파킨슨병의 신경영상학적 특징

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Parkinson's disease neuroimaging

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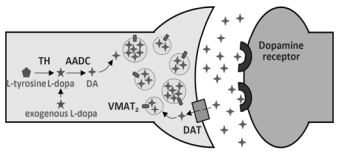
Outline of Talk

1. **Pre- and postsynaptic imaging**
2. **Metabolic network change specific for Parkinson's disease**
3. **Morphological changes**
4. **Imaging for cardiac sympathetic denervation**

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

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%

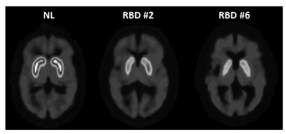
Mild dopaminergic dysfunction in idiopathic RBD patients

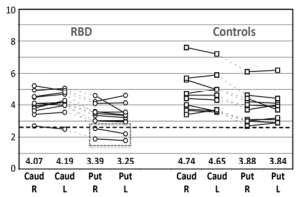
(1) *Albin (2000)*

- ^{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





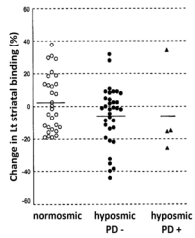
Albin RL, Neurology 2000;55:1410, Stiansny-Kolster K, Brain 2005;128:126

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 hyosmic 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%

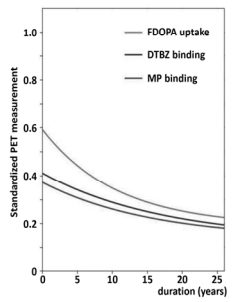
(2) *Adams (2005) & Sossi (2010)*

- 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%

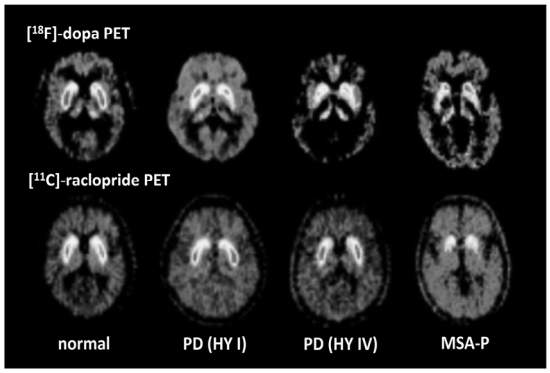
(3) *Nandhagopal (2011)*

- 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



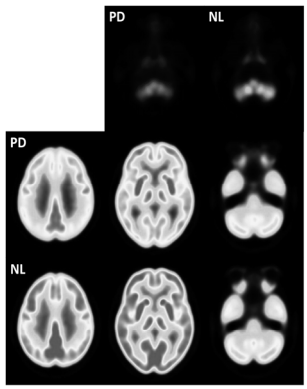
Ghaemi M, J Neurol Neurosurg Psychiatry 2002;73:517

Functional imaging with FDG PET
Metabolic network & differential diagnosis

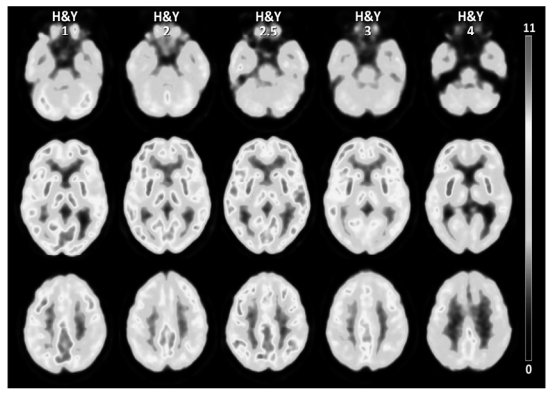
FDG PET : PD

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

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

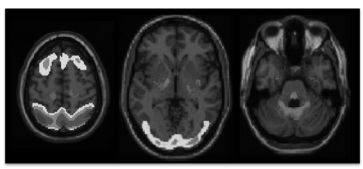


FDG PET : PD - H&Y stage

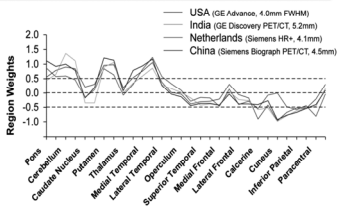


Metabolic network analysis in Parkinson's disease shows Parkinson's Disease Related Pattern (PDRP).

