Role of imaging in parkinsonism

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Nuclear Medicine Resident

- **Recommended reading**:

- The role of functional dopamine-transporter SPECT imaging in parkinsonian syndromes, part 1.

Booth TC, Nathan M, Waldman AD, Quigley AM, Schapira AH, Buscombe J. AJNR Am J Neuroradiol part 1 and 2

UW Nuclear Medicine Clinical Case Conference – DS 1524
CME Disclosure Statement - 2015

I, Dr. Santhosh Gaddikeri have no financial relationships to disclose.

Planning Committee:

Dr. Hubert Vesselle has disclosed his financial relationship with MIM Software for consulting.

Dr. Lewis has no financial relationships to disclose.

*If there is a financial relationship to disclose, please replace "no financial relationships" with the name of any commercial entity and the type of relationship with which you or your spouse/partner have an affiliation. Otherwise, delete this smaller print before including as the first slide in your case conference presentation.

Introduction

- Definition: Clinical syndrome characterized by bradykinesia and at-least one of the following symptoms: resting tremor, muscular rigidity, and postural instability
- First described by James Parkinson in 1817
- Progressive neurologic degenerative disease, usually begin between the age of 45 and 70 years. Peak in sixth decade
- Exact cause not well known. Multifactorial including trauma (Punch-Drunk syndrome), toxins (MPTP), genetic disorders
- Smoking and coffee drinking may have mild protective effects
- Slight predominance in white males

introduction

Adams and Victor's Principles of Neurology, 9e > Chapter 39. Degenerative Diseases of the Nervous System

Print

Table 39-2 Genetic Defects Associated with Parkinson Disease

Notation	Chromosome	Gene	Genetics	Age of Onset	Lewy Bodies	Special Features
Park1	4q21	α-synuclein	AD	30–40 years	+	Two main mutations—A53T, A30P—promote oligomerization of α-synuclein.
Park2	6q25	parkin	AR	20–40 years	–	Accounts for 50% of early onset inherited PD; 20% of "sporadic" early onset cases.
Park3	2p13		AD	Late onset	–	Resembles idiopathic PD.
Park5	4p14	*UCH-L1*	AD	50's	+	Gene is ubiquitin carboxyterminal hydrolase L1. Mutations decreased recycling of ubiquitin monomers.
Park6	1p35-36	*PINK1*	AR	varies		Mitochondrial gene.
Park7	1p36	*DJ-1*	AR	30's	?	Slow progression; gene plays role in cellular response to oxidative stress.
Park8	12 cent	*LRRK2*	AD	late	±	Ashkenazic Jews. Protein is dardarin, a novel kinase.
NR4A2	2q22	*NURR1*	AD		?	Gene is implicated in the formation and identity of dopaminergic neurons.

AD, autosomal dominant; AR, autosomal recessive; PD, Parkinson disease.

introduction

Adams and Victor's Principles of Neurology, 9e > Chapter 39. Degenerative Diseases of the Nervous System

Print

Table 39-3 Initial Symptoms in Patients with Parkinson Disease

Tremor	70%
Gait disturbance	11%
Stiffness	10%
Slowness	10%
Muscle aches	8%
Loss of dexterity	7%
Handwriting disturbance	5%
Depression, nervousness, other psychiatric disturbance	4%
Speech disturbance	3%

Source: Adapted from Hoehn and Yahr's study of 183 idiopathic cases, 1967

introduction

Tremor:

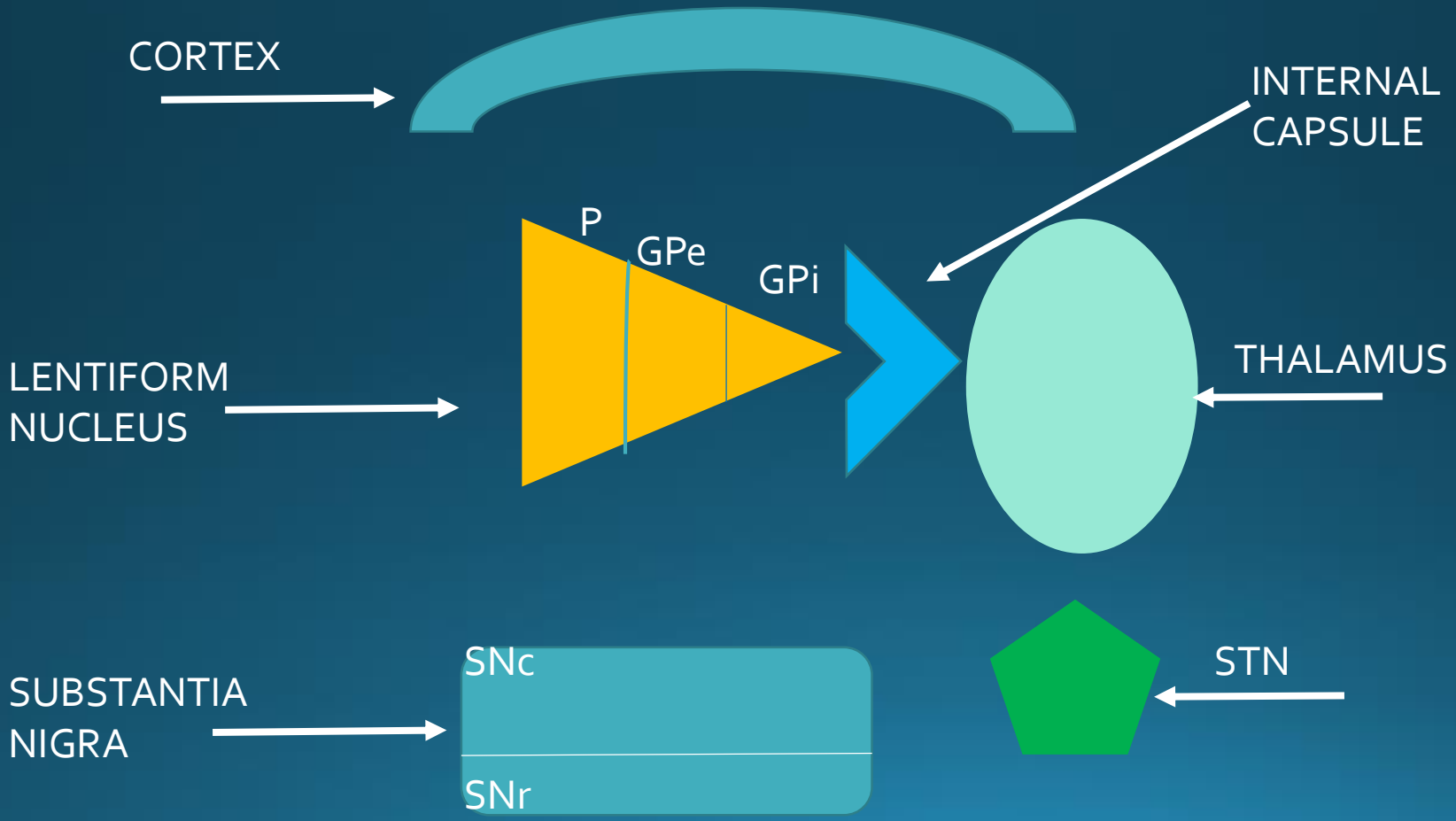
- Resting tremor
- Pill-rolling tremor
- Alternating activity in the agonist and antagonist muscle groups on EMG (alternating tremor)
- Around 4/Sec
- One side of the body is always involved by tremor and rigidity before the other. Tremor always remain asymmetrical as the disease advance

questions

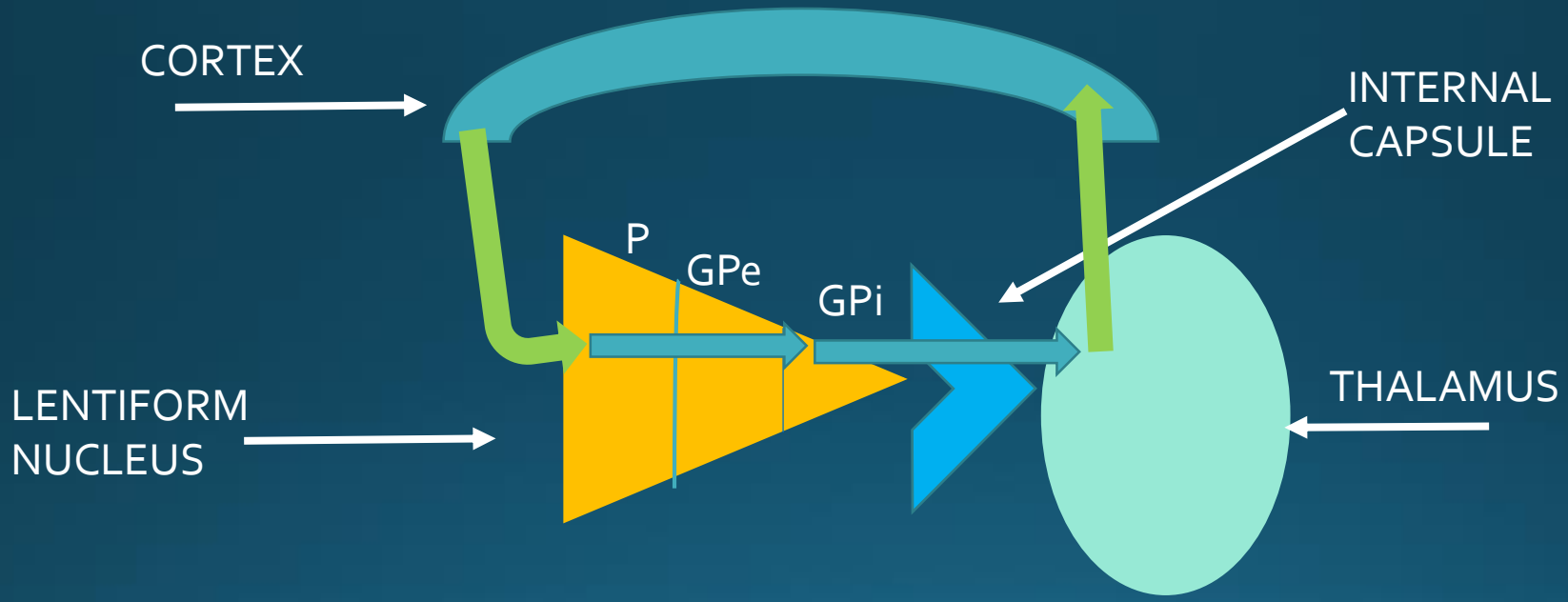
1. What is diagnostic accuracy of clinical criteria in the diagnosis of PD
2. Potential role of DAT SPECT
3. Potential role of 18F-FDOPA PET
4. Role of MRI
5. Appropriate imaging as per the ACR-AC for

