Recent Advance in Nuclear Neurology: SPECT and PET Imaging of Dopamine Transporters in Parkinson's Disease and Other Movement Disorders

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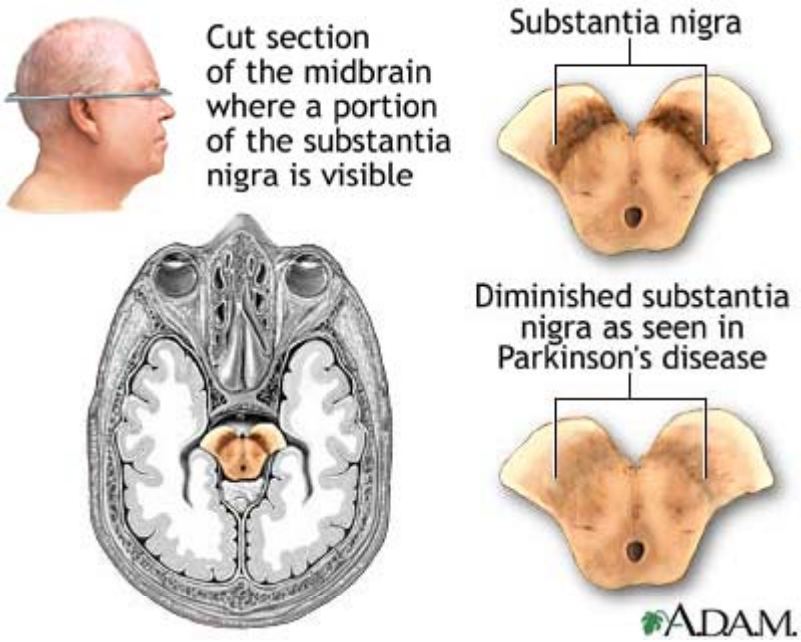
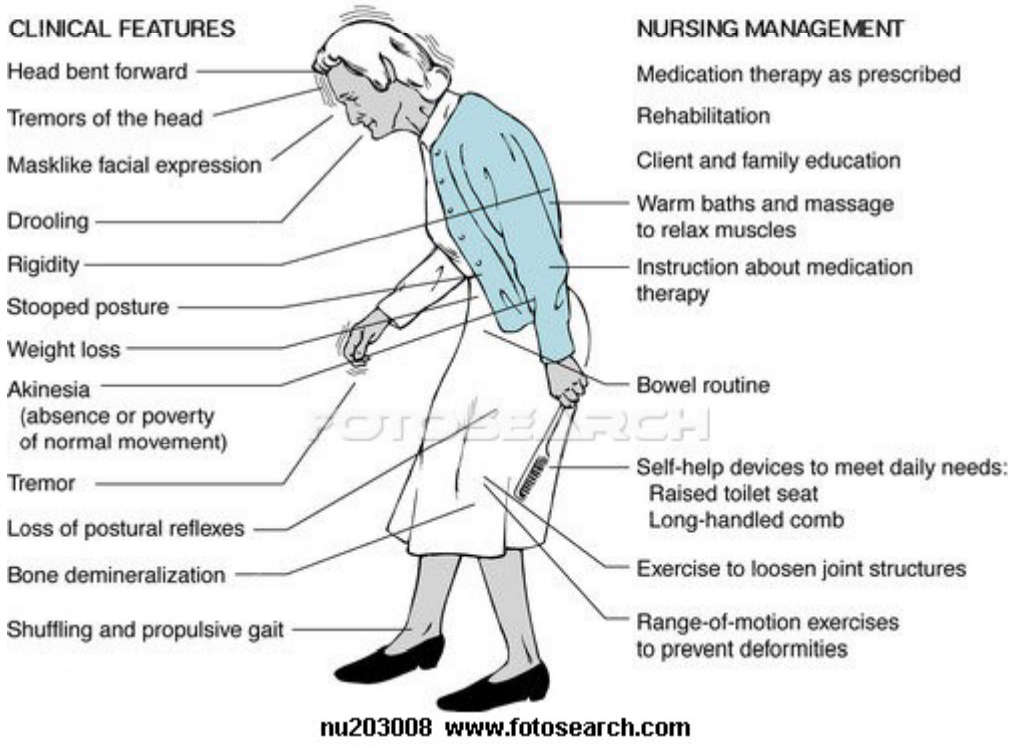
Parkinson’s disease





Parkinson's disease and other parkinsonism

Etiologic categories of parkinsonism*

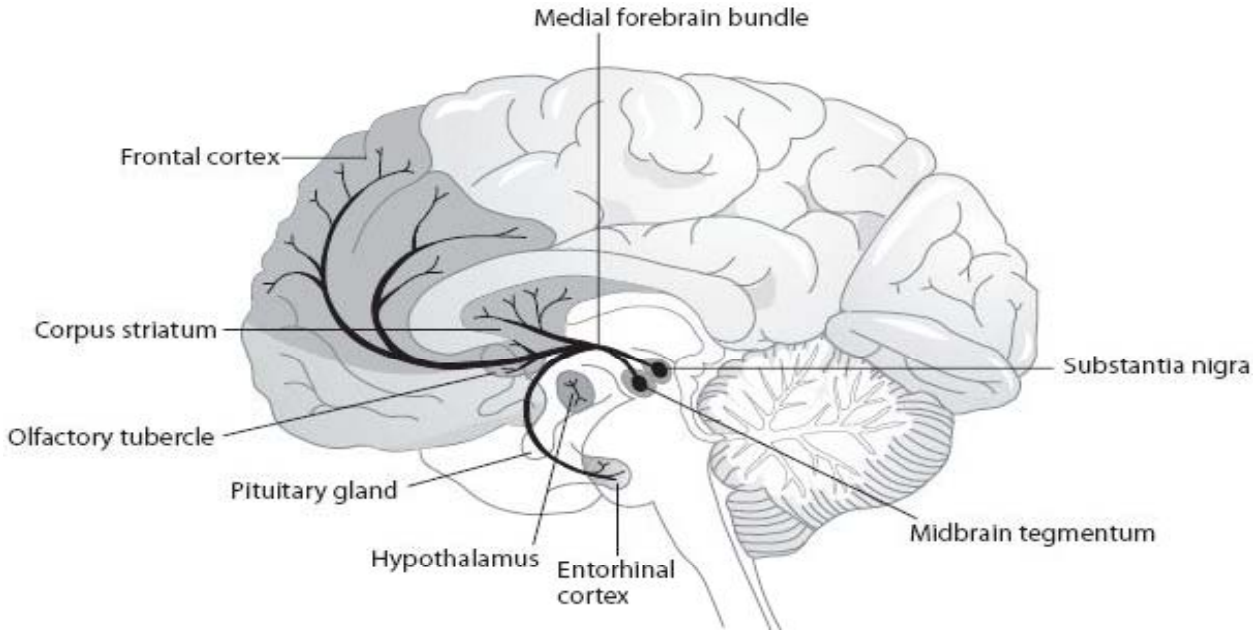
	Number of Patients	Percentage
Parkinson's disease	1595	77.7
Parkinsonism plus	250	12.2
PSP	154	7.5
SDS	35	1.7
OPCA	23	1.1
CBGD	18	0.9
SND	9	0.4
PD/AD	8	0.4
PD/ALS	3	0.1
Secondary parkinsonism	168	8.2
Heredodegenerative parkinsonism	12	0.6
Unknown	27	1.3

**Baylor College of Medicine, Parkinson's Disease Center and Movement Disorders Clinic (N =2052)*
CBGD = Corticobasal ganglionic degeneration; OPCA = olivopontocerebellar atrophy; PD/AD = parkinsonism with severe dementia; PD/ALS = Parkinson's disease with motor neuron disease; PSP = progressive supranuclear palsy; SDS = Shy-Drager syndrome; SND = strialonigral degeneralion