Decreased
premotor
post. parietal
occipital

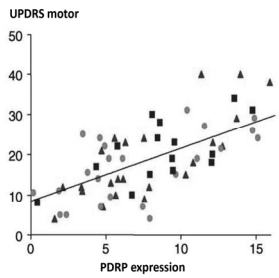


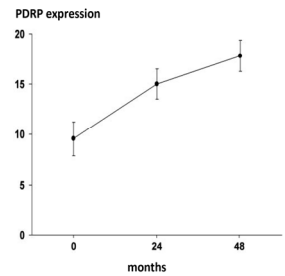
Increased
primary motor
putamen
GP
thalamus
pons
cerebellum



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.

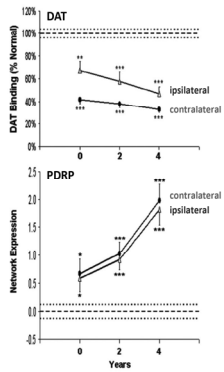




Eidelberg D, Trends Neurosci 2009;32:548, Huang C, Brain 2007;130:1834

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 17.8 ± 4.6
- 2nd FU after 3.9 ± 0.7 years
  - UPDRS motor 14.8 ± 4.3



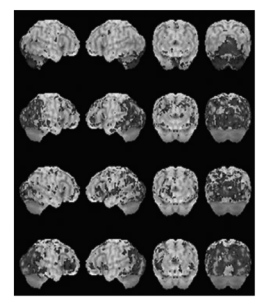
Tang CC, J Neurosci 2010;30:1049

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

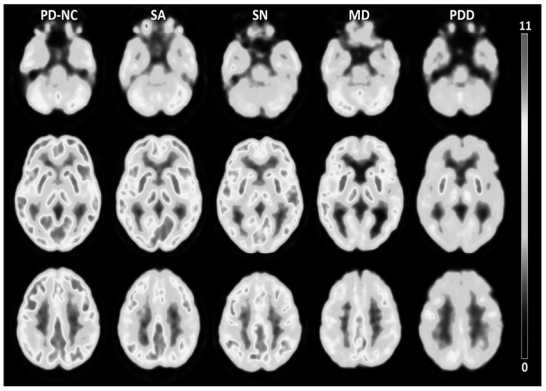
(2) *Ge (Abstract 2013)*
- [^{18}F]-FDG PET study in 10 iRBD patients
- Higher PDRP expression than normal controls not as high as PD

(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

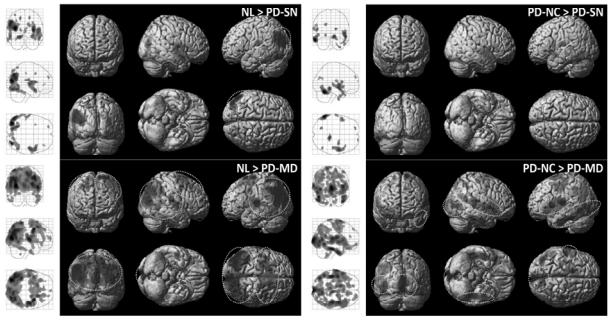


Fujishiro H, Psychogeriatrics 2010;10:144, Ge J, J Nucl Med 2013;54(Suppl 2):1779, Holtbernd F, Neurology 2013;80(Meeting Abstracts 1): 519.004