- PD with typical features and levodopa responsive
- PD with atypical features and levodopa resistant

pathophysiology



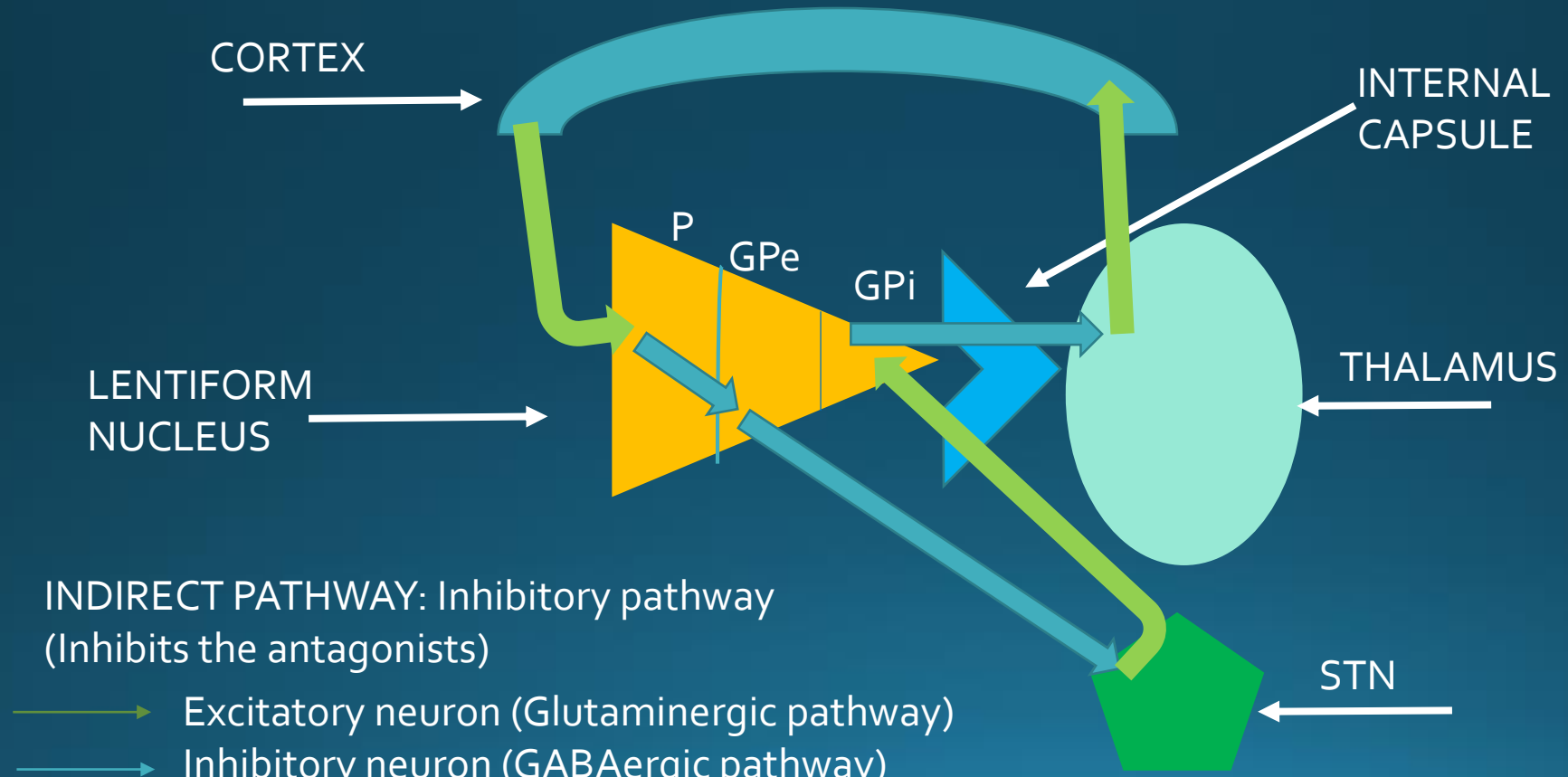
pathophysiology



DIRECT PATHWAY: Stimulatory pathway (Activates the agonists)

- Excitatory neuron (Glutaminergic pathway)
- Inhibitory neuron (GABAergic pathway)

pathophysiology

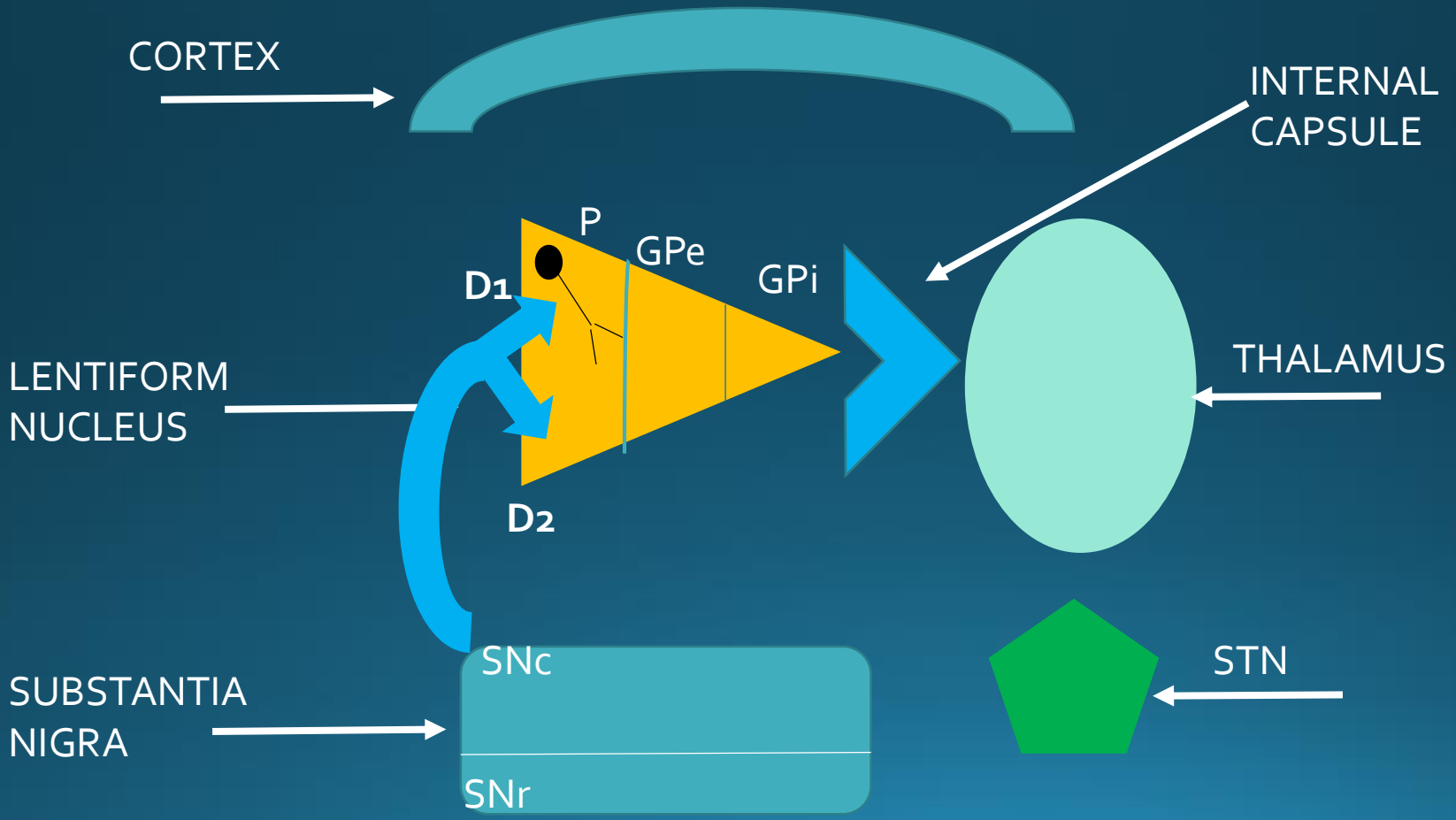


INDIRECT PATHWAY: Inhibitory pathway
(Inhibits the antagonists)

Excitatory neuron (Glutaminergic pathway)

Inhibitory neuron (GABAergic pathway)

pathophysiology



pathophysiology

- Parkinsonism is divided into two categories:

1. With nigro-striatal dopaminergic cell loss: PD and APD (including MSA-P, PSP, CBD (corticobasilar degeneration) and DLB (Diffuse Lewi body) disease
2. Without nigro-striatal dopaminergic cell loss: Psychogenic parkinsonism, dystonic tremor, dopa-responsive dystonia and drug induced parkinsonism

- Parkinson disease (PD) is the most common cause of Parkinsonism. It is a neurodegenerative process and is idiopathic

How do we make a diagnosis of parkinsonism?

TABLE 2. *Accuracy of predictors of Parkinson's disease*

Reference	PD cases/all cases	Diagnostic criteria	Sens.	Spec.	PPV	NPV	Comments and recommendation
Ward and Gibb[7]	24/34	2 of 3 of T, B, R	75	40			Details poor
		3 of 3 of T, B, R	67	14			Details poor
Hughes et al.[8]	76/100	2 of 3 of T, B, R	99	8	77	67	Retrospective
		3 of 3 of T, B, R	65	71	88	40	Retrospective
		Asymmetrical limb rigidity; no oculomotor signs; moderate to excellent levodopa response			86	89	

Superscript numbers correspond to the list of References.
Validity values are given as percentages.
T, tremor; B, bradykinesia; R, rigidity; Sens., sensitivity; Spec., specificity; PPV, positive predictive value; NPV, negative predictive value; dx, diagnosis.

Can J Neurol Sci. 1991 Aug;18(3):275-8.

Accuracy of clinical diagnosis in parkinsonism--a prospective study.

Rajput AH[1], Rozdilsky B, Rajput A.

Author information

Abstract

Clinical diagnosis of Parkinson's syndrome (PS) is reasonably easy in most cases but the distinction between different variants of PS may be difficult in early cases. The correct diagnosis is not only important for counselling and management of patients but also in conducting pharmacological and epidemiological studies. There is very little critical literature on the pathological verification of the clinical diagnosis in PS. We report our 22 years experience to address that issue. Between 1968 and 1990, 65 PS patients came to autopsy. Complete data are available in 59 (M-50, F-19) cases. The initial diagnosis made by a qualified neurologist was idiopathic Parkinson's disease (IPD) in 43 cases. Of those 28 (65%) had Lewy body pathology. After a mean duration of 12 years the final diagnosis was IPD in 41 cases which was confirmed in 31 (76%). The IPD could not be clinically distinguished from cases with severe substantia nigra neuronal loss without inclusions or from those with neurofibrillary tangle inclusions and neuronal loss at the anatomical sites typically involved in IPD. All progressive supra-nuclear palsy, olivopontocerebellar atrophy, Jakob-Creutzfeldt's disease and the majority of the multiple system atrophy cases were diagnosed correctly during life. The correct clinical diagnosis in most non-IPD variants of PS was possible within 5 years of onset (range: 2 months to 18 years). We recommend that studies aimed at including only the IPD cases restrict the enrollment to those cases that have had PS motor manifestations for five years or longer duration.