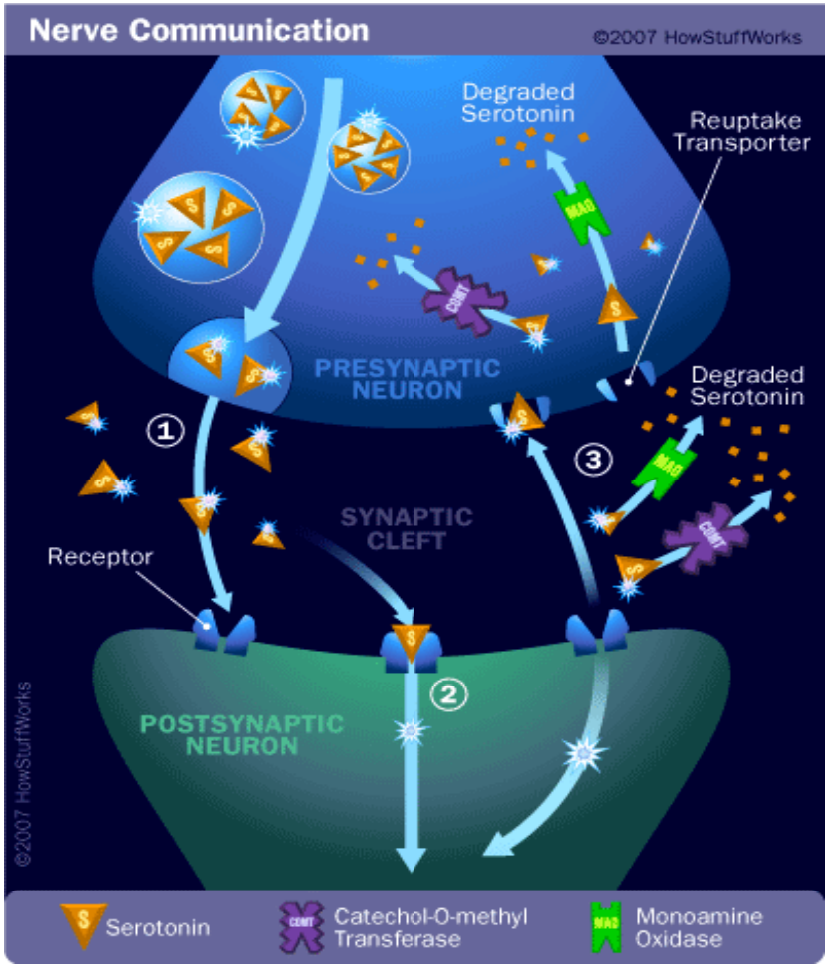
The Clinical Problem:
Differential diagnosis of parkinsonism

- Misdiagnosis: 20-30% in the early stage
- Why important?
  - Decide on treatment regimens
  - Provide prognosis
  - Investigate etiology and pathogenesis
  - Develop new therapeutic strategies

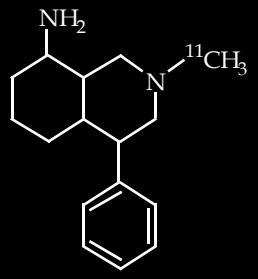
Dopaminergic pathways in the brain



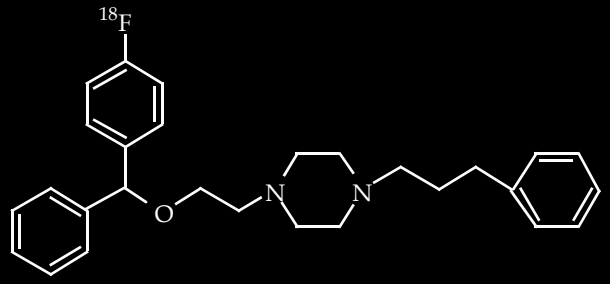
Dopamine transporter as a marker of dopaminergic neuronal integrity



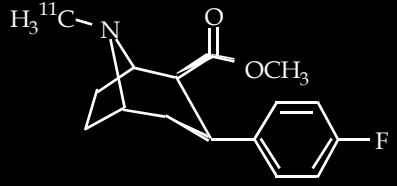
Radiotracers for Imaging Dopamine Transporters



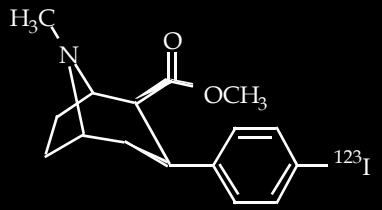
^{11}C-Nomifensin



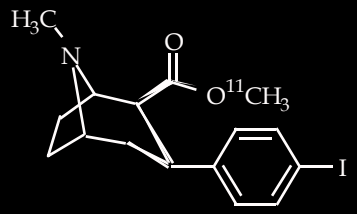
^{18}F-GBR 13119



^{11}C-CFT (WIN 35,428)



^{123}I-β-CIT (RTI-55)



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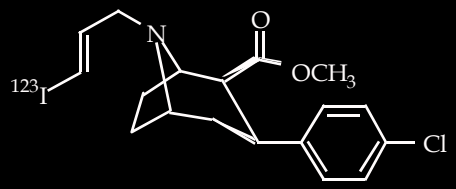
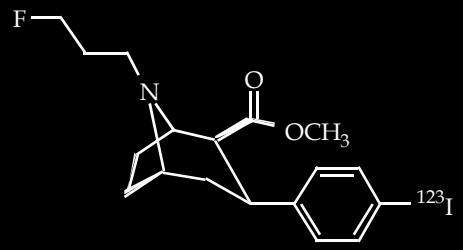
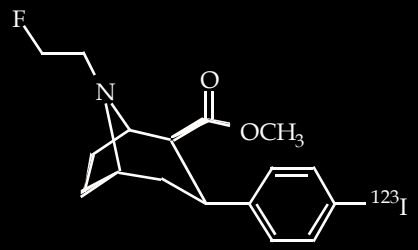


^{123}I-IPT



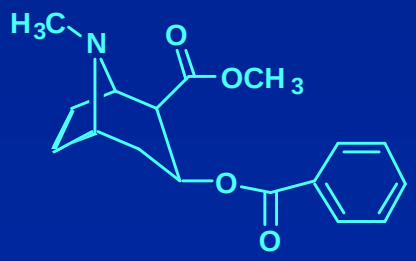
^{123}I-β-CIT-FP



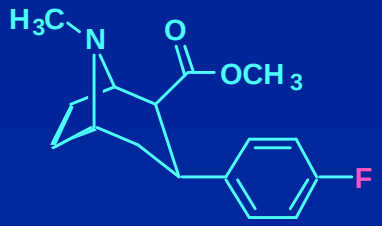
^{123}I-β-CIT-FE

In Vitro Radioligand Binding Data for Cocaine and 3-(4-Halophenyl) Analogues

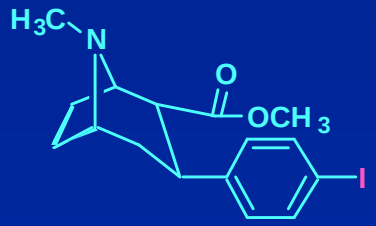
	Displacement of [^{3}H]CFT		Displacement of [^{3}H]paroxetine	
Analogue	IC_{50} (nM)	Hill slope (nH)	IC_{50} (nM)	Hill slope (nH)
Cocaine	221 ± 14	0.69 ± 0.06	207 ± 66	0.73 ± 0.12
β-CFT	15.3 ± 1.2	0.75 ± 0.01	479 ± 59	1.34 ± 0.22
α-CIT	87.6 ± 2.9	0.70 ± 0.01	210 ± 86	0.73 ± 0.04
β-CIT	1.6 ± 0.15	0.79 ± 0.04	3.8 ± 0.53	0.82 ± 0.08