FDG PET : PD - cognitive function

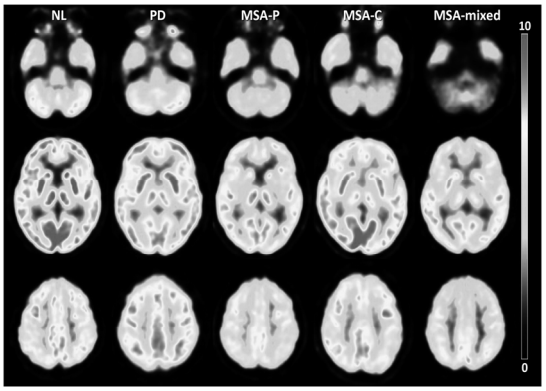


FDG PET : PD - cognitive function

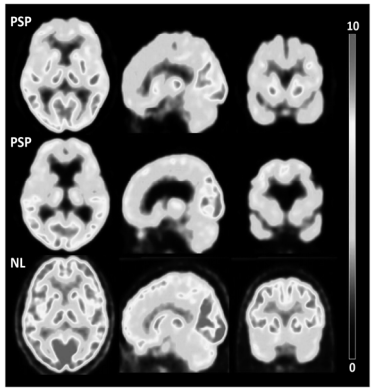


Lyoo CH, Eur Neurol 2010;64:65

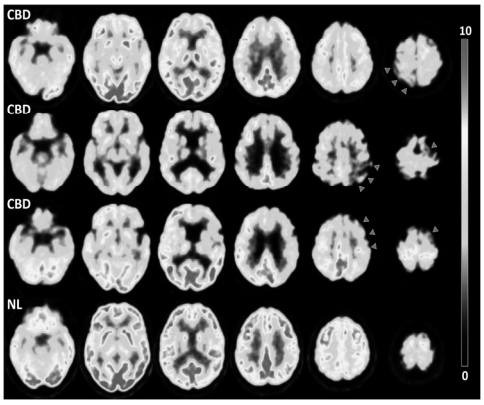
FDG PET : MSA clinical types



FDG PET : PSP



FDG PET : CBD



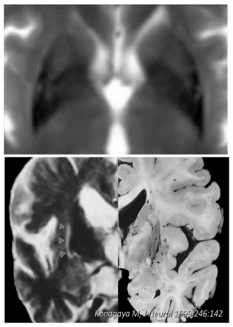
Structural imaging
MR-based differential diagnosis, volumetry & cortical thickness

Putaminal changes in MR images in MSA

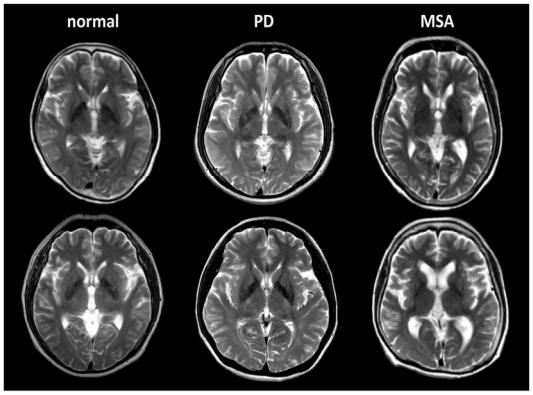
Atrophy of posterior putamen

Hypointense signal change in putamen
- astrocytic gliosis, iron deposition
- normal aging
- high sensitivity (up to 94%), low specificity

Hyperintense (putaminal) rim sign
- astrocytic gliosis, iron deposition
- formation of intertissue spaces
- *Watanabe et al. (2002)*
  - 48 / 139 (35%) MSA patients
  - (disease duration around 4yrs)



Differential diagnosis with PD

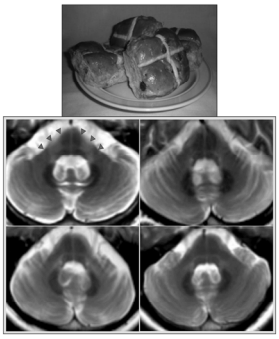


Ponto-cerebellar changes in MR in MSA-C

Atrophy of pons, cerebellum

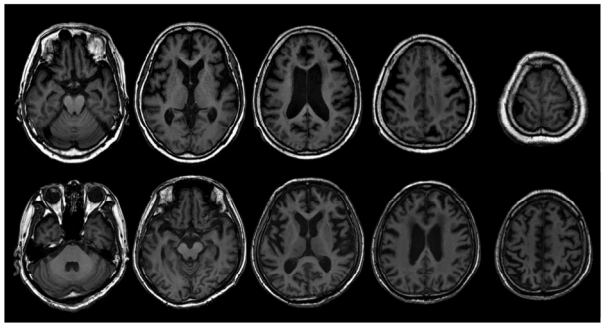
Hot cross bun sign
- degeneration : pontocerebellar fiber
  pontine raphe neurons
- preservation : pontine tegmentum
  corticospinal tract
- Watanabe et al. (2002)
  - 88 / 139 (63%) MSA patients

Middle cerebellar peduncle sign
- pontocerebellar fiber degeneration
- *Schrag et al. (1998)*
  - 13% in 0.5T, 22% in 1.5T MRI



Cortical atrophy in PSP

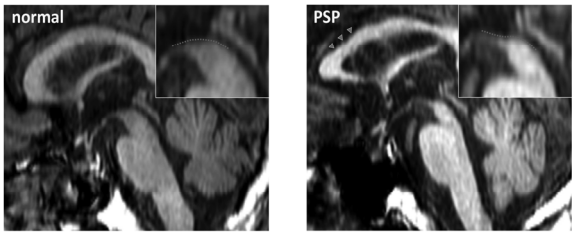
Cortical atrophy in frontotemporal cortex