PMID: 1913360 [PubMed - indexed for MEDLINE]

UK, Unit

Why do we care to differentiate parkinsonism from other mimics

Because they differ in

1. Molecular pathogenesis
2. Treatment response and
3. Prognosis

This is where imaging plays a role

Dopamine transporter spect (dat spect)

- DAT SPECT is used to detect nigrostriatal dopaminergic cell loss
- Helps in distinguishing parkinsonism that results due to loss of nigrostriatal cells (e.g; PD, MSA-P, PSP, CBD and DLB disease) from similar clinical mimics without nigrostriatal cell loss (e.g; psychogenic parkinsonism, dystonic tremor, dopa-responsive dystonia and drug induced parkinsonism)
- When clinical symptoms occur there is already loss of at-least 50% to 80% of the nigro-striatal dopaminergic neurons
- On average there is 5.5-7.1% loss of dopaminergic neurons in PD annually. The rate is much higher in APD

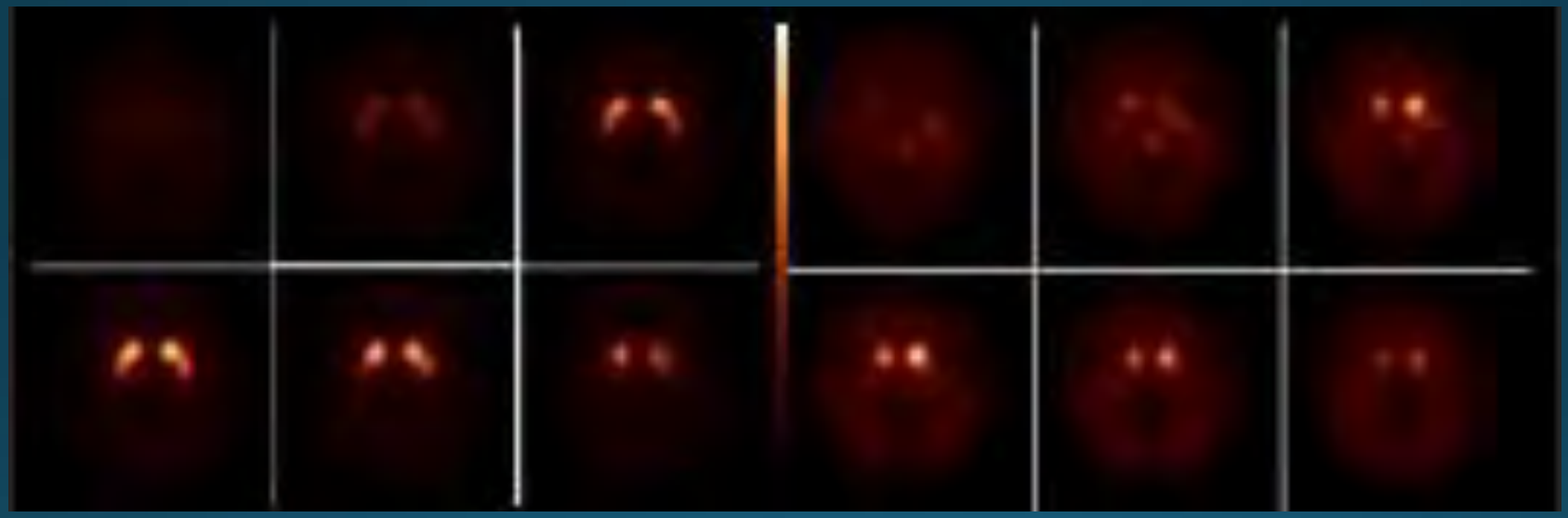
Dopamine transporter spect (dat spect)

- Radiotracers target D2/D3 receptors
- Radiotracers used include:
  - ^{123}I FP-CIT [fluoroprpyl-carbomethoxy-3β-4-iodoprophenyltropane
  - ^{123}I Iodobenzamide
  - ^{123}I Iodobenzofuran

Dopamine transporter spect (dat spect)

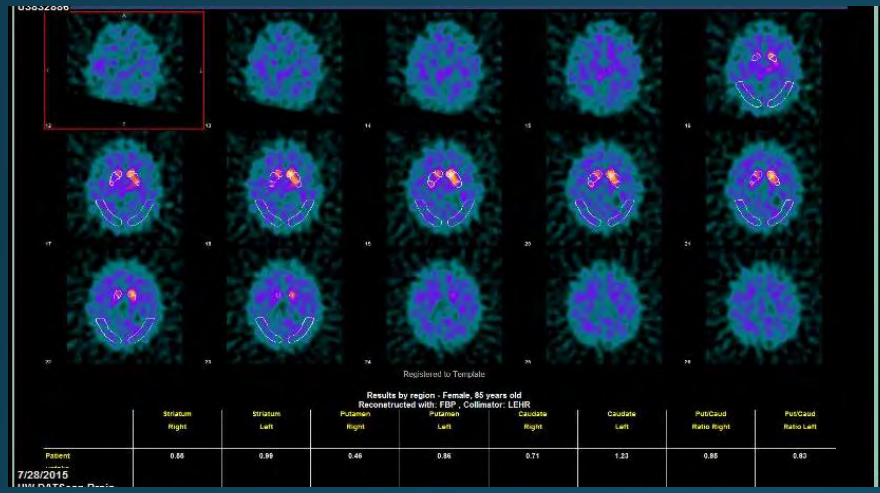
- Current reference standard (or gold standard) for detection of nigrostriatal cell loss is pathological evaluation, which is not a practical for evaluation of new diagnostic tools for early diagnosis
- Many believe DAT SPECT is a most suitable to act as a reference standard in detection of early nigrostriatal cell loss in patients with early stage parkinsonism

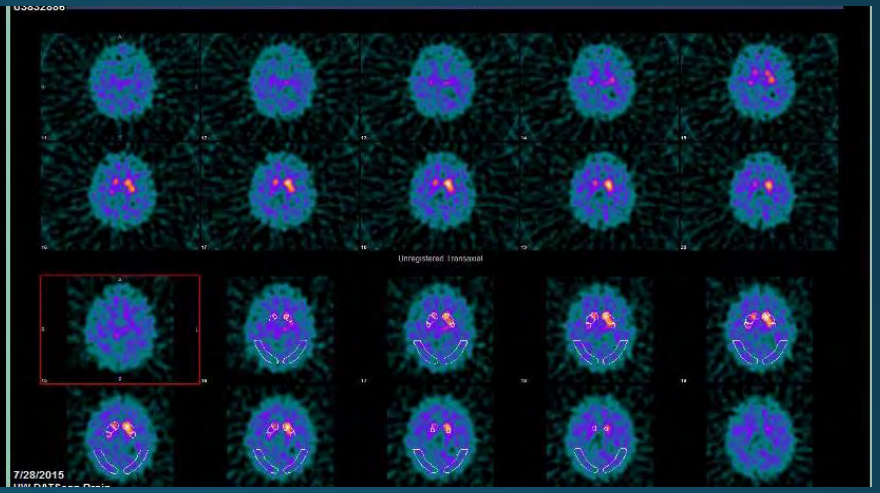
Dopamine transporter spect (dat spect)

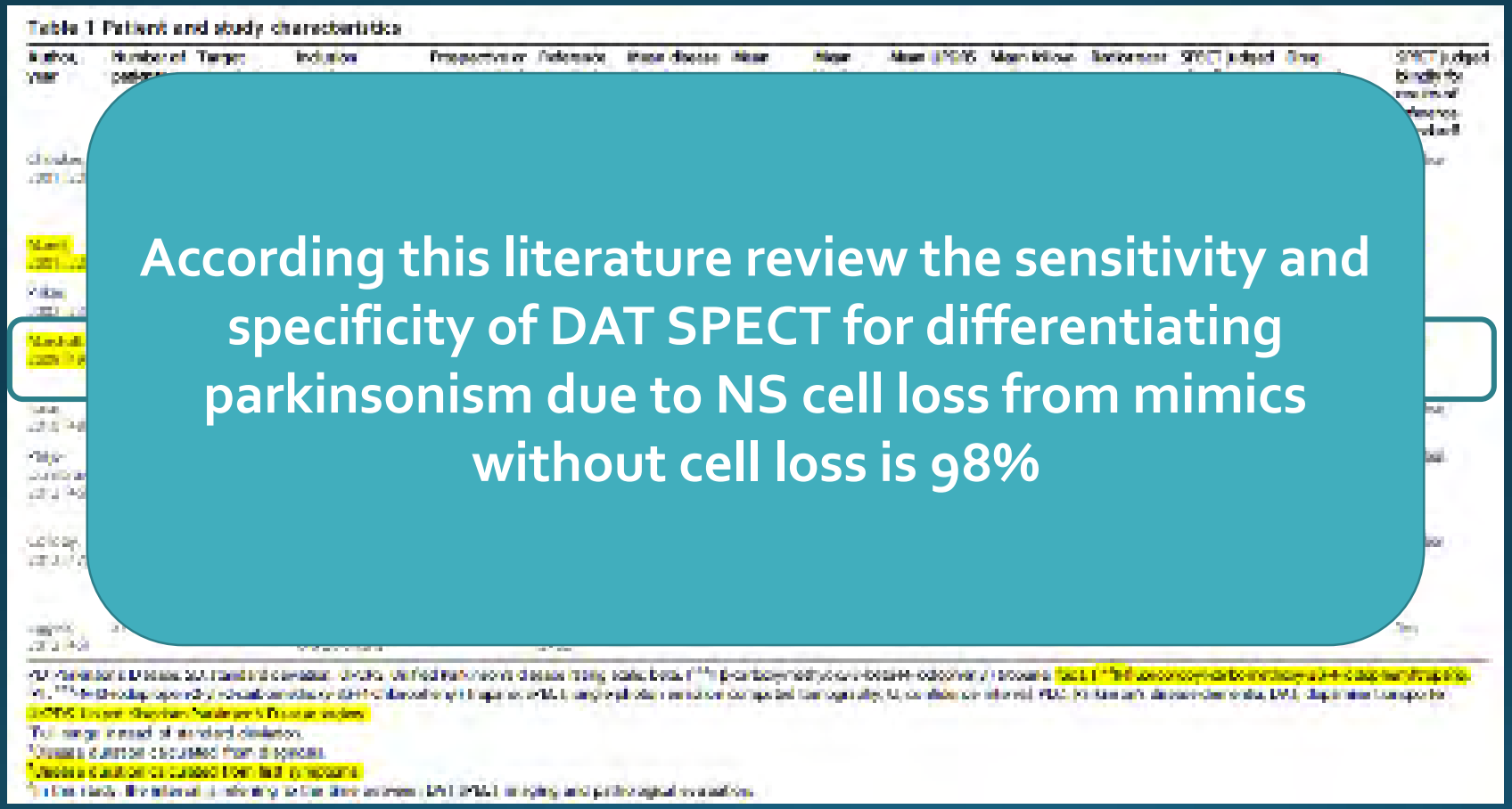


Axial DAT SPECT (I-123 FP-CIT) images of healthy control (left) and a patient with PD (right) at the level of striatum. Intense symmetrical DAT binding in the striatum of healthy control and asymmetrical DAT binding bilaterally in PD patient

