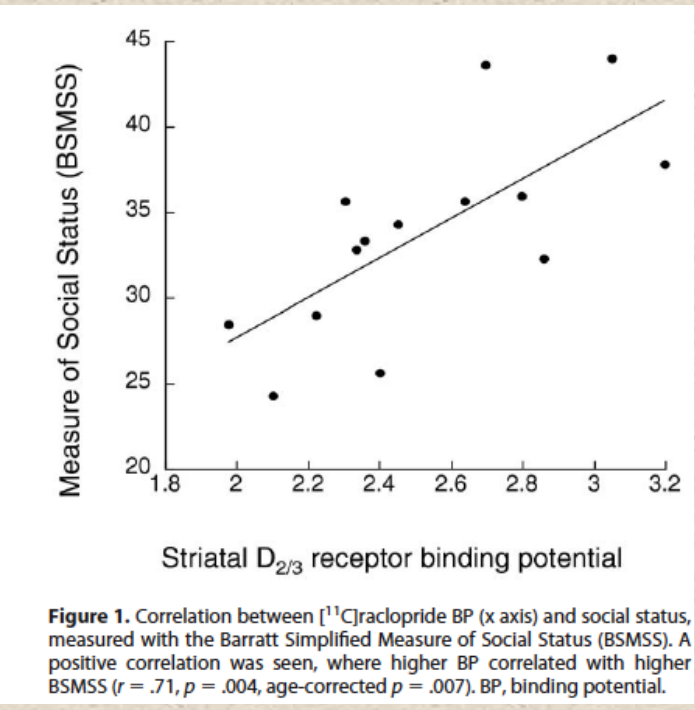
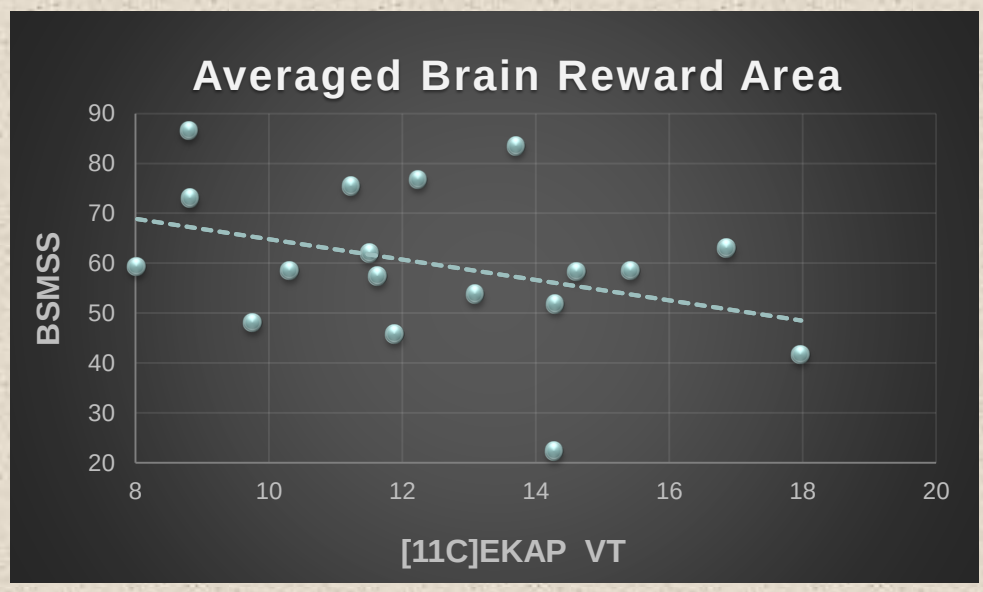


Figure 1. Correlation between [^{11}C]raclopride BP (x axis) and social status, measured with the Barratt Simplified Measure of Social Status (BSMSS). A positive correlation was seen, where higher BP correlated with higher BSMSS ($r = .71$, $p = .004$, age-corrected $p = .007$). BP, binding potential.

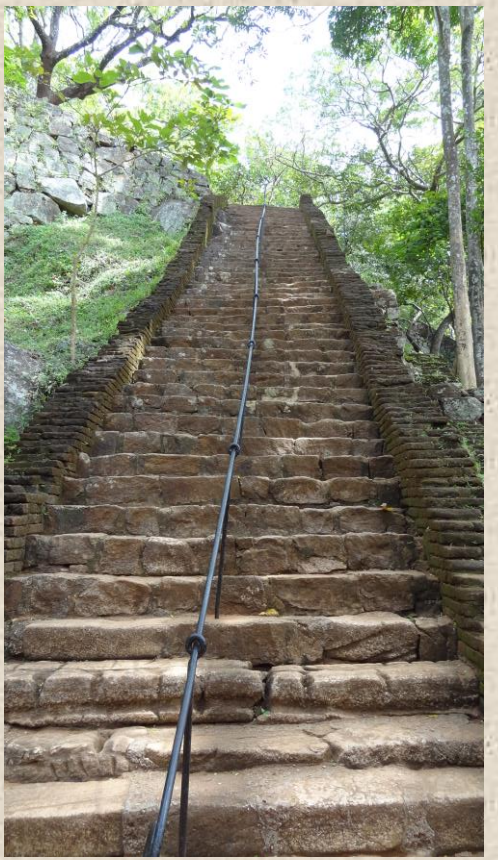


Martinez et al, 2010. Biological Psychiatry 275-278
Matuskey et al. 2019. Neuropsychopharmacology

Discussion

- PET imaging can be successfully used to investigate the underlying physiology of addiction
- This can provide us *in-vivo* evidence in living humans
- Has been used to study the role of dopamine and other neurotransmitter systems (e.g. $5HT_{1B}$ or KOR)
- Translational-can bridge preclinical to clinical and provide valuable insight into pharmacologic treatments before large scale clinical studies are begun

The Future…



The Future…

- Environmental factors
- New targets
- Temporal events

The Future…

- E… mental factors
- New tar…
- Temporal even…

BETTER TREATMENTS!

It Takes a Village

- Dept. of Psychiatry: Gustavo Angarita, Patrick Wohunsky, Edward Gaiser, Brian Pittman, Zubin Bhagwagar, Marc Potenza, Robert Malison