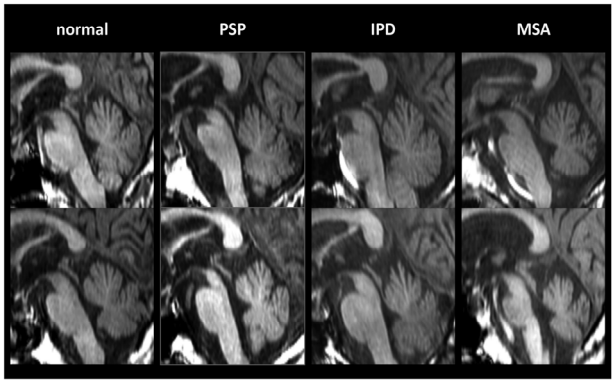
Midbrain atrophy characterizes PSP.

Atrophy of corpus callosum

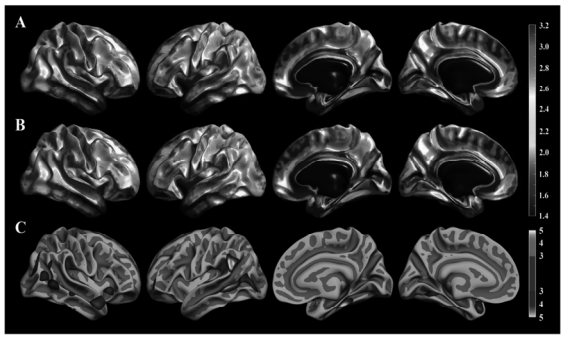
Hummingbird sign



Humming bird sign helps differential diagnosis.



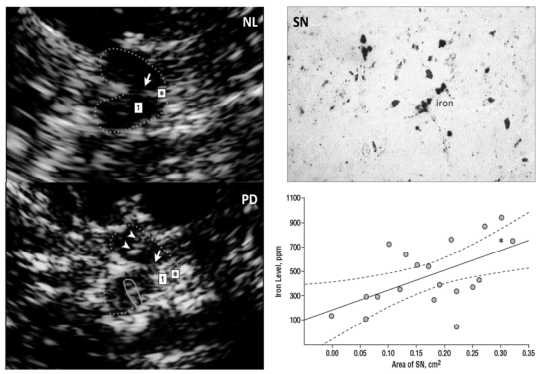
Widespread cortical thinning in temporoparietal cortex of mild non-demented PD



Lyoo CH, Mov Disord 2010;25:496

Structural imaging
Transcranial sonography

Iron deposition in substantia nigra in PD patients makes hyperechogenicity in trancranial sonography.



Berg D, Arch Neurol 2002;59:999

SN hyperechogenicity is a stable trait marker for predisposition to development of PD rather than a severity marker.

Longitudinal TCS study

1) ***Berg (2005)***
   - 27 PD with H&Y stage 1.8 ± 0.6 (1 - 3) at baseline
   - No change in SN hyperechogenicity area after 5 years
2) ***Mahlknecht (2012)***
   - 28 controls with normoechogenic SN and 29 hyperechogenic SN at baseline
   - No change in SN echogenicity and hyperechogenic area after 3.6 years
3) ***Behenke (2013)***
   - 50 PD with H&Y stage 1.6 ± 0.7 (1 - 3) at baseline
   - No change in SN hyperechogenicity area after 6.4 years
   - No correlation between baseline hyperechogenicity area and change in severity

Berg D, Mov Disord 2005;20:383, Mahlknecht P, Mov Disord 2012;27:1192, Behnke S, Mov Disord 2013;28:455

TCS is promising for screening the population at risk for developing PD.