Suwijn et al; EJNMMI Research, 2015

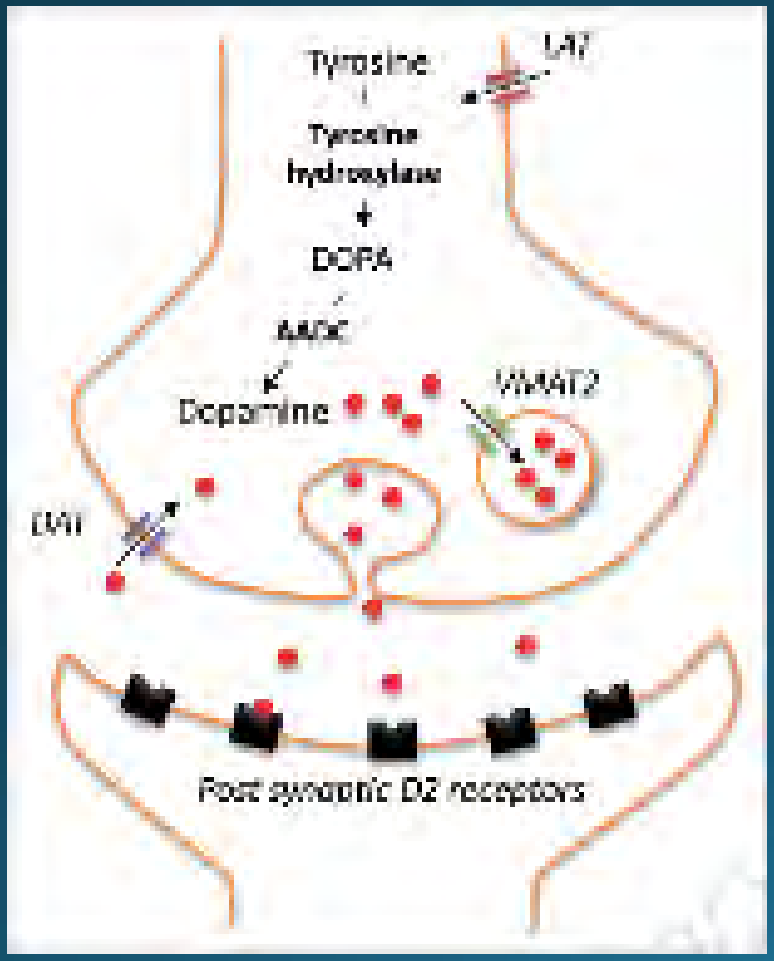

Registered to Template
Results by region - Female, 85 years old
Reconstructed with: FBP , Collimator: LEHR
Striatum Right
Striatum Left
Putamen Right
Putamen Left
Caudate Right
Caudate Left
Put/Caud Ratio Right
Put/Caud Ratio Left
Patient
0.66
0.99
0.46
0.86
0.71
1.23
0.65
0.83
7/28/2015


Unregistered Transaxial
7/28/2015



Suwijn et al; EJNMMI Research, 2015

Fluorodopa f-18 PET



- Useful in detecting nigrostriatal dopaminergic cell loss and hence in the diagnosis of neurodegenerative parkinsonism
- L-Dihydroxyphenylamine (l-DOPA) labelled with Flurine-18 transported into the presynaptic neurons by LAT (large amino acid transporter)
- L-DOPA converted to flurodopamine by AADC (aromatic acid decarboxylase)
- Flurodopmine is stored in to presynaptic vescicles by VMAT2 (type 2 vescicular monoamine transporter)
- Therefore F18-FDOPA uptake reflect the presynaptic vesicular storage capacity of nigrostriatal neurons

Darcourt J et al; Q J Nucl Med Mol Imaging, 2014.

Fluorodopa f-18 PET

J Nucl Med. 1996 Nov;37(11):1760-5.

Comparative nigrostriatal dopaminergic imaging with iodine-123-beta CIT-FP/SPECT and fluorine-18-FDOPA/PET.

Ishikawa T[1], Dhawan V, Kazumata K, Chaly T, Mandel F, Neumeyer J, Margouleff C, Babchyck B, Zanzi I, Eidelberg D

Ann Neurol. 1994 Nov;36(5):759-64.

Longitudinal fluorodopa positron emission tomographic studies of the evolution of idiopathic parkinsonism.

Vingerhoets FJ[1], Snow BJ, Lee CS, Schulzer M, Mak E, Calne DB.

⊕ Author information

Abstract

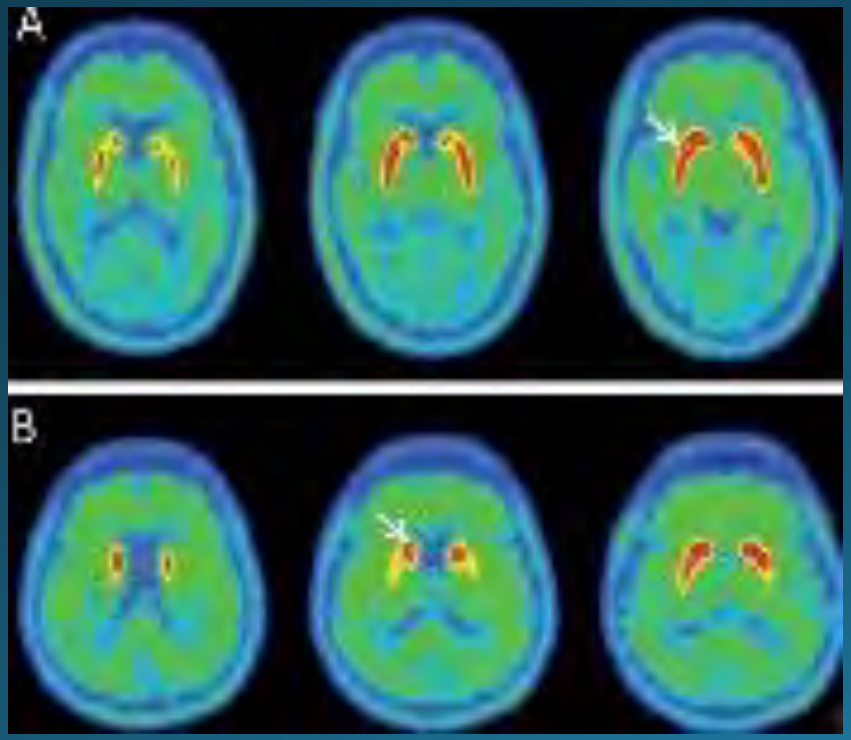
Previous estimates of the rate of progression of the nigral pathology underlying idiopathic parkinsonism (IP) have been derived mainly from pathological studies that have an inherent selection bias. Fluorodopa positron emission tomography (PET) is a reliable tool for assessing nigrostriatal dopaminergic function in vivo. We performed fluorodopa PET on two occasions, 7 years apart, on 16 patients with IP (age at the time of the first scan, 51 +/- 14 yr [mean +/- SD]) and 10 normal controls (age, 54 +/- 16 yr). For the patients with IP, the average duration of symptoms from the time of diagnosis to the first scan was 4.5 years (range, 1-12 yr); their PET index (striatal-occipital)/occipital ratio, dropped by 1.7% per year, from 0.49 +/- 0.08 to 0.43 +/- 0.08 ($p < 0.001$). The normals' ratio decreased by 0.3% per year from 0.77 +/- 0.05 to 0.75 +/- 0.10 ($p = 0.33$). The ratios in the IP group progressed significantly faster than the controls ($p = 0.036$). The rate of decline in IP represents 7.8% per decade, expressed as a fraction of the normals' initial mean value at 54 years of age. These results also permit power analysis for the design of future studies assessing the effect of treatment on the underlying pathology in IP.

progression

- 18F-FDOPA-PET cannot differentiate between IPA and APD

Fluorodopa f 18 PET

In Parkinson patients there is preferential reduction in uptake in the region of posterior putamen early in the disease



A: Healthy control
B: PD patient with decreased FDOPA uptake in the posterior putamen

Darcourt J et al; Q J Nucl Med Mol Imaging, 2014.

MRI

- Conventional MRI (T1WI, T2WI and PD)
- Advanced MR imaging:

1. Susceptibility weighted imaging (SWI)
2. MR volumetry
3. Diffusion weighted imaging (DWI)
4. Diffusion tensor imaging (DTI)
5. MR spectroscopy (MRS)

Conventional mri

- Routine T1WI, T2WI and proton density imaging
- For most part it is going to be normal in early PD
- Role is to exclude other causes like vascular lesions, MS, tumor, NPH, striopallidodental calcinosis or NBIA
- Late in the disease process (PD) there may be smudgy appearance of SNc from lateral to medial
- Sometimes may help identify features pointing to specific type of APD
- Presence of at-least two abnormalities on conventional MRI has a reasonable **sensitivity of 78%** and **specificity of 76%** to identify patients with APD

Conventional mri

AJNR Am J Neuroradiol. 2000 Apr;21(4):697-701.

Structural changes of the substantia nigra in Parkinson's disease as revealed by MR imaging.

Hutchinson M[1], Raff U.

AJNR Am J Neuroradiol. 2007 Feb;28(2):309-13.

Imaging degeneration of the substantia nigra in Parkinson disease with inversion-recovery MR imaging.

Minati L[1], Grisoli M, Carella F, De Simone T, Bruzzone MG, Savoiardo M.

