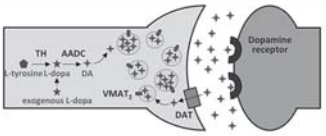
PET-based differential diagnosis of parkinsonism

Chul Hyoung Lyoo
강남세브란스병원 신경과

Pre- & postsynaptic imaging

Dopaminergic presynaptic nerve terminal and postsynaptic dopamine receptor imaging



		SPECT	PET	
Presynaptic	AADC		[^{18}F]-DOPA	
	$VMAT_2$		[^{11}C]-DTBZ	
	DAT	[^{123}I]-β-CIT [^{123}I]-FPCIT [^{123}I]-IPT [^{123}I]-Altropane [^{123}I]-PE2I [^{99m}Tc]-TRODAT [^{99m}Tc]-technepine	[^{11}C]-Cocaine [^{11}C]-β-CIT [^{11}C]-Methylphenidate [^{11}C]-PE2I [^{18}F]-FPCIT	[^{11}C]-CFT (WIN 35428) [^{11}C]-Nomifensine [^{11}C]-RTI-32 [^{11}C]-Altropane [^{18}F]-CFT (WIN 35428) [^{18}F]-FECNT
Postsynaptic	D_1, D_5	[^{123}I]-SCH23982	[^{11}C]-SCH23390	[^{11}C]-SKF
	D_2, D_3, D_4	[^{123}I]-IBZM [^{123}I]-Epidepride	[^{11}C]-Raclopride [^{18}F]-Fallypride	[^{11}C]-NMSP

Estimation of annual reduction of dopaminergic terminal and premotor period based on longitudinal presynaptic dopaminergic imaging

	Type of imaging	Parameter	Annual reduction in PD	Annual reduction in controls	estimated preclinical period
Vingerhoets FJG *Ann Neurol 1994;36:759*	^{18}F-FDOPA PET	S/NS ratio	1.7%	0.3%	40 - 50 yrs
Morrish PK *JNNP 1998;64:314*	^{18}F-FDOPA PET	K_i	8.9%	-	6.5 yrs
Nurmi E *Ann Neurol 2000;47:804*	^{18}F-CFT PET	S/NS ratio	13.1%	2.1%	-
Nurmi E *Mov Disord 2001;16:608*	^{18}F-FDOPA PET	K_i	ant. put 8.3% post. put 10.3%	ant. put 0.3% post. put 0.5%	6.5 yrs
Marek K *Neurology 2001;57:2089*	^{123}I-β-CIT SPECT	S/NS ratio	11.2%	0.80	-
Pirker W *Mov Disord 2002;17:45*	^{123}I-β-CIT SPECT	S/NS ratio	early (<5yr) 7.1% late (>5yr) 2.4%	-	-
Hilker R *Arch Neurol 2005;62:378*	^{18}F-FDOPA PET	K_i	6.3%	-	5.6 yrs
Pavese N *Neuroimage 2011;56:1463*	^{18}F-FDOPA PET	K_i	8.1%	-	-

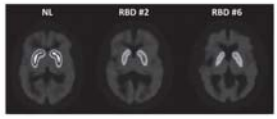
Mild reduction of putaminal dopaminergic input in asymptomatic carriers of monogenic mutation

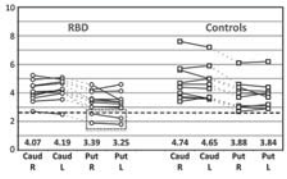
	Gene	Asymptomatic carriers (n)	PET tracers	Reduction of putaminal uptake
Khan NL *Ann Neurol 2002;52:849*	*pink1*	3	^{18}F-FDOPA	-35%
Khan NL *Brain 2002;125:2248*	*parkin*	4	^{18}F-FDOPA	-30%
Khan NL *Neurology 2005;64:134*	*parkin*	13	^{18}F-FDOPA	-25%
Adams JR *Brain 2005;128:2777*	*LRRK2*	6	^{18}F-FDOPA ^{11}C-DTBZ ^{11}C-MP	-5% -12% -23%
Nandhagopal R *Neurology 2005;64:134*	*LRRK2*	7	^{18}F-FDOPA ^{11}C-DTBZ ^{11}C-MP	-12% -24% -32%
Sossi V *Mov Disord 2010;25:2717*	*LRRK2*	6	^{18}F-FDOPA ^{11}C-DTBZ ^{11}C-MP	-5% -18% -23%