	Baseline	1st FU *(Arch Neurol 2011)*		2nd FU *(Mov Disord 2013)*		
		Non-PD Group	PD Group	Non-PD Group	PD Group	Total PD Group
N	1535	1524 (99.3%)	11 (0.7%)	1261 (99.2%)	10 (0.8%)	21 (1.6%)
Baseline SN +	1400	254 / 1390 (18.3%)	8 / 10 (80%)	203 / 1158 (17.5%)	6 / 7 (85.7%)	14 / 17 (82.4%)

(1) First follow-up of initially healthy elderly after 3 years to find incident PD
- Found 11 incident PD out of 1535 subjects
- Relative risk for subject with baseline SN + to develop PD was 17.37

(2) Second follow-up examination after 5 years
- Found 10 newly diagnosed PD out of 1271 subjects
- Overall relative risk for subjects with baseline SN + to develop PD was 20.6

Berg D, Arch Neurol 2011;68:932, Berg D, Mov Disord 2013;28:216

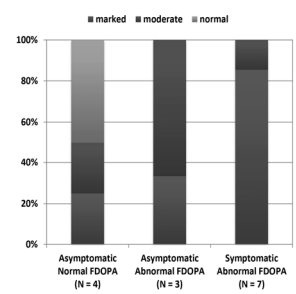
Asymptomatic *parkin* mutation carriers show SN hyperechogenicity.

TCS in *parkin* mutation carriers

1) 7 Symptomatic
   age 65.6 ± 14.4 years
   duration 13.6 ± 11.3 years
   UPDRS motor 39.1 ± 20.5
2) 7 Asymptomatic
   age 34.6 ± 5.1 years

*** Asymptomatic mutation carriers also shows SN hyperechogenicity.**

*** SN echogenicity size correlated with younger age at onset.**



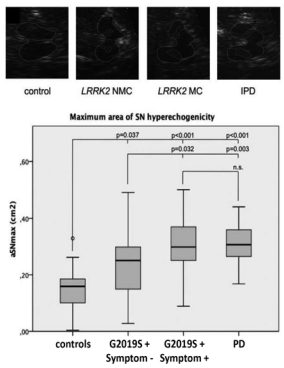
Walter U, Mov Disord 2004;19:1445

Asymptomatic LRRK2 G2019S mutation carriers show SN hyperechogenicity.

TCS in LRRK2 G2019S mutation carriers

1) 40 controls
2) 24 with G2019S without symptom
3) 34 with G2019S with symptom
   UPDRS motor : 14.3 ± 10.6
4) 28 PD
   UPDRS motor : 18.7 ± 11.5

*** SN pathoanatomical changes may not be different betweeen idiopathic and LRRK2 associated PD.**



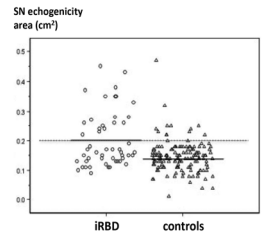
Bruggemann N, Mov Disord 2011;26:885

Higher prevalence of SN hyperechogenicity in patients with idiopathic RBD than controls

TCS study in 55 iRBD & 165 controls

1) Greater SN hyperechogenicity area
   - iRBD : 0.20 ± 0.09 cm^2
   - controls : 0.14 ± 0.05 cm^2
2) Higher prevalence of SN hyperechogenicity
   - 19 / 51 (37.3%) in iRBD group
   - 16 / 149 (10.7%) in control group

*** iRBD patients with SN Hyperechogenicity represent premotor stage of PD.**



Stockner H, Mov Disord 2009;24:1906

Imaging for cardiac postganglionic sympathetic nerve ending

Cardiac sympathetic denervation already starts before the appearance of motor symptoms, and worsens with Braak's pathological stage of PD.

Cardiac sympathetic nerve in iLBD, PD

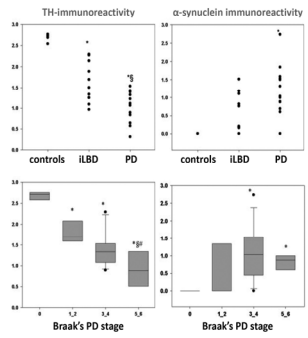
- 4 normal, 11 iLBD, 14 PD
- sympathetic nerve fiber in epicardium
- tyrosine hydroxylase, α-synuclein

Decreased TH + fibers in iLBD

Increased α-syn + neurites in iLBD

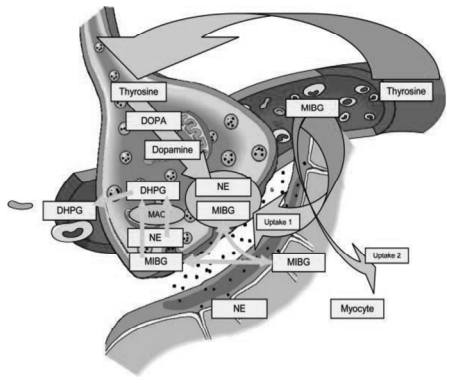
Density of α-syn + neurites correlated

- Braak's PD stage
- H&Y stage
- duration



Fujishiro H, Mov Disord 2008;23:1085

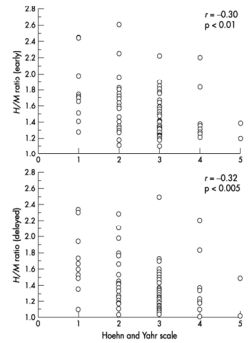
MIBG, norepinephrine analogue, for visualization of cardiac postganglionic sympathetic nerve ending