⊕ Author information

Abstract

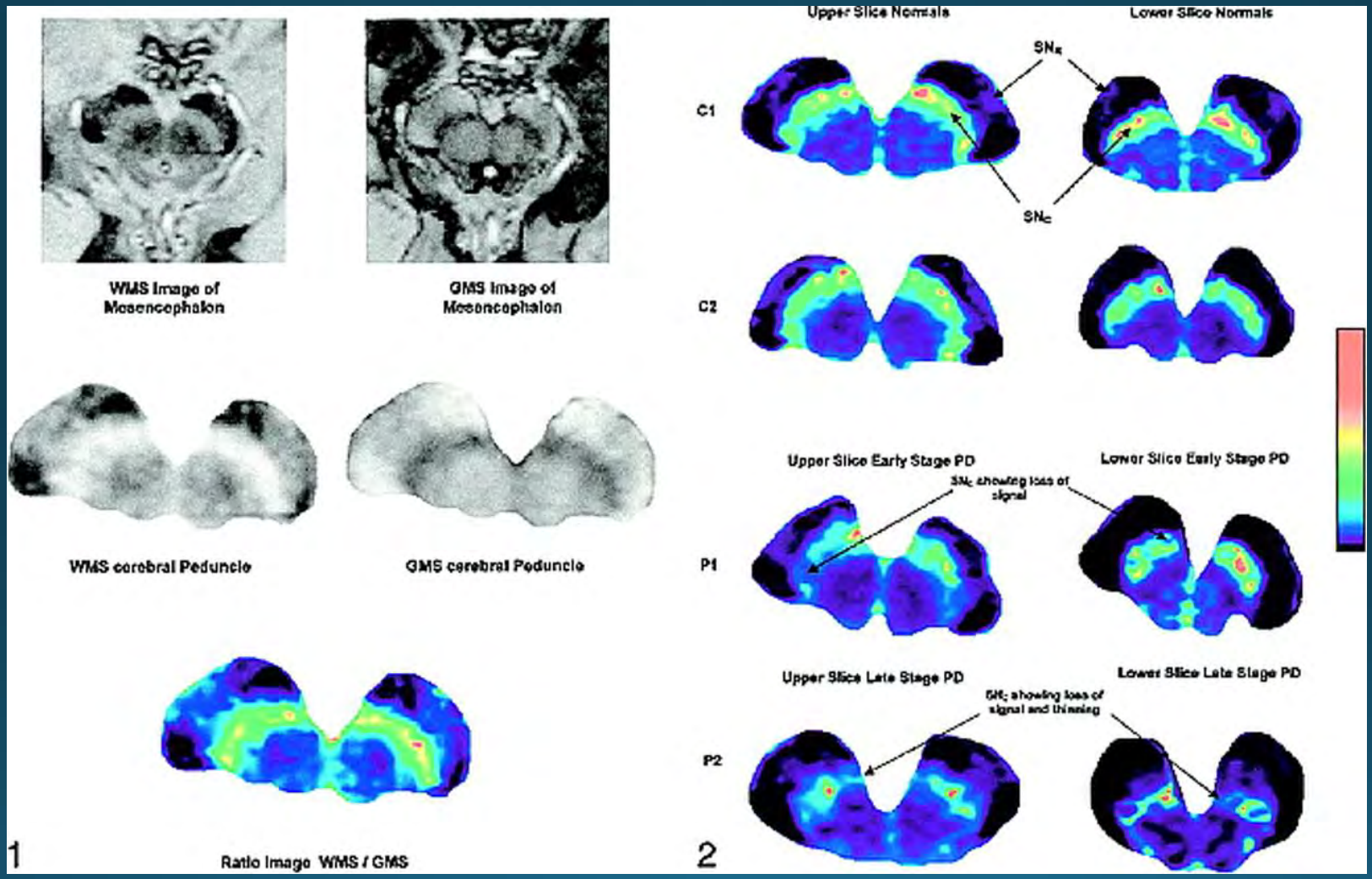
BACKGROUND AND PURPOSE: Visualizing with MR imaging and obtaining quantitative indexes of degeneration of the substantia nigra in Parkinson disease have been long-sought goals. We investigated the potential role of area and T1 contrast measurements in differentiating patients from controls and their age-related changes.

METHODS: Eight patients with Parkinson disease, 8 age-matched controls, and 8 young controls were imaged. We obtained the pixel-wise difference between 2 sets of inversion-recovery images, acquired parallel to the bicommissural plane, with different inversion times. Pixel-intensity ratios between lateral and medial nigral regions, and nigral area and substantia-nigra/midbrain area ratios were computed.

RESULTS: Compared with that of controls, loss of substantia nigra was evident in patients, its borders taking a smoother and more irregular appearance. Patients were characterized by a lateral-to-medial gradient, due to reduced hypointensity of the lateral portion of the substantia nigra and relative sparing of its medial portion. The visible nigral area was significantly smaller in patients compared with matched controls (P = .04). The substantia nigra/midbrain area ratio enabled considerably better separation (P = .0001). The lateral/medial pixel-intensity ratio was significantly higher in patients compared with matched controls (P = .01) and in young controls compared with age-matched controls (P = .01).

CONCLUSION: Inversion-recovery sequences may provide a convenient way to visualize nigral degeneration. Relative area and pixel-intensity measurements may integrate other techniques (such as diffusion-tensor imaging on nigrostriatal pathways) in the neuroradiologic diagnosis and follow-up of Parkinson disease by quantitatively assessing the degeneration of the substantia nigra.

Upper row displays an example of axial WMS and GMS MR acquisition images of the mesencephalon in a control participant.



Michael Hutchinson, and Ulrich Raff AJNR Am J Neuroradiol 2000;21:697-701

AJNR
AMERICAN JOURNAL OF NEURORADIOLOGY

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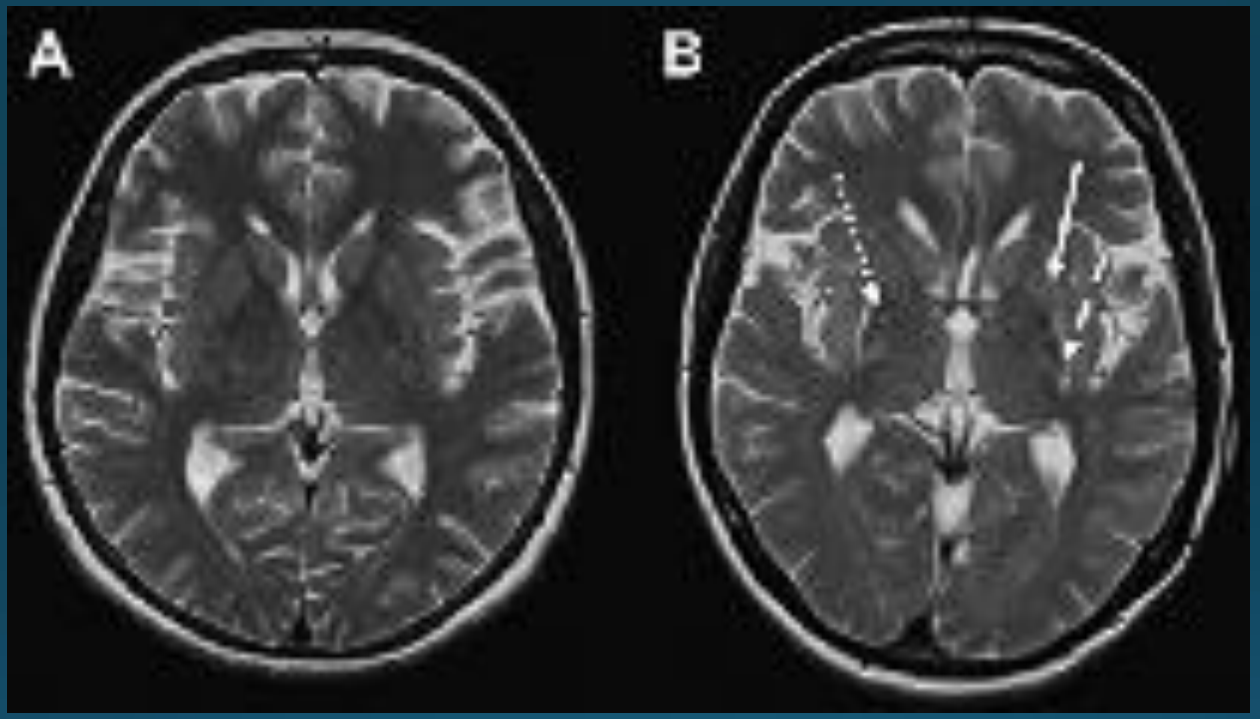
Conventional mri

MSA-P

- Hypointensity of the dorsal putamen
- Hyperintense putaminal rim
- Pontine atrophy
- “Hot-cross bun” sign
- Cerebellar atrophy
- Hyperintensity in the middle cerebellar peduncle (MCP sign)



Neuroimaging Clin N Am. 2010 Feb;20(1):29-55. doi: 10.1016/j.nic.2009.08.016.

Brain magnetic resonance imaging techniques in the diagnosis of parkinsonian syndromes.

Seppi K[1], Poewe W.

J Neuroimaging. 2006 Jan;16(1):73-7.

The "cross" signs in patients with multiple system atrophy: a quantitative study.

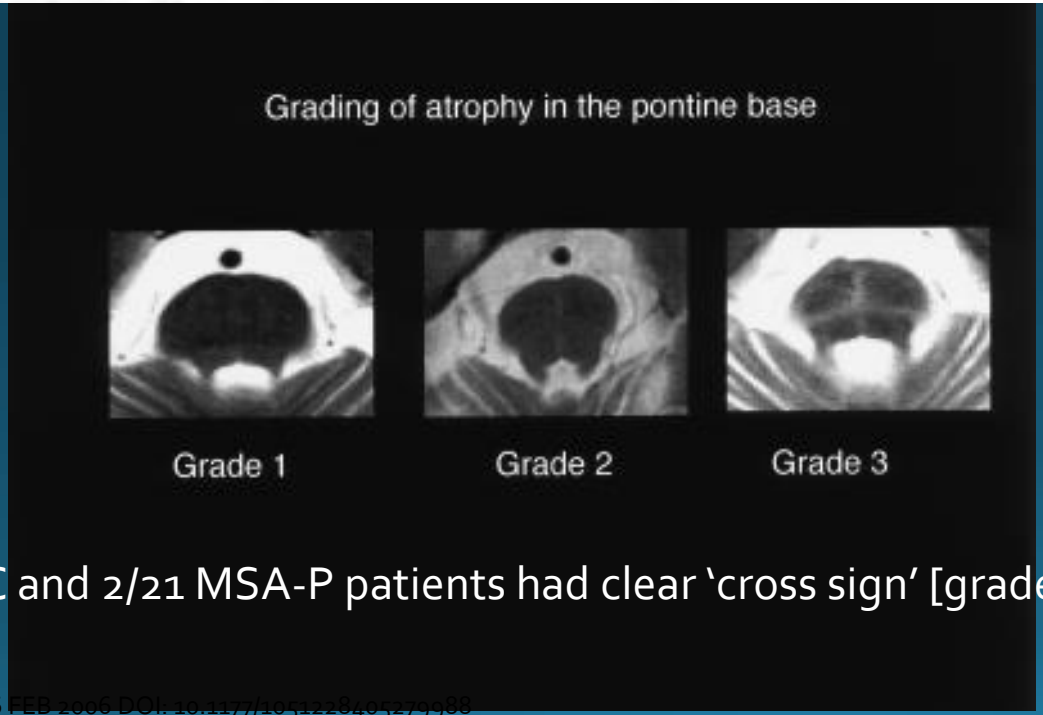
Abe K[1], Hirota T, Yokoe M, Mihara M, Sakoda S

Author information

Abstract

Patients with multiple system atrophy (MSA) may show the "cross" sign in the pontine base that has been considered as an expression of the degeneration of pontine neurons and transverse pontocerebellar fibers. However, correlations between pontine base atrophy and existence of "cross" sign have not been fully investigated. The authors studied 68 patients with MSA (47 MSA-C [predominantly cerebellar ataxia], 21 MSA-P [predominantly parkinsonism], mean [+/-SD] 58.7 +/- 10.9 years). T1-weighted (T1W) sagittal and axial images and T2-weighted (T2W) axial images were obtained for all patients and controls. To measure the areas of pontine basis and cerebellar vermis, the authors used midsagittal T1W images and analyzed a bit map transformed on a computer. They classified atrophy in the pontine base into 3 grades. There is significant correlation between atrophies of pontine base and existence of the cross sign. All patients with a smaller area of pontine base 2 standard deviations below those of normal controls had the cross sign. This supports that existence of the cross sign depends only on the extent of pontine base atrophies.