Mild dopaminergic dysfunction in idiopathic RBD patients

(1) *Albin (2000)*
- ^{11}C-DTBZ PET study
- 4 / 6 iRBD patients showed low uptake
  1) anterior putamen : 81.9% of normal
  2) posterior putamen : 77.7% of normal

(2) *Stiansny-Kolster (2005)*
- ^{123}I-FPCIT SPECT study
- 3 / 11 RBD showed parkinsonian signs
  2 / 3 : very mild (< 5 UPDRS motor)
  1 / 3 : PD (UPDRS motor 21)
- Slightly lower uptake in RBD
  putamen : 84% of normal



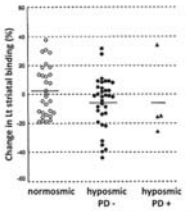


Albin RL, Neurology 2000;55:1410, Stiansny-Kolster K, Brain 2005;128:126

10% of individuals with hyposmia may progress to clinically overt PD in 2-year FU period.

Longitudinal study for hyposmia
- 361 asymptomatic relatives of PD
  1) 38 normosmic subjects
  2) 40 hyposmic subjects
- ^{123}I-β-CIT SPECT at baseline & 2-year FU
- All normosmic subjects
  no change in ^{123}I-β-CIT SPECT uptake
  not progress to clinical PD
- 4 / 40 (10%) hyposmic subjects
  most strongly reduced baseline uptake
  developed clinical PD

	normosmic			hyposmic		
	1st	2nd	change	1st	2nd	change
L striatum	6.35	6.39	0.6%	6.33	5.92	-6.5%
R striatum	6.41	6.46	0.8%	6.41	5.91	-7.8%



Ponsen MM, Ann Neurol 2004;56:173

Compensatory up-regulation of AADC activity and down-regulation of DAT function in premotor to early stage of PD

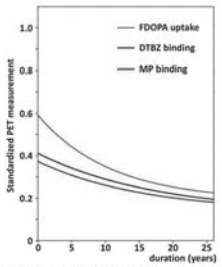
(1) *Lee (2000)*
- Cross sectional multi-tracer PET

	Putaminal uptake standardized to normal mean uptake (%)		
	^{18}F-FDOPA	^{11}C-DTBZ	^{11}C-MP
H&Y stage 1	54.7%	43.3%	36.7%
H&Y stage 2 - 3	40.5%	32.7%	28.4%

(2) *Adams (2005) & Sossi (2010)*
- Asymptomatic LRRK2 mutation carriers

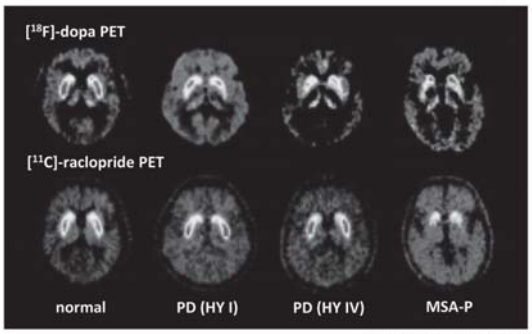
	Putaminal uptake standardized to normal mean uptake (%)		
	^{18}F-FDOPA	^{11}C-DTBZ	^{11}C-MP
Adams (2005)	95%	88%	77%
Sossi (2010)	95%	82%	77%

(3) *Nandhagopal (2011)*
- Longitudinal multi-tracer PET in 78 PD



Lee CS, Ann Neurol 2000;47:493, Adams JR, Brain 2005;128:2777, Sossi V, Mov Disord 2010;25:2717, Nandhagopal R, Brain 2011:134;3290