Rascol O, Mov Disord 2009;24(Suppl 2):S732

Cardiac ^{123}I-MIBG uptake correlates negatively with disease severity and is reduced in early stage of PD and may precede motor symptoms.

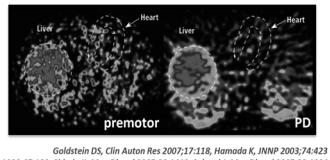
(1) Correlation with H&Y stage



(2) Reduced ^{123}I-MIBG uptake in early PD

	Patients in H&Y stage I (n)	Abnormal MIBG uptake (n)	%
Nagayama (2005)	18	7	39%
Orimo S (1999)	8	4	50%
Shindo (2005)	18	13	72%
Spiegel (2007)	57	53	93%

(3) 5 year FU study of 6-[^{18}F]-Fluorodopamine PET



Goldstein DS, Clin Auton Res 2007;17:118, Hamada K, JNNP 2003;74:423
Nagayama H, JNNP 2005;76:249, Orimo S, JNNP 1999;67:189, Shindo K, Mov Disord 2005;20:1419, Spiegel J, Mov Disord 2007;22:1004

Heterogeneous cardiac ^{123}I-MIBG uptake pattern in PD associated with monogenic mutation

(1) *Orimo S (2005)*

3 *parkin*-associated PD

- preserved tyrosine hydroxylase immunoreactive nerve fibers in cardiac epicardium
- preserved ^{123}I-MIBG uptake in two patients who underwent ^{123}I-MIBG scan study

(2) *Suzuki (2007)*

1 *parkin*-associated PD : preserved cardiac ^{123}I-MIBG uptake

(3) *Kanai (2009)*

1 *ATP13A2*-associated PD : preserved cardiac ^{123}I-MIBG uptake

(4) *Quattrone (2008)*

4 Parkin-associated PD : 3 / 4 preserved cardiac ^{123}I-MIBG uptake

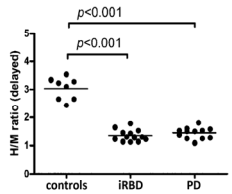
2 DJ-1-associated PD : 1 / 2 preserved cardiac ^{123}I-MIBG uptake

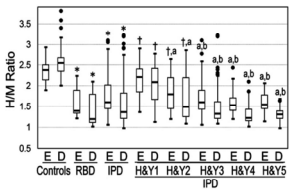
2 PINK-1-associated PD : 1 / 2 preserved cardiac ^{123}I-MIBG uptake

6 LRRK2-associated PD : 3 / 6 preserved cardiac ^{123}I-MIBG uptake

Orimo S, Mov Disord 2005;20:1350, Suzuki M, Mov Disord 2005;20:634, Kanai K, Mov Disord 2009;24:1403, Quattrone A, Mov Disord 2008;23:71,

Cardiac ^{123}I-MIBG uptake is reduced markedly in patients with idiopathic RBD and even worse than those with very early stage PD.





(1) *Miyamoto (2006)*

a) 13 iRBD : duration 5.5 ± 3.7 yrs

b) 12 PD : H&Y 2.3 ± 0.8

* All iRBD patients showed reduced cardiac ^{123}I-MIBG uptake.

(2) *Kashihara (2010)*

a) 13 iRBD : duration 2.8 ± 3.1 yrs

b) 222 PD : H&Y stage 1 - 5

* cardiac ^{123}I-MIBG uptake was more markedly reduced in RBD than early PD

* RBD may not necessarily be a prodromal condition of PD.

Miyamoto T, Neurology 2006;67:2236, Kashihara K, Parkinsonism Relat Disord 2010;16:252

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. Midbrain hyperechogenicity in transcranial sonography is stable biomarker for predisposition to future development of Parkinson's disease.
4. Cardiac ^{123}I-MIBG may be abnormal in the premotor stage of PD, but is much less sensitive for genetic PD than the other types of imaging modalities.