PMID: 16483280 [PubMed - indexed for MEDLINE]



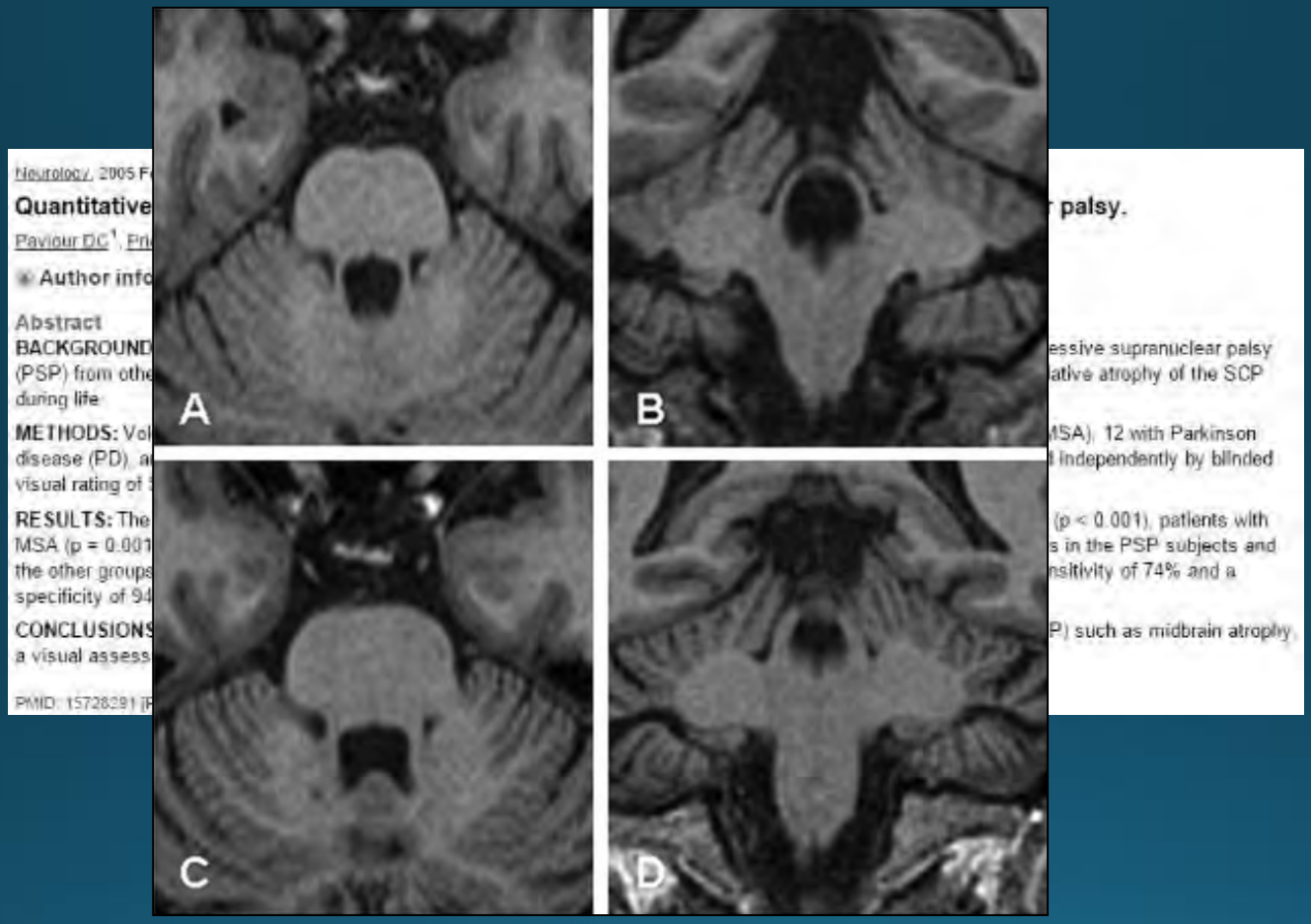
12/47 MSA-C and 2/21 MSA-P patients had clear 'cross sign' [grade 3]

Journal of Neuroimaging
Volume 16, Issue 1, pages 73-77, 16 FEB 2006 DOI: 10.1177/1051228405279988
http://onlinelibrary.wiley.com/doi/10.1177/1051228405279988/full#f2

Conventional mri

PSP

- Midbrain atrophy (penguin silhouette or humming bird sign), reduced AP diameter of midbrain or decreased midbrain to pons ratio
- Atrophy of inferior olives
- Superior cerebellar peduncle atrophy and increased T2 signal



SCP atrophy has a sensitivity of 74% and a specificity of 94% in identifying PSP cases

Figure 1

Neurology. 2005 Jun 28;64(12):2050-5

New and reliable MRI diagnosis for progressive supranuclear palsy.

Oba H[1], Yagishita A, Terada H, Barkovich AJ, Kutomi K, Yamauchi T, Furui S, Shimizu T, Uchigata M, Matsumura K, Sonoo M, Sakai M, Takada K, Harasawa A, Takeshita K, Kohtake H, Tanaka H, Suzuki S.

Author Information

Abstract

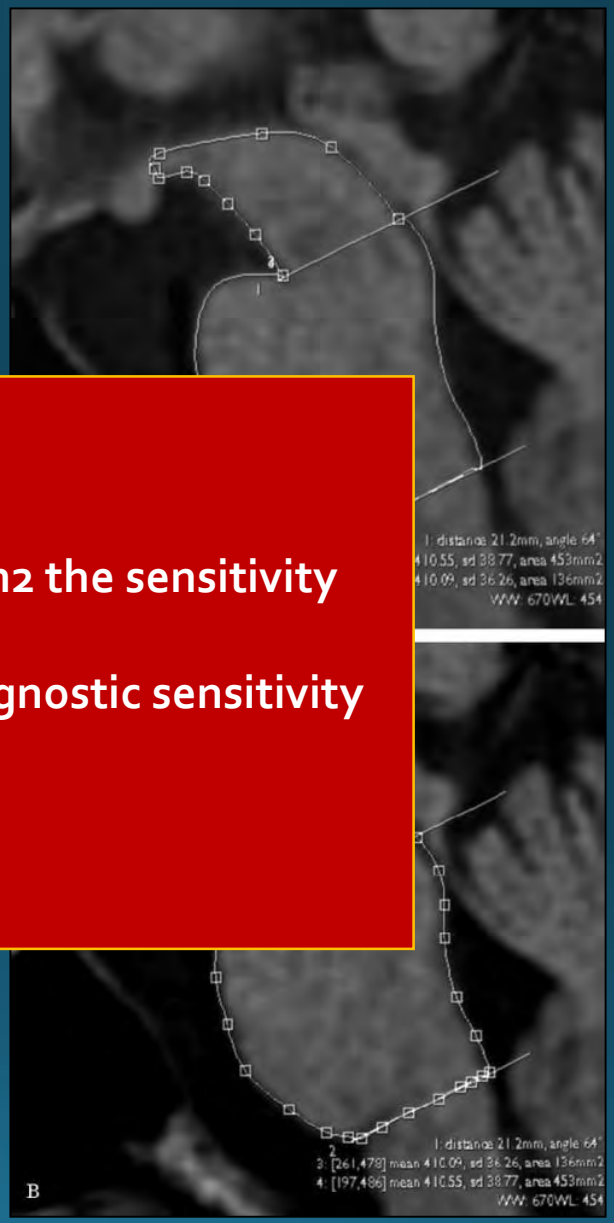
OBJECTIVE: To evaluate the area of the midbrain and pons on mid-sagittal MRI in patients with progressive supranuclear palsy (PSP), Parkinson disease (PD), and multiple-system atrophy of the Parkinson type (MSA-P), compare these appearances and values with those of normal control subjects, and establish diagnostic MRI criteria for the diagnosis of PSP

METHODS: The autho
normal control subject
workstation. The ratio

RESULTS: The averag
and MSA-P (97.2 mm2
patients with PSP and
areas with values from
smaller than that in tho
the PSP group and the

CONCLUSION: The ar

- **Midbrain tegmentum area cut off at 70 mm2 the sensitivity was 100% and specificity 91.3%**
- **Midbrain/pons ratio cut off at 0.15, the diagnostic sensitivity and specificity were 100%**



Scheme fo
sagittal MI
magnified
drawn to p
the quadri
line so as t
midbrain (illustrated by boxes in A) was traced around the edges of line 1 and the delta-shaped midbrain tegmentum above it. The area of the pons (illustrated by boxes in B) was the area inside the line traced along the anterior and posterior margins of the pons and along lines 1 and 2.

Wolters Kluwer Health | OvidSP

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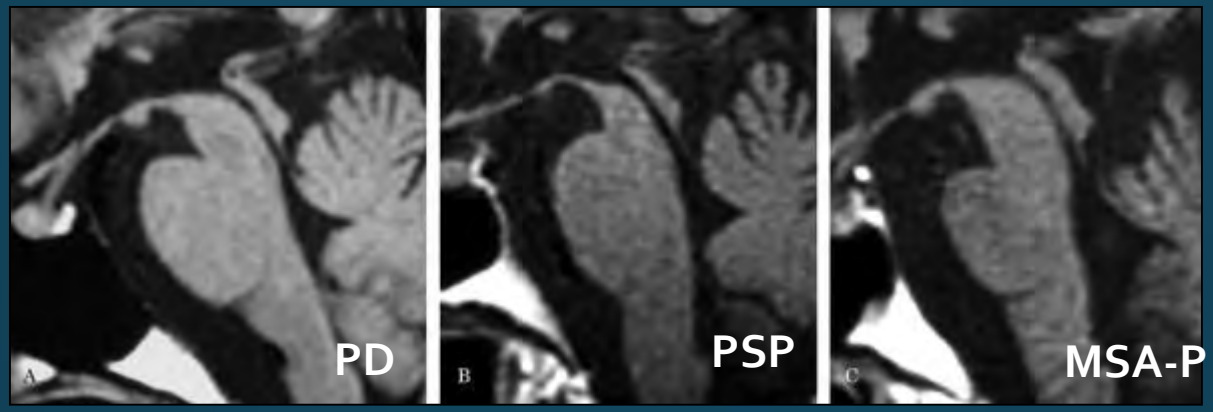

New radiographic sign for the diagnosis of progressive supranuclear palsy (PSP). Midsagittal MR image of a patient with Parkinson disease (PD) does not show any apparent abnormality (A), while that of a patient with PSP shows marked atrophy of midbrain tegmentum (B), and a patient with multiple-system atrophy of the Parkinson type (MSA-P) shows marked atrophy of pons (C). The midbrain to pons ratio is always small in the patients with PSP. In patients with PSP, the shapes of midbrain tegmentum (bird's head) and pons (bird's body) on midsagittal MR images look like a lateral view of a standing penguin (especially the king penguin) with a small head and big body. Recognition of this penguin silhouette sign should strongly raise suspicion for the diagnosis of PSP.

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CBD

- Not many studies available
- Cortical atrophy predominantly in the frontal and parietal lobes
- Mild increased T2 signal along the cortex an subcortical white matter

Susceptibility weighted imaging

- SW
  pat
  sen

AJNR Am J Neuroradiol. 2015 Mar;36(3):454-60. doi: 10.3174/ajnr.A4140. Epub 2014 Oct 22.

Susceptibility-weighted imaging improves the diagnostic accuracy of 3T brain MRI in the work-up of parkinsonism.

Meijer FJ[1], van Rumund A[2], Fasen BA[3], Tituaer I[2], Aerts M[2], Esselink R[2], Bloem BR[2], Verbeek MM[4], Goraj B[5]

Author information

Abstract

BACKGROUND AND PURPOSE: The differentiation between Parkinson disease and atypical parkinsonian syndromes can be challenging in clinical practice, especially in early disease stages. Brain MR imaging can help to increase certainty about the diagnosis. Our goal was to evaluate the added value of SWI in relation to conventional 3T brain MR imaging for the diagnostic work-up of early-stage parkinsonism.

MATERIALS AND METHODS: This was a prospective observational cohort study of 65 patients presenting with parkinsonism but with an uncertain initial clinical diagnosis. At baseline, 3T brain MR imaging with conventional and SWI sequences was performed. After clinical follow-up, probable diagnoses could be made in 56 patients, 38 patients diagnosed with Parkinson disease and 18 patients diagnosed with atypical parkinsonian syndromes, including 12 patients diagnosed with multiple system atrophy-parkinsonian form. In addition, 13 healthy controls were evaluated with SWI. Abnormal findings on conventional brain MR imaging were grouped into disease-specific scores. SWI was analyzed by a region-of-interest method of different brain structures. One-way ANOVA was performed to analyze group differences. Receiver operating characteristic analyses were performed to evaluate the diagnostic accuracy of conventional brain MR imaging separately and combined with SWI.

RESULTS: Disease-specific scores of conventional brain MR imaging had a high specificity for atypical parkinsonian syndromes (80%-90%), but sensitivity was limited (50%-80%). The mean SWI signal intensity of the putamen was significantly lower for multiple system atrophy-parkinsonian form than for Parkinson disease and controls ($P < .001$). The presence of severe dorsal putaminal hypointensity improved the accuracy of brain MR imaging. The area under the curve was increased from 0.75 to 0.83 for identifying multiple system atrophy-parkinsonian form, and it was increased from 0.76 to 0.82 for identifying atypical parkinsonian syndromes as a group.

CONCLUSIONS: SWI improves the diagnostic accuracy of 3T brain MR imaging in the work-up of parkinsonism by identifying severe putaminal hypointensity as a sign indicative of multiple system atrophy-parkinsonian form.

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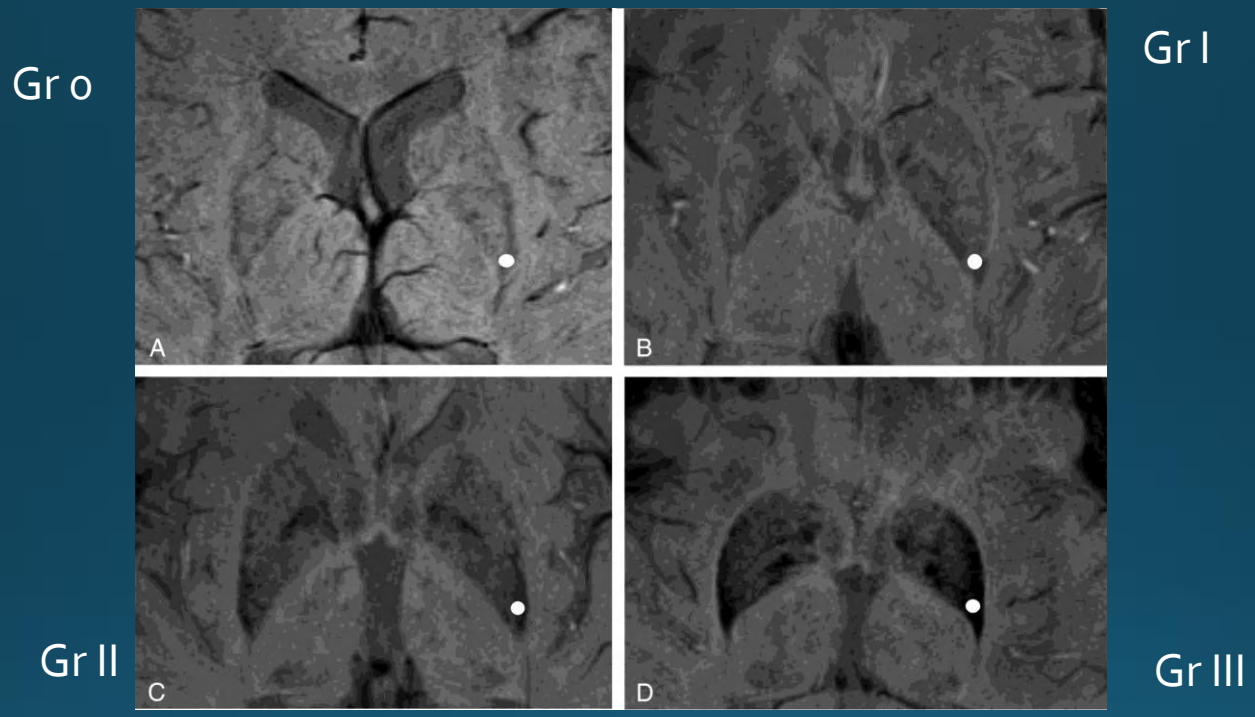
A–D, SWI with a circular region of interest in the left dorsal putamen.



F.J.A. Meijer et al. AJNR Am J Neuroradiol 2015;36:454-460

AJNR
AMERICAN JOURNAL OF NEURORADIOLOGY

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Susceptibility weighted imaging

Mov Disord. 2015 Jul;30(8):1068-76. doi: 10.1002/mds.26171. Epub 2015 Mar 15.

Dorsolateral nigral hyperintensity on 3.0T susceptibility-weighted imaging in neurodegenerative Parkinsonism.

Reiter E[1], Mueller C[1], Pinter B[1], Krismer F[1], Scherfler C[1,2], Esterhammer R[3,2], Kremser C[3,2], Schocke M[3,2], Wenning GK[1], Poewe W[1,2], Seppi K[1,2]

Author information

Abstract

BACKGROUND: Absence of a hyperintense, ovoid area within the dorsolateral border of the otherwise hypointense pars compacta of the substantia nigra (referred to as dorsolateral nigral hyperintensity) on iron-sensitive high-field magnetic resonance imaging sequences seems to be a typical finding for patients with Parkinson's disease (PD).

OBJECTIVE: This study was undertaken to evaluate the diagnostic value of the dorsolateral nigral hyperintensity in a cohort of patients with neurodegenerative parkinsonism including PD, multiple system atrophy (MSA), and progressive supranuclear palsy (PSP) as well as healthy controls using high-field susceptibility-weighted imaging (SWI) at 3.0 Tesla (T).

METHODS: Absence of dorsolateral nigral hyperintensity was assessed on visual inspection of anonymized 3.0T SWI scans in a case-control study including 148 patients with neurodegenerative parkinsonism (PD: n = 104; MSA: n = 22; PSP: n = 22) and 42 healthy controls.

RESULTS: Dorsolateral nigral hyperintensity was absent unilaterally in all patients with MSA or PSP, in 83 of 90 patients with PD, but only in one of the healthy controls resulting in an overall correct classification of 95.2% in discriminating neurodegenerative parkinsonism from controls in the per-protocol analysis. Overall correct classification was 93.2% in the intent-to-diagnose analysis, including also SWI scans with poor quality (12.1% of all scans) for nigral evaluation.

CONCLUSION: Visual assessment of dorsolateral nigral hyperintensity on high-field SWI scans may serve as a new simple diagnostic imaging marker for neurodegenerative parkinsonian disorders. © 2015 International Parkinson and Movement Disorder Society.