Pre & postsynaptic imaging : PD *vs.* MSA



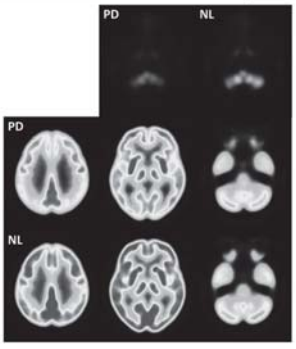
Ghaemi M, J Neurol Neurosurg Psychiatry 2002;73:517

Functional imaging with FDG PET
Metabolic network & differential diagnosis

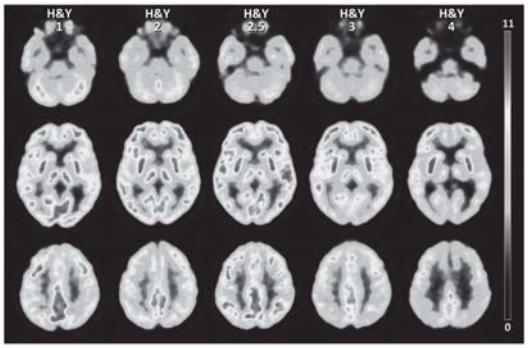
FDG PET : PD

Decreased metabolism
- parieto-occipital cortex
- SMA
- dorsolateral prefrontal cortex

Increased metabolism
- primary motor cortex
- putamen
- thalamus
- pons
- cerebellar vermis/cortex

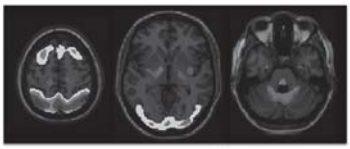


FDG PET : PD - H&Y stage

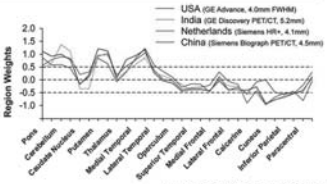


Metabolic network analysis in Parkinson's disease shows Parkinson's Disease Related Pattern (PDRP).

Decreased
premotor
post. parietal
occipital

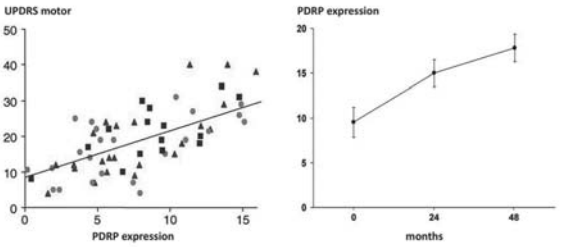


Increased
primary motor
putamen
GP
thalamus
pons
cerebellum



Huang C, Brain 2007;130:1834, Eidelberg D, Trends Neurosci 2009;32:548

PDRP expression correlates with disease severity and increases with the progression of disease in prospective study.

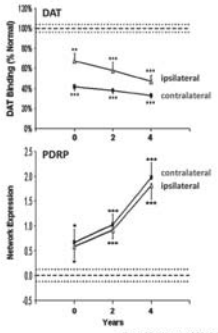


Eidelberg D, Trends Neurosci 2009;32:548, Huang C, Brain 2007;130:1834

PDRP expression precedes the appearance of motor signs.

Longitudinal study for PDRP change

- 15 early PD with hemiparkinsonism
  - H&Y stage 1 - 1.5
  - UPDRS motor 9.0 ± 4.5
  - 0 or 1 of UPDRS score on less affected limb
  - Dopaminergic deficit in [^{18}F]-FPCIT PET
- 1st FU after 2.1 ± 0.6 years
  - UPDRS motor 14.8 ± 4.3
- 2nd FU after 3.9 ± 0.7 years
  - UPDRS motor 17.8 ± 4.6



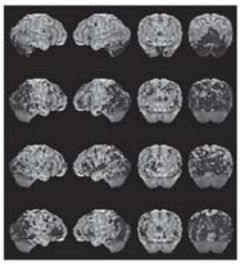
Tang CC, J Neurosci 2010;30:1049

Diffuse occipital hypometabolism and increased expression of PDRP in idiopathic RBD patients