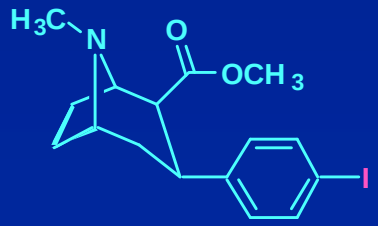
Cocaine



β-CFT

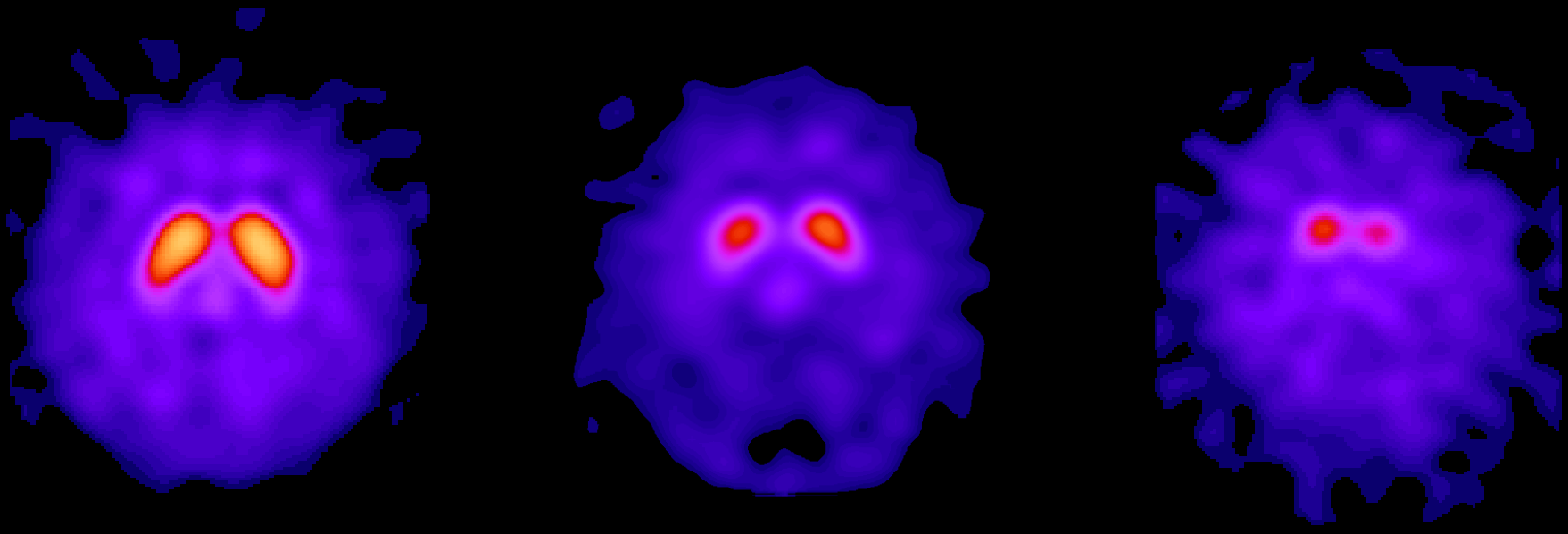


α-CIT



β-CIT

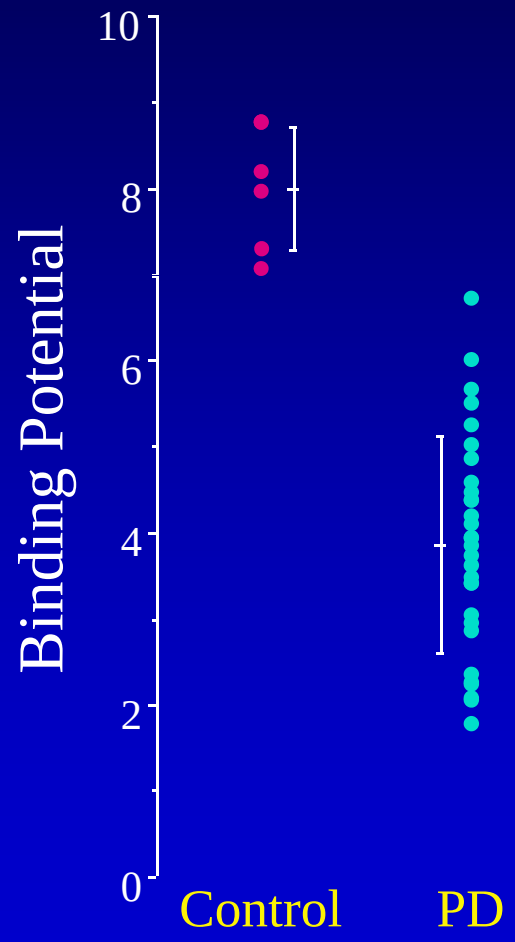
Dopamine Transporter Imaging in PD ([^{123}I]β-CIT SPECT)



Healthy control Hoehn-Yahr stage 1 Hoehn-Yahr stage 3

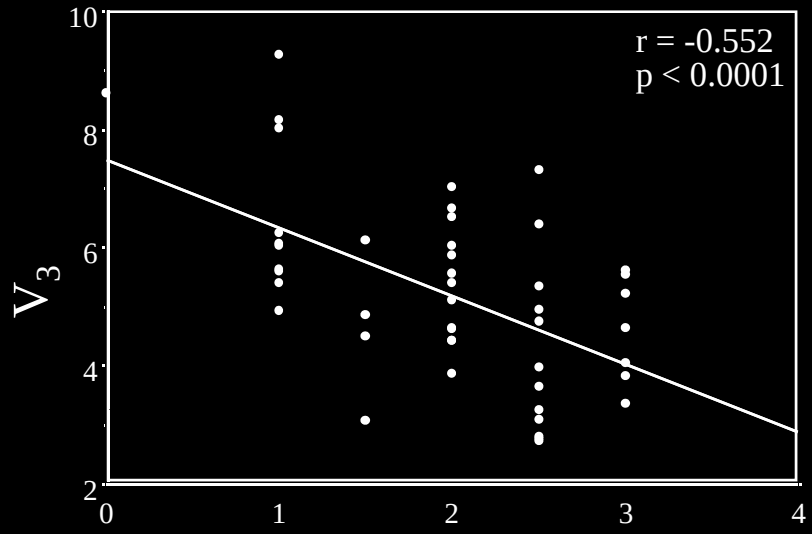
Kim et al., 1995

[^{123}I]β-CIT binding (Control vs. PD)

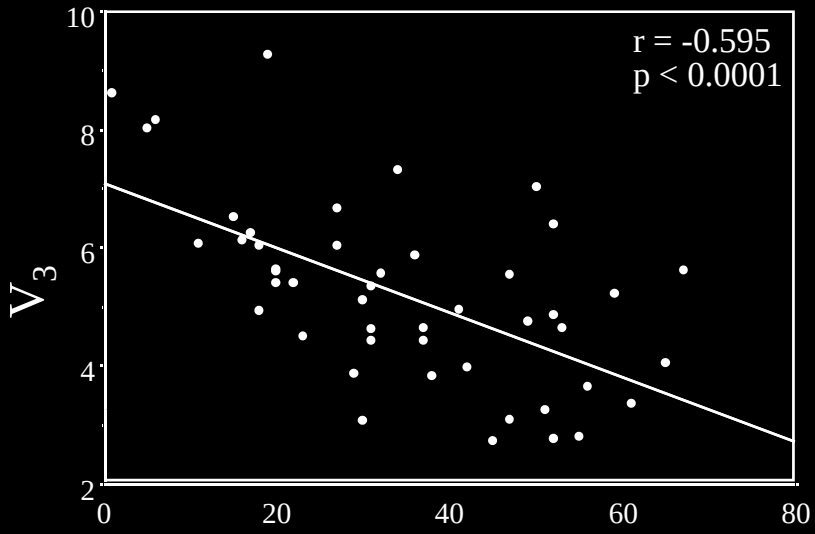


Kim et al., 1995

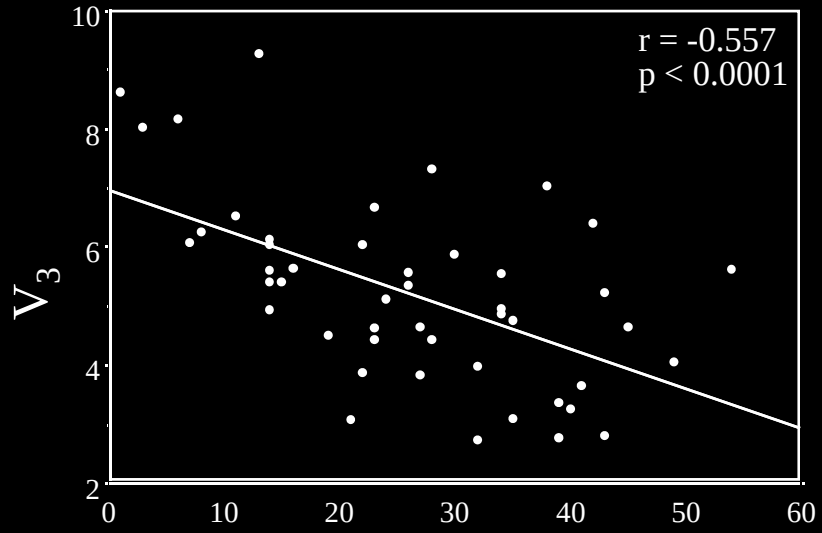
DA Transporter Density versus Clinical Severity



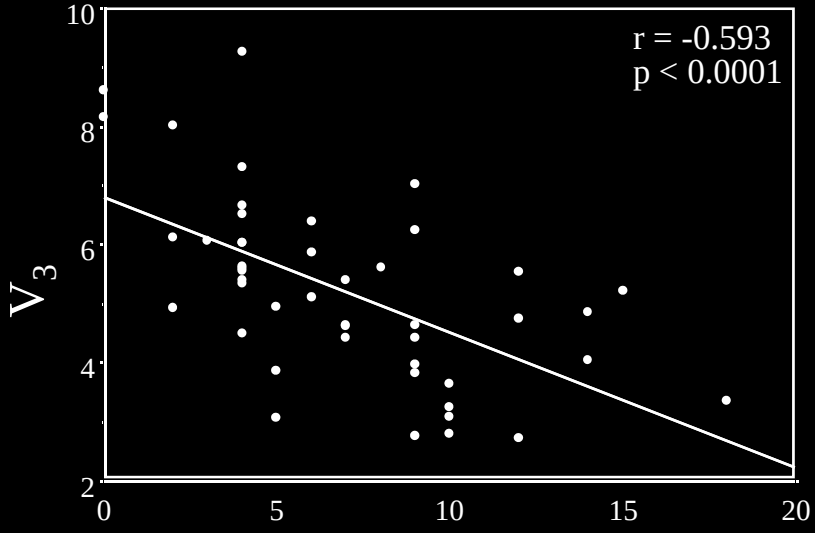
Hoehn-Yahr Stage



Total Score of UPDRS



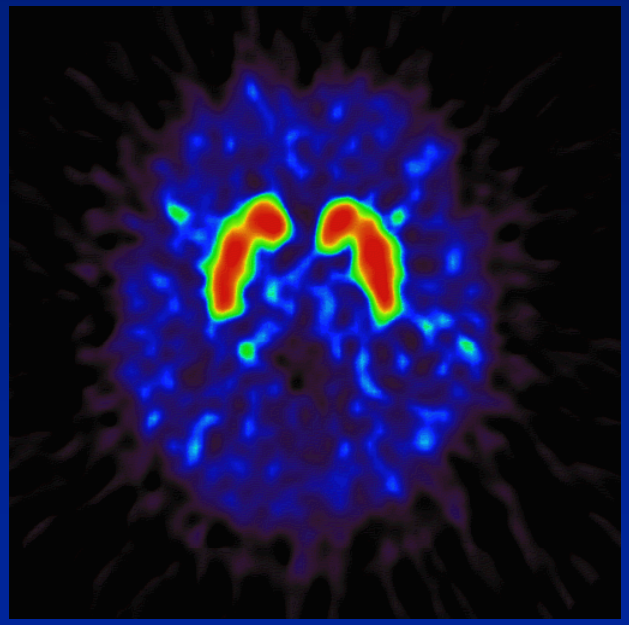
Motor Score of UPDRS



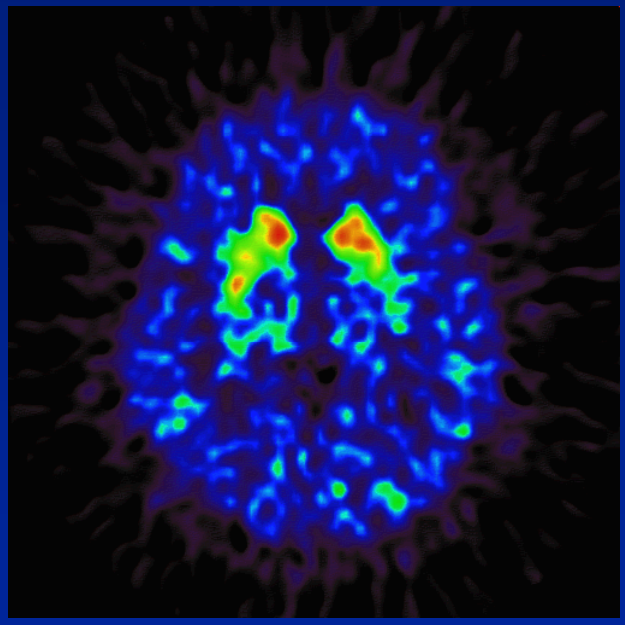
ADL Score of UPDRS

Kim et al., 1995

[^{11}C]WIN 35,428 PET Study



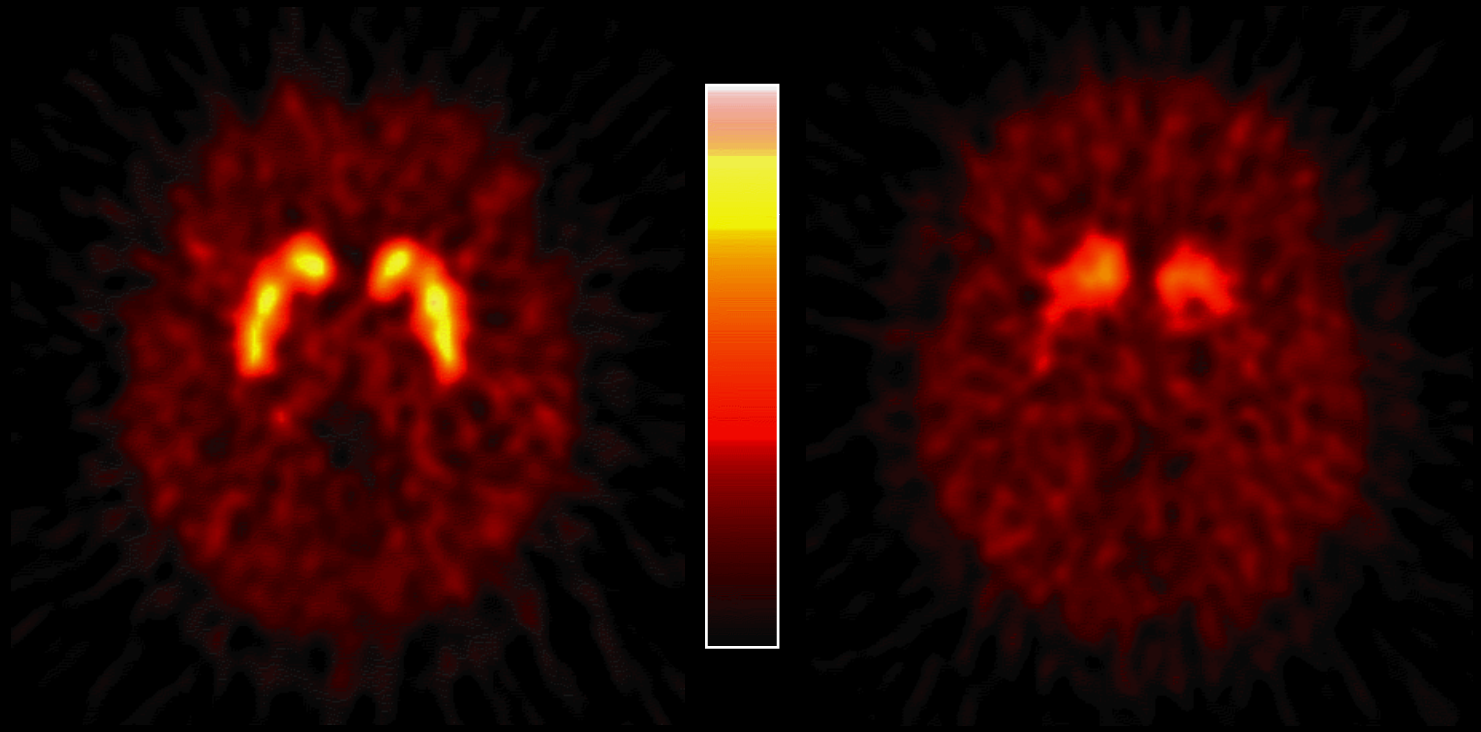
Healthy control



PD

Kim et al., 1996

[^{11}C]WIN 35,428 PET Study

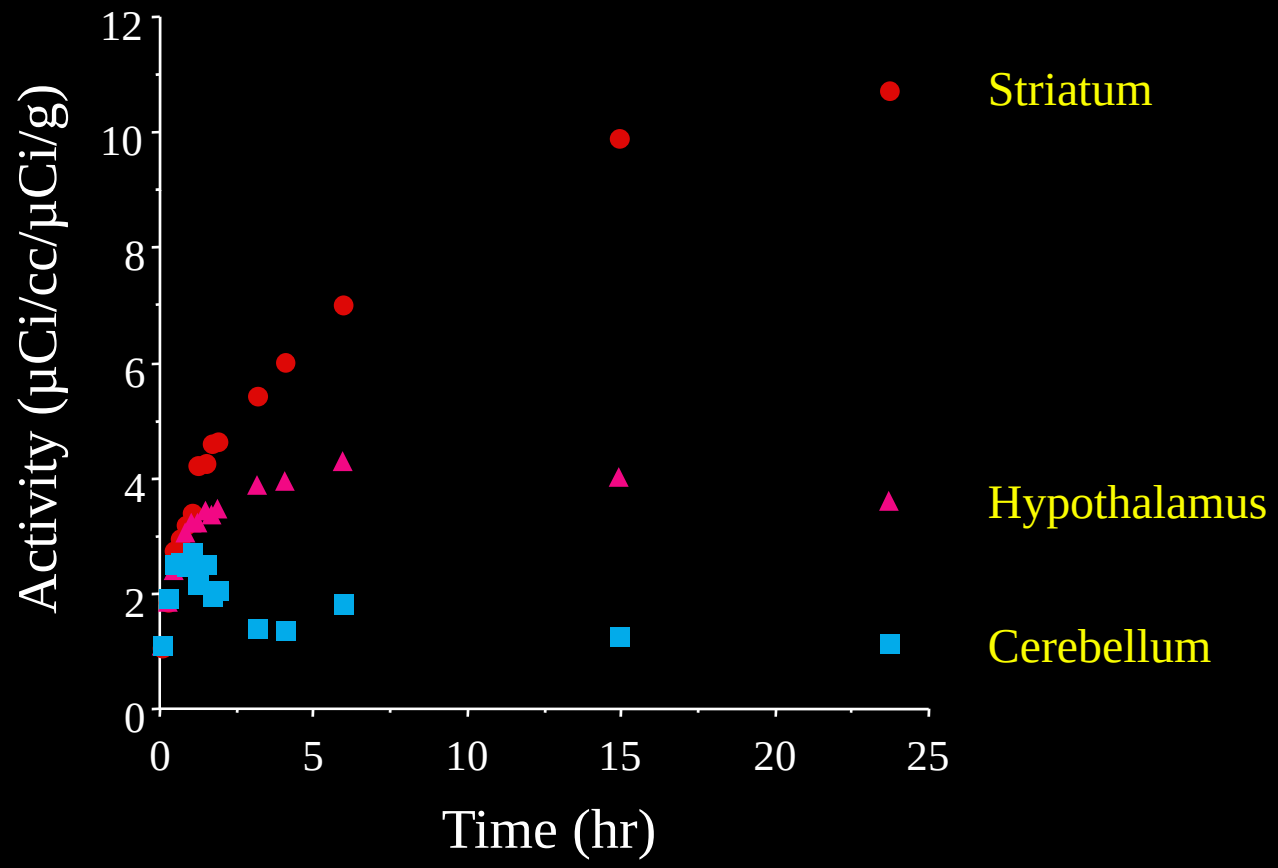


Healthy control

Hemi-Parkinson’s disease

Kim et al., 1996

[^{123}I]β-CIT Time-Activity Curves in a Healthy Control



Kim et al., 1995

Affinity of N-(Fluoroalkyl)tropanes for DA and 5-HT Transporters

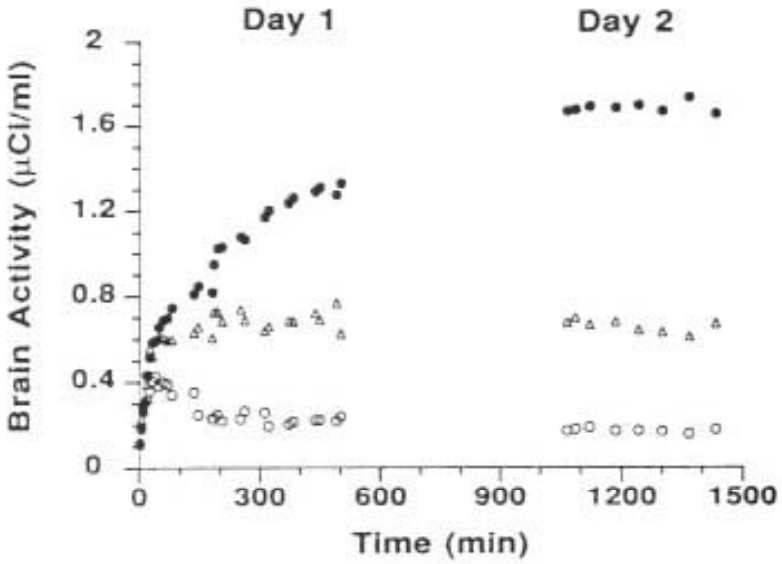
Compound	DA transporters* Ki (n*M*)	5-HT transporters† Ki (n*M*)	DA selectivity 5-HT Ki/DA Ki
β-CIT	1.40 ± 0.20	2.35 ± 0.42	1.68
FP-CIT	3.50 ± 0.39	9.73 ± 0.58	2.78
FE-CIT	4.00 ± 0.73	14.53 ± 3.52	3.6

* *Neumeyer et al., 1994*

† *Abi-Dargham et al., 1996*

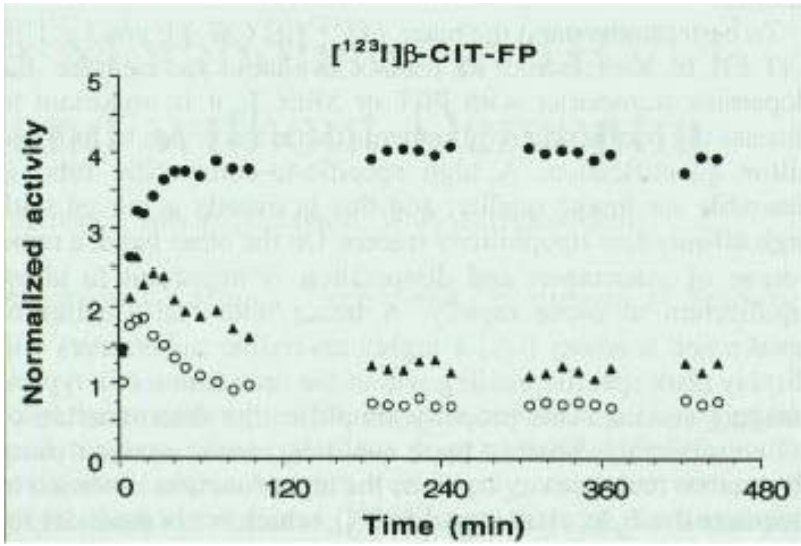
[^{123}I]FP-CIT: Faster kinetics and higher selectivity for dopamine transporters

[^{123}I]β-CIT



Laruelle et al., 1993

[^{123}I]FP-CIT



Abi-Dargham et al., 1996

Differentiation of dementia with Lewy bodies from Alzheimer's disease using FDG PET and [^{123}I]FP-CIT SPECT

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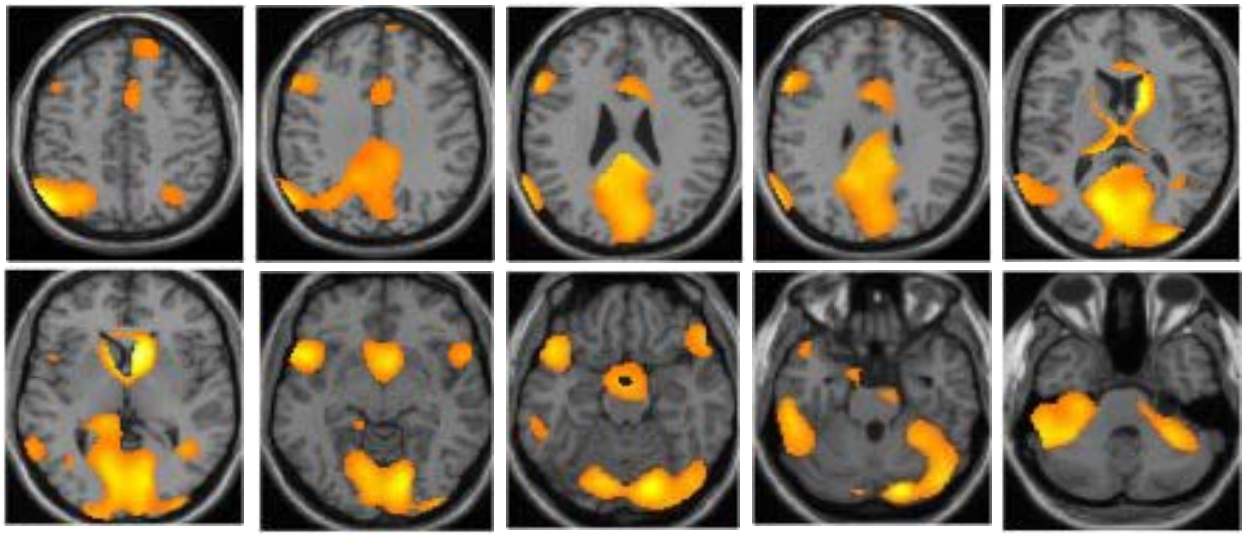
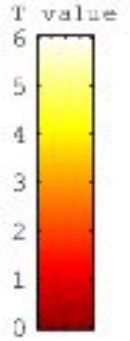
* Neumeyer *et al*., 1994
†Abi-Dargham *et al*., 1996

Regional brain metabolic alterations in DLB

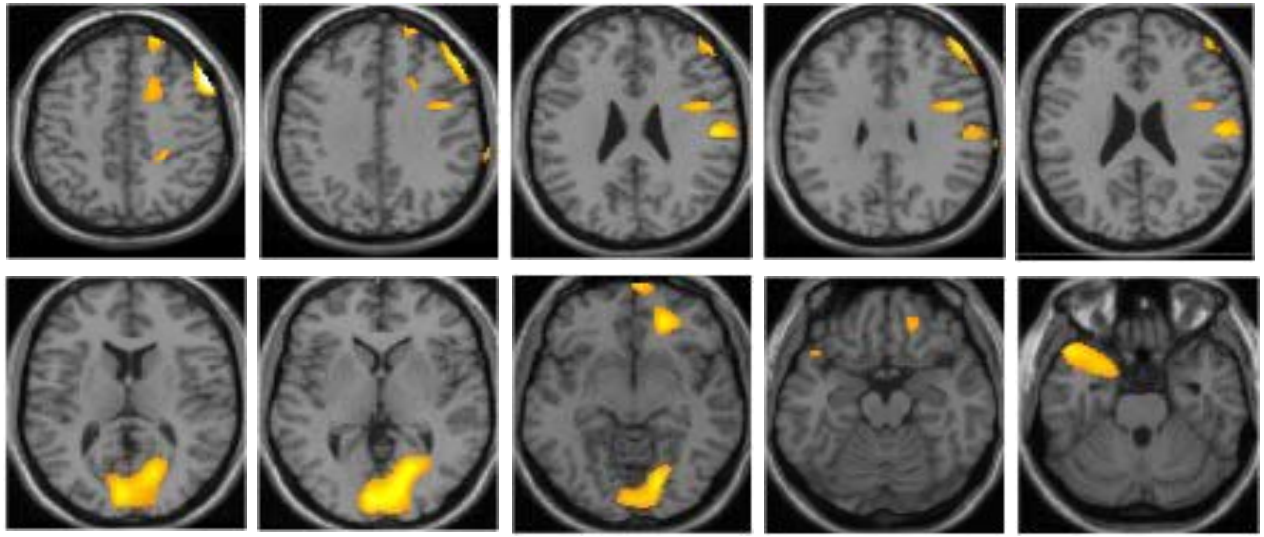
Hypometabolic regions in DLB compared with controls

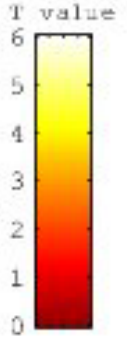




p < 0.01 uncorrected
k = 100

Hypometabolic regions in DLB compared with AD

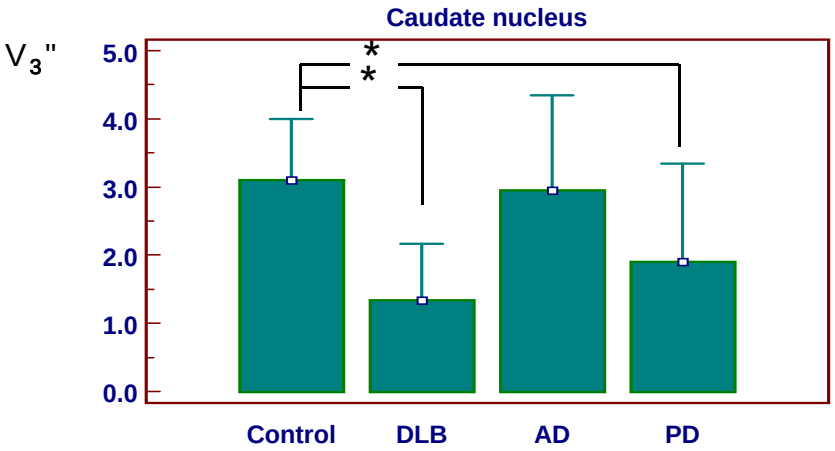


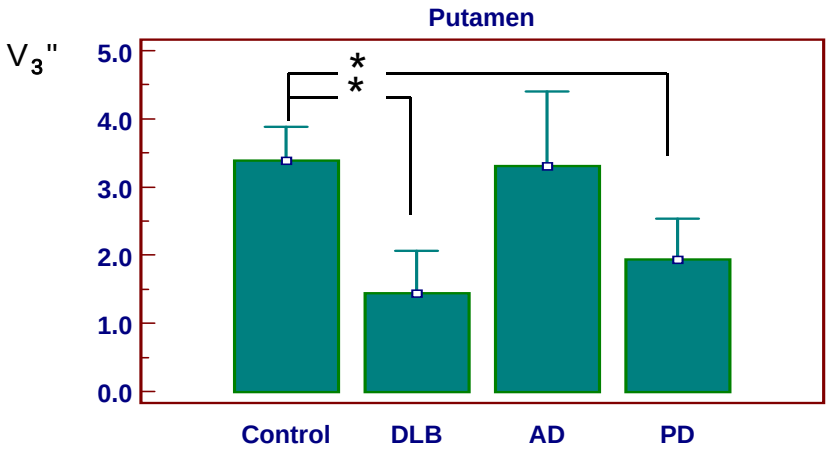


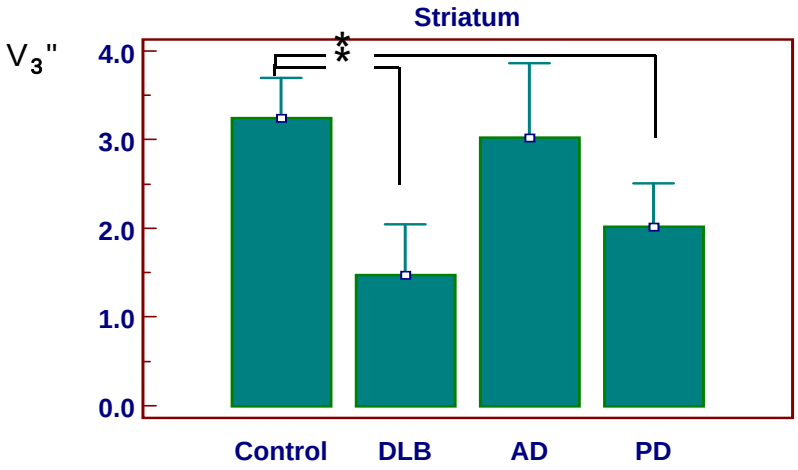
p < 0.01 uncorrected
k = 100

Kim et al., 2004

DAT availability in patients with DLB, AD, and PD ([^{123}I]FP-CIT SPECT study)



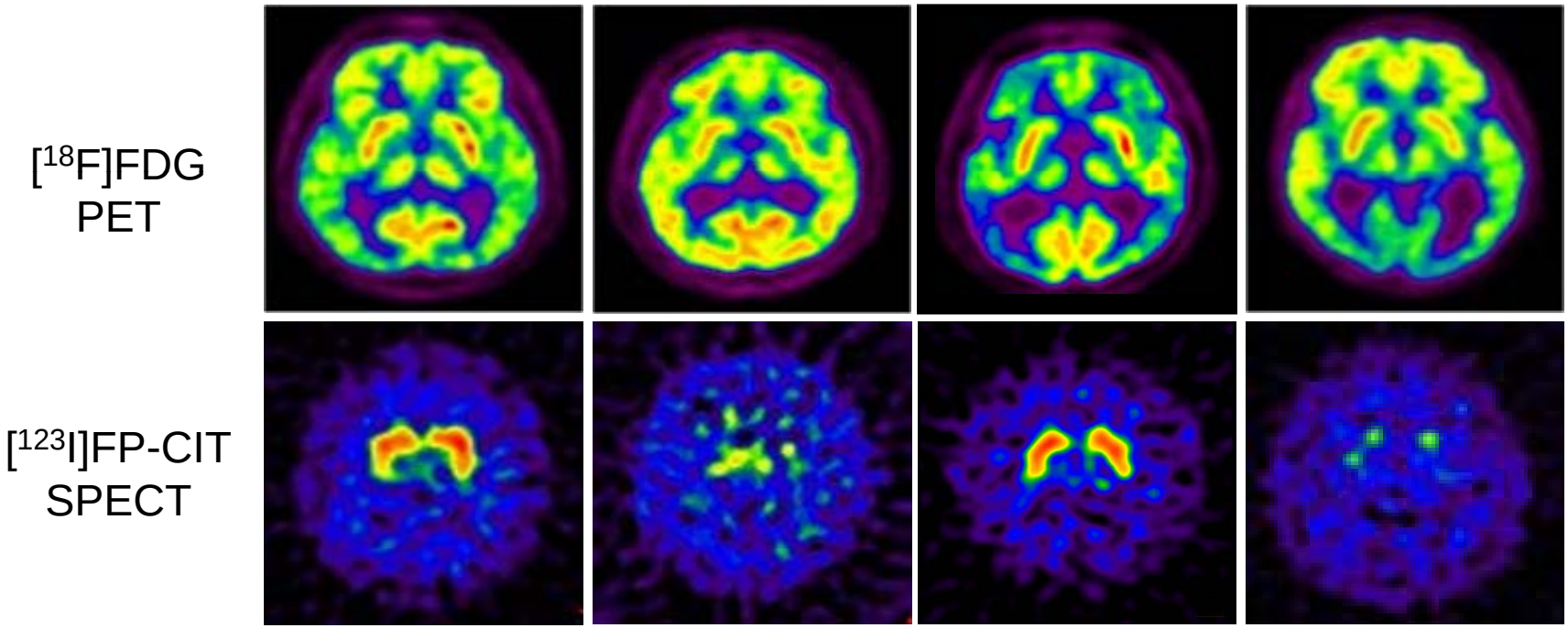




*$p < 0.001$

Kim et al., 2004

Metabolic and Dopaminergic Alterations in Neurodegenerative Diseases



Kim et al., 2004

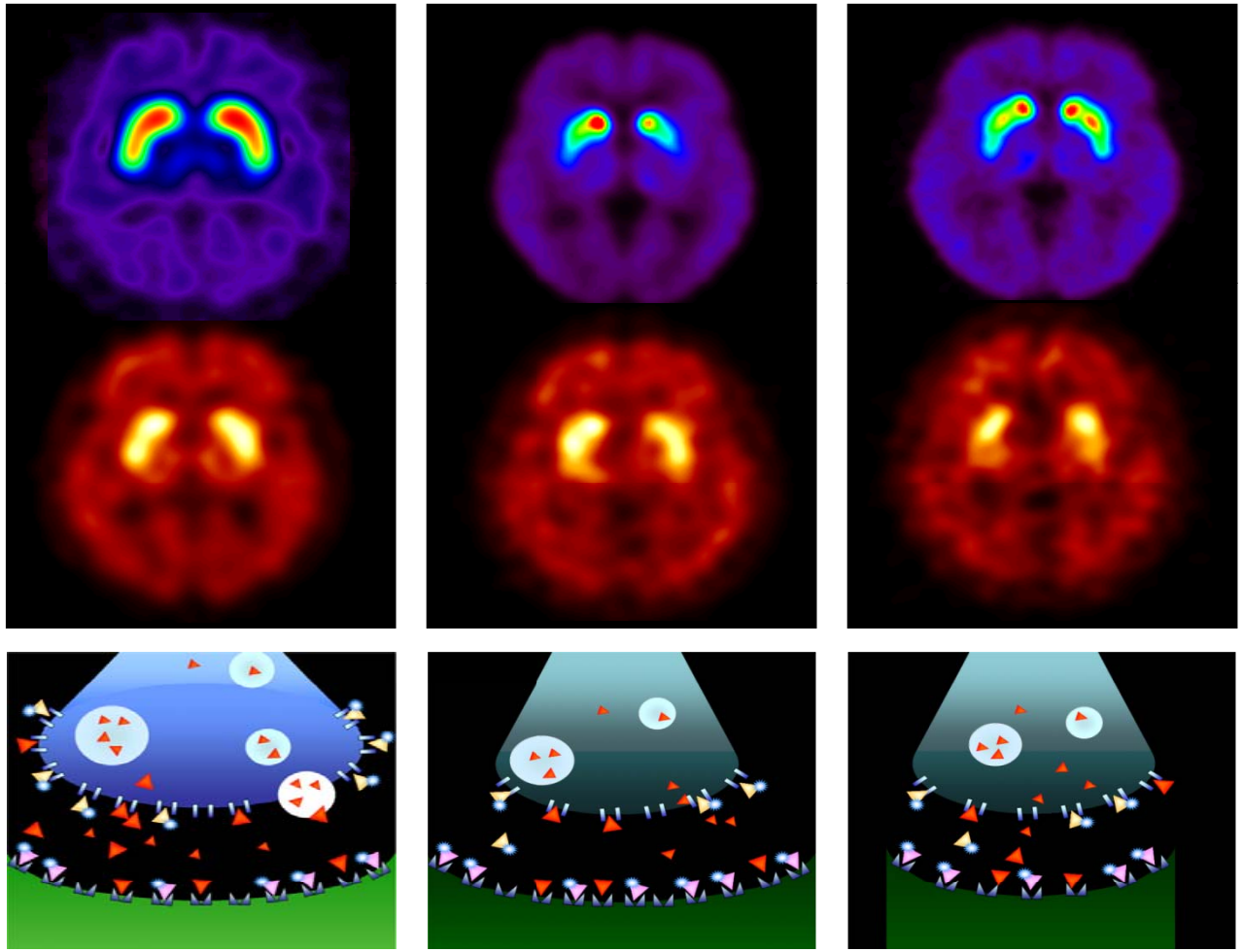
MSA versus PD

	MSA	PD
Onset	6th decade of life	6th decade of life
Prevalence	1.9-4.9/100,000	1-3% of people > 65 y
Features	Parkinsonism, cerebellar ataxia, pyramidal signs, autonomic failure	Tremor, rigidity, hypokinesia
Pathology	Glial cytoplasmic inclusions	Lewy bodies
Main involvement sites	Striatonigral systems, olivopontocerebellar systems, pontomedullary reticular formation,serotonergic neurons of the medullary raphe, etc.	Subtantia nigra pars compacta
Diagnosis	Clinical criteria	Clinical criteria
Treatment	Symptomatic	L-dopa
Response to L-dopa	**Poor**	Good
Prognosis	**Poor**	Relatively good

Dopamine transporter and dopamine D_2 receptor changes in PD and MSA ([^{123}I]FP-CIT/[^{123}I]IBZM SPECT studies)

[^{123}I]FP-CIT SPECT (Dopamine transporter: presynaptic)

[^{123}I]IBZM SPECT (Dopamine D_2 receptor: postsynaptic)

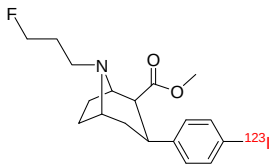


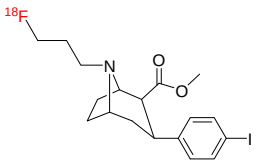
Control **PD** **MSA-P**

Kim et al., 2005

Advantages of SPECT radiotracer for DAT imaging ([^{123}I]FP-CIT versus [^{18}F]FP-CIT)

	SPECT radiotracer ([^{123}I]FP-CIT)	PET radiotracer ([^{18}F]FP-CIT)
Kinetic	Excellent for imaging and quantification	Excellent for imaging and quantification
Cyclotron and related facilities	Not needed	Needed
PET system	Not needed	Needed
Half-life	13 h	110 min
On-site radiolabeling	Yes	No
Availability	High	Low
Labeling efficiency	50%-80%	20%
Amount of precursor per study	micrograms	milligrams
Cost	Low	High



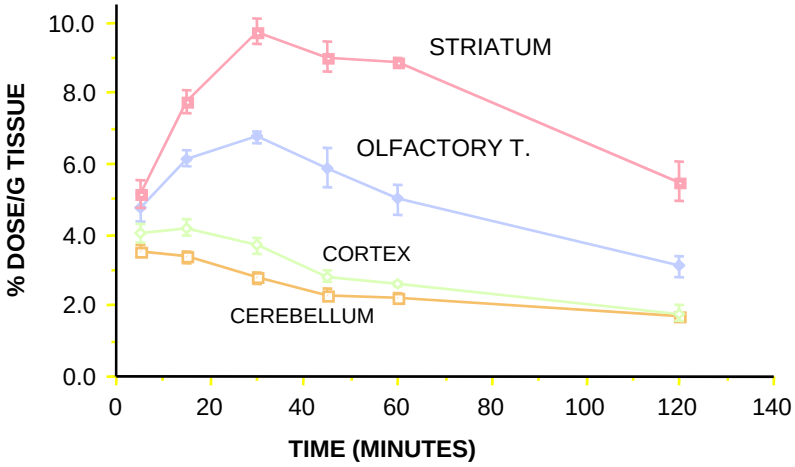


Preclinical Imaging
- the molecular imaging advantage

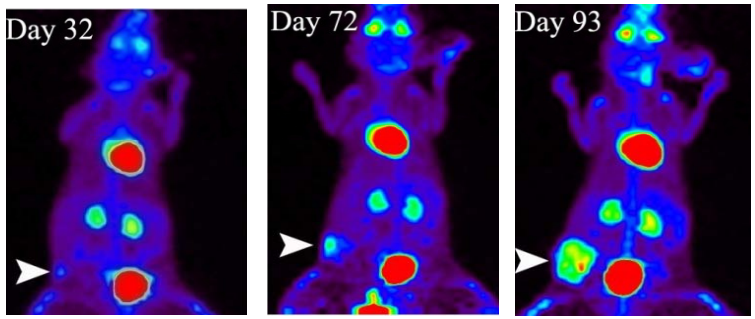
- Longitudinal imaging within individual subjects
- Entire PK/PD studies in individual subjects
- Whole-body analysis of PK/PD
- Quantitative evaluation
- No Histology required (in most cases)

- **Improving scientific data**
- **Accelerating development**
- **Reducing costs**

Killing animals



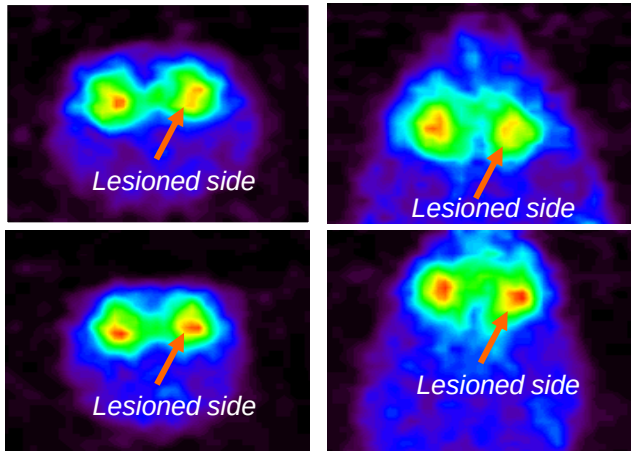
Imaging animals



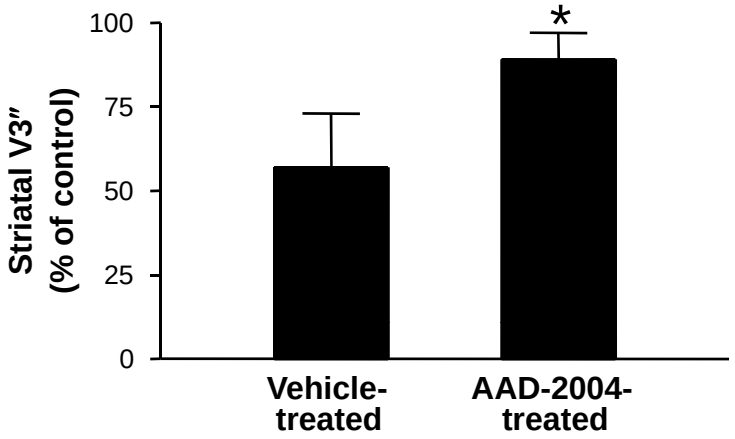
Neuroprotective effect of AAD-2004 on the dopaminergic system (I-124-FP-CIT DAT microPET imaging in rat PD model)

Vehicle-treated
(DAT density -41%)

AAD-2004-treated
(DAT density -2%)



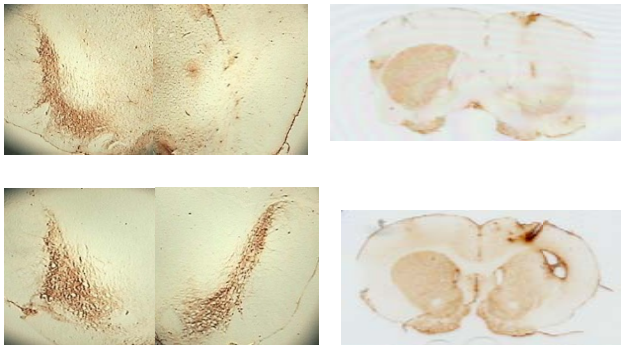
Transverse Coronal



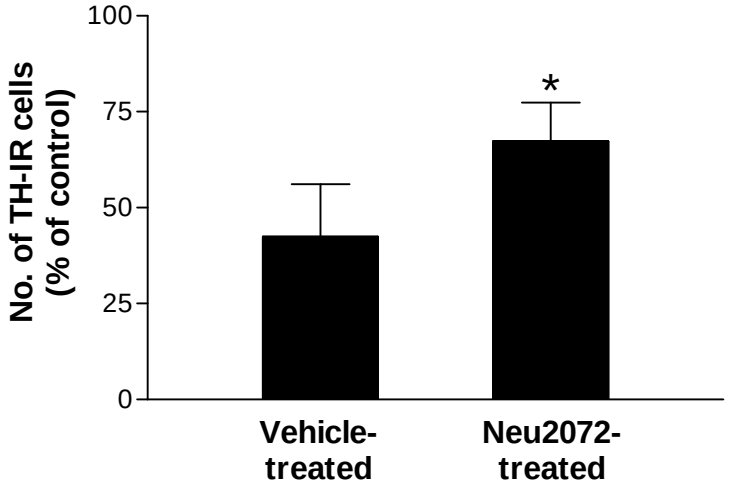
TH immunohistochemistry

Vehicle-treated

AAD-2004-treated



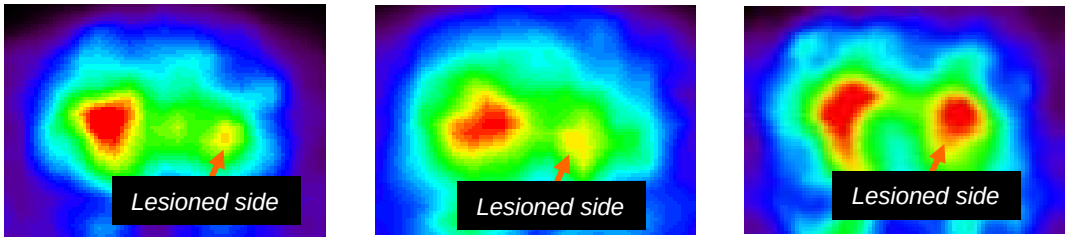
SN STR



Kim, et al., 2005

Neuroprotective effect of NeuProtec on the dopaminergic system (I-124-FP-CIT DAT microPET imaging in rat PD model)

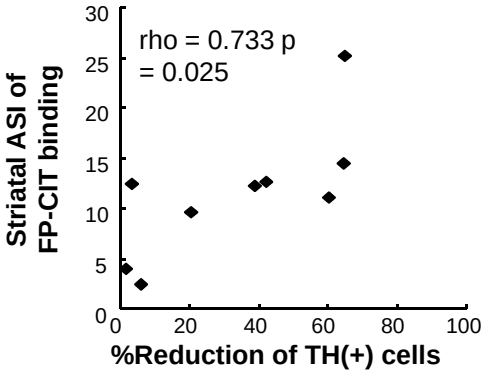
microPET



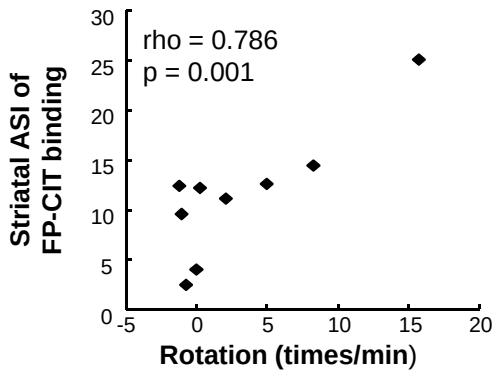
TH staining

Control **SureCero** **NeuProtec**

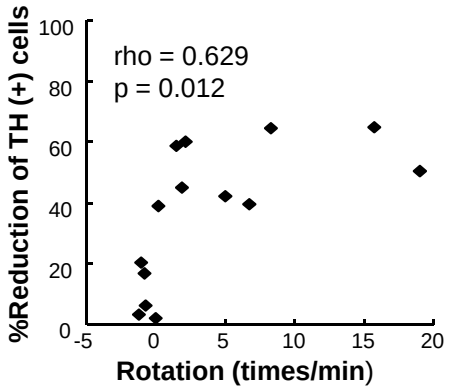
FP-CIT binding vs. TH immunostaining



FP-CIT binding vs. Rotation test

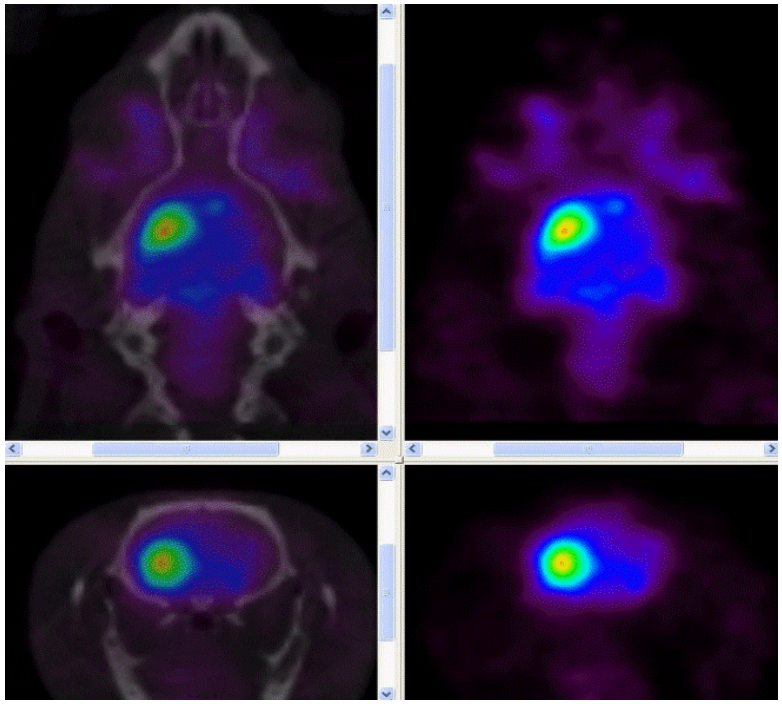


TH immunostaining vs. Rotation test

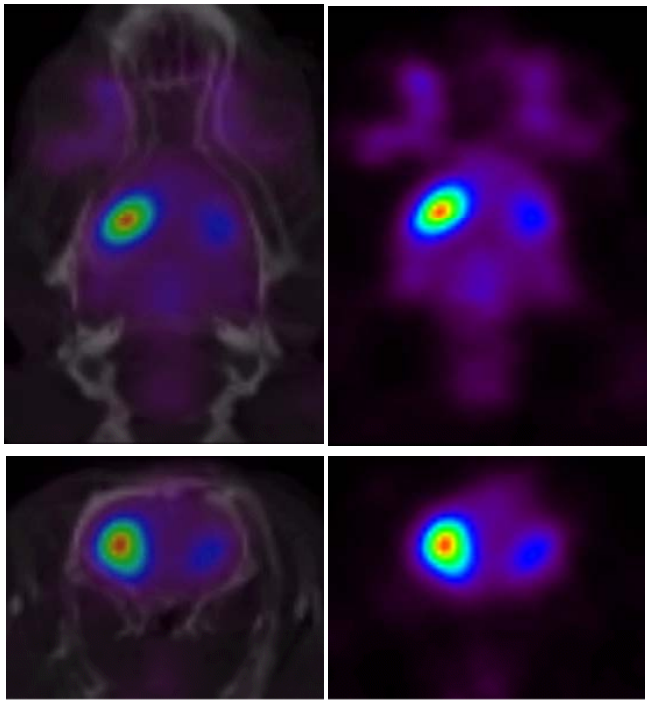


Kim, et al., 2007

Effect of stem cell therapy
([^{123}I]β-CIT DAT nanoSPECT imaging in rat PD model)



Vehicle-treated
(DAT density -95%)



Stem cell-treated
(DAT density -71%)

Kim, et al., 2009

Dopamine transporter imaging

- In vivo assessment of dopaminergic neuronal integrity
- Early diagnosis of Parkinson’s disease
- Differential diagnosis of parkinsonism
- Monitoring of disease progression
- Evaluation of treatment efficacy
- Pharmaceutical development

Going together for molecular neuroimaging in Asian countries

If you are interested in SPECT and/or PET imaging of dopamine transporters, please contact me at kse@snu.ac.kr.

We will be happy to provide you with precursors of dopamine transporter radiotracers along with iodine-123 and assist you with radiolabeling.

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