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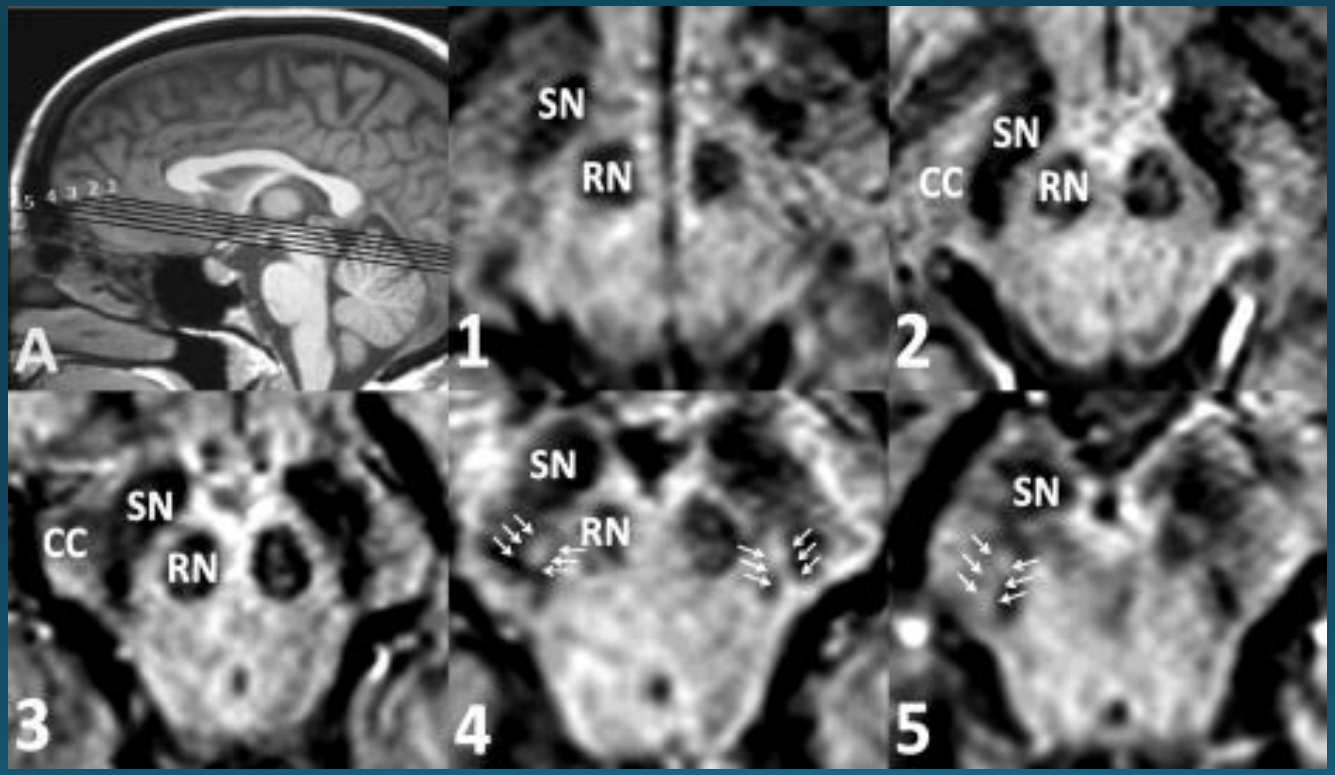
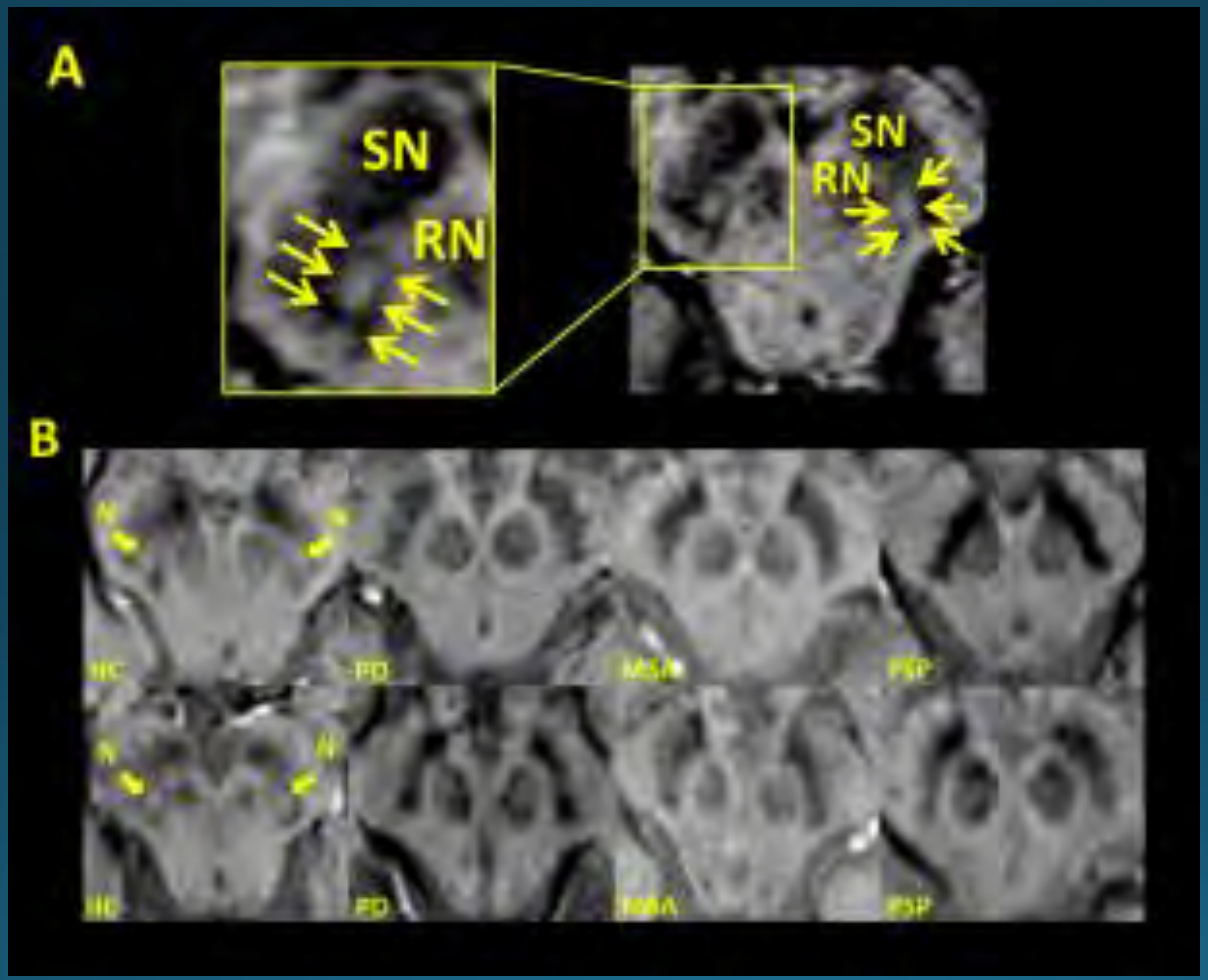
Dorsolateral nigral hyperintensity on 3.0T susceptibility-weighted imaging in neurodegenerative Parkinsonism



Healthy controls

Movement Disorders
Volume 30, Issue 8, pages 1068-1076, 15 MAR 2015 DOI: 10.1002/mds.26171
http://onlinelibrary.wiley.com/doi/10.1002/mds.26171/full#mds26171-fig-0001

Dorsolateral nigral hyperintensity on 3.0T susceptibility-weighted imaging in neurodegenerative Parkinsonism

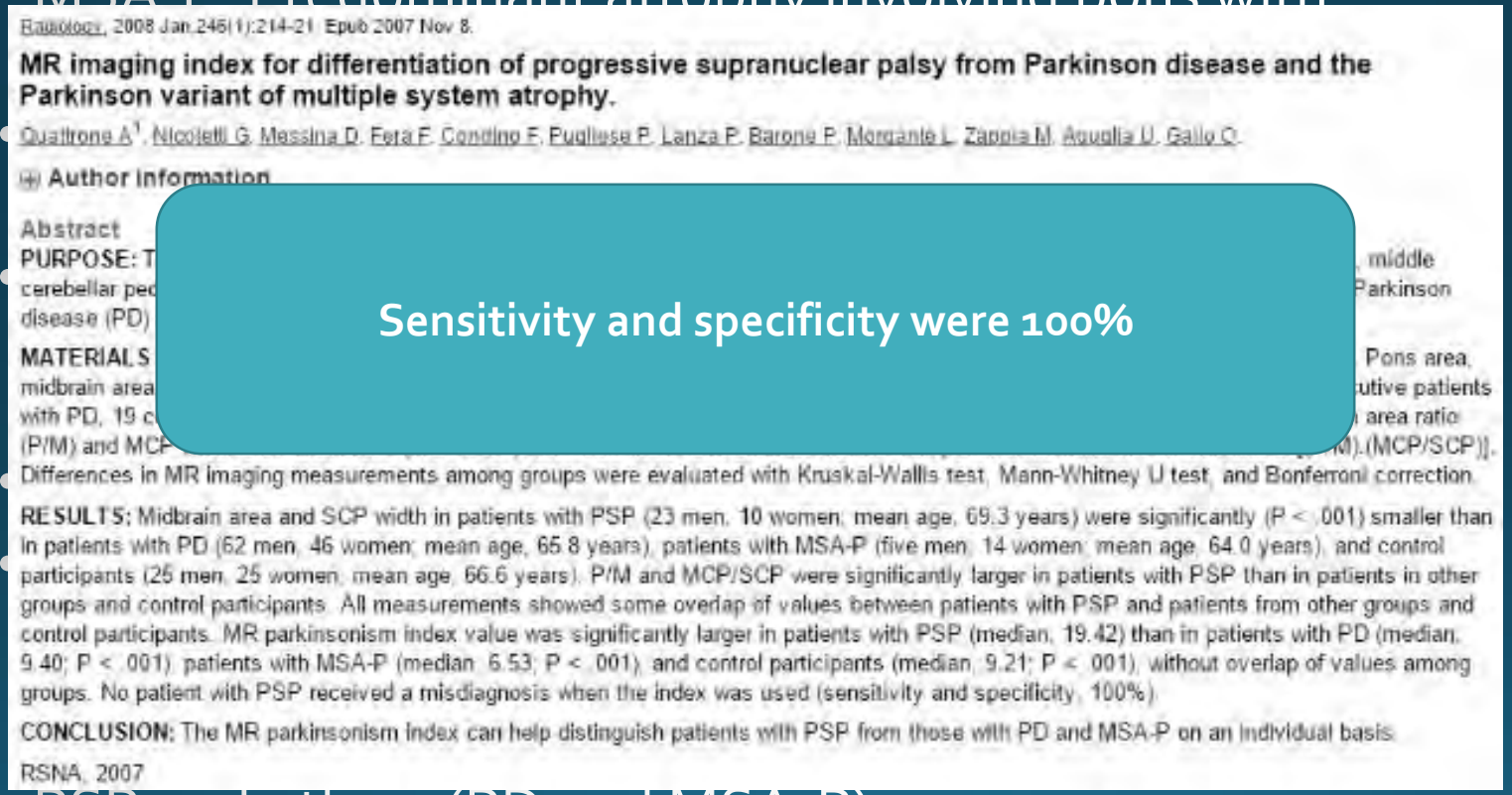


Looks like volume averaging??

Movement Disorders
Volume 30, Issue 8, pages 1068-1076, 15 MAR 2015 DOI: 10.1002/mds.26171
http://onlinelibrary.wiley.com/doi/10.1002/mds.26171/full#mds26171-fig-0002

MRI volumetry

- MSA-P: Predominant atrophy involving pons with
- PSP and others (PD and MSA-P)



Radiology. 2008 Jan;246(1):214-21. Epub 2007 Nov 8.

MR imaging index for differentiation of progressive supranuclear palsy from Parkinson disease and the Parkinson variant of multiple system atrophy.

Quattrone A[1], Nicoletti G, Messina D, Fera F, Condino F, Pugliese P, Lanza P, Barone P, Morgante L, Zappia M, Aguglia U, Gallo O.

Author information

Abstract

PURPOSE: T … middle cerebellar pe… Parkinson disease (PD) …

MATERIALS … Pons area, midbrain area… utive patients with PD, 19 c… area ratio (P/M) and MCP… M).(MCP/SCP)]. Differences in MR imaging measurements among groups were evaluated with Kruskal-Wallis test, Mann-Whitney U test, and Bonferroni correction.

RESULTS: Midbrain area and SCP width in patients with PSP (23 men, 10 women; mean age, 69.3 years) were significantly ($P < .001$) smaller than in patients with PD (62 men, 46 women; mean age, 65.8 years), patients with MSA-P (five men, 14 women; mean age, 64.0 years), and control participants (25 men, 25 women; mean age, 66.6 years). P/M and MCP/SCP were significantly larger in patients with PSP than in patients in other groups and control participants. All measurements showed some overlap of values between patients with PSP and patients from other groups and control participants. MR parkinsonism index value was significantly larger in patients with PSP (median, 19.42) than in patients with PD (median, 9.40; $P < .001$), patients with MSA-P (median, 6.53; $P < .001$), and control participants (median, 9.21; $P < .001$), without overlap of values among groups. No patient with PSP received a misdiagnosis when the index