(1) *Fujishiro (2010)*
- [^{18}F]-FDG PET study in 9 iRBD patients
- Diffuse occipital hypometabolism in 4 patients

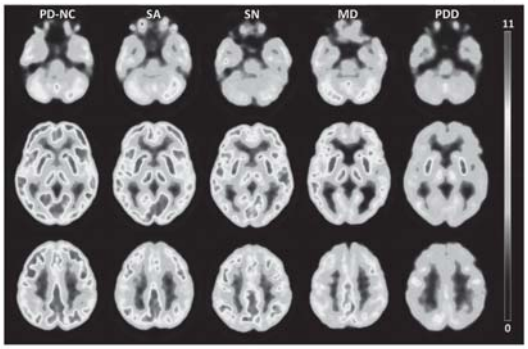
(2) *Ge (Abstract 2013)*
- [^{18}F]-FDG PET study in 10 iRBD patients
- Higher PDRP expression than normal controls
  not as high as PD

(3) *Holtbernd (Abstract 2013)*
- ^{99m}Tc-ECD SPECT in 18 iRBD patients
- 5 converted to PD and 3 to DLB after 3 yrs' FU
- PDRP expression level at baseline
  Increased to the level of asymptomatic side of PD
  Correlated with development of PD & DLB

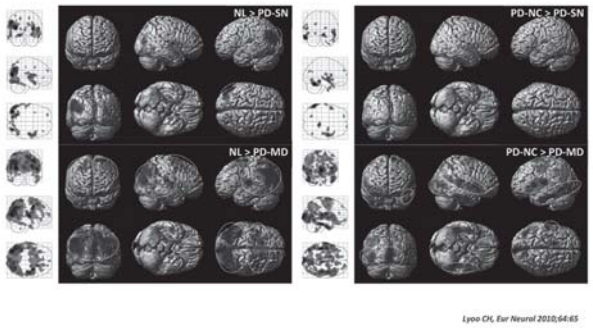


Fujishiro H, Psychogeriatrics 2010;10:144, Ge J, J Nucl Med 2013;54(Suppl 2):1779, Holtbernd F, Neurology 2013;80(Meeting Abstracts 1): 519.004

FDG PET : PD - cognitive function

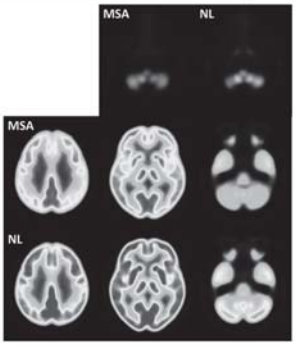


FDG PET : PD - cognitive function

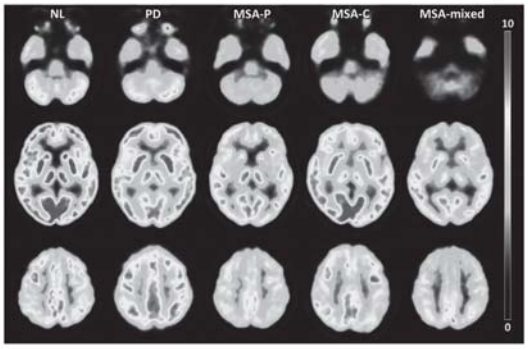


FDG PET : MSA

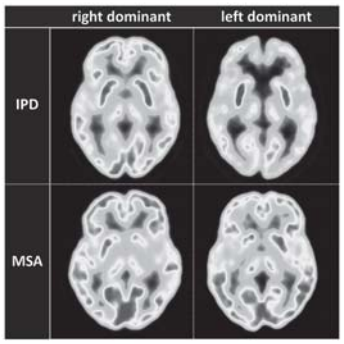
Decreased metabolism
- putamen (posterolateral)
- caudate
- brainstem
- cerebellar vermis/cortex
- fronto-temporal cortex



FDG PET : MSA clinical types



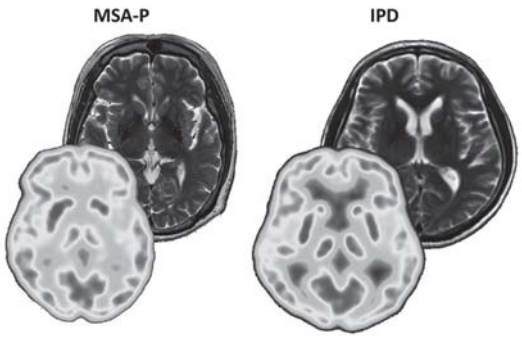
Asymmetry of putaminal metabolism can be useful marker for differential diagnosis of PD and MSA.



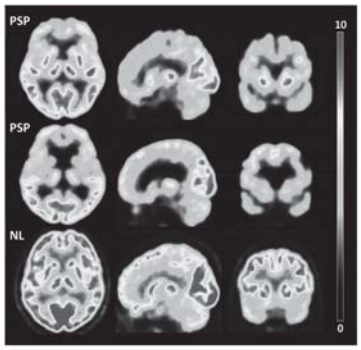
Demonstration of cases

Case 1	Case 2
Case 1 (F/61) 1.5yr ago : right hand bradykinesia 1yr ago : right leg dragging no rest tremor no cerebellar dysfunction no autonomic symptom	Case 2 (M/58) 1.5yr ago : left leg dragging 1yr ago : left hand bradykinesia no rest tremor no cerebellar dysfunction autonomic failure orthostatic hypotension + erectile dysfunction +

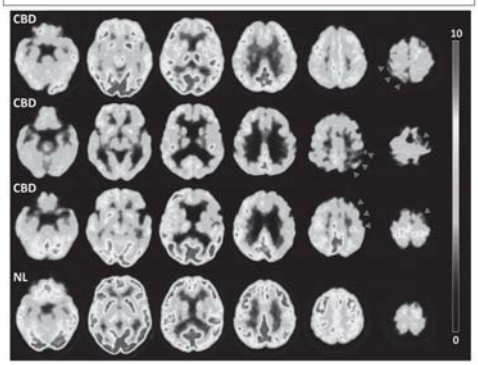
Prominent putaminal hypometabolism contralateral to the clinically worse side can be a supportive feature for diagnosing MSA.



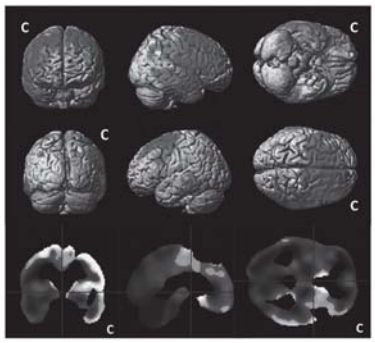
FDG PET : PSP



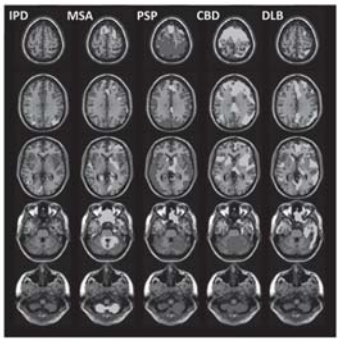
FDG PET : CBD



Voxel-based comparison results showing asymmetric hypometabolic areas in CBD



Single subject voxel-based differential diagnosis by using SPM



Summary

1. Imaging for presynaptic dopaminergic function is strong biomarker for disease progression and for early diagnosis of PD. Compensatory up-regulation of AADC activity makes ^{18}F-FDOPA PET less efficient to detect premotor stage of PD.
2. Characteristic changes in metabolic network in PD reflects disease progression and helps differential diagnosis with other types of parkinson plus syndromes.
3. Asymmetry of putaminal hypometabolism can be a marker for differential diagnosis of PD and MSA.
4. Combination of clinical characteristics, MR and PET images can provide better information for differential diagnosis of parkinsonian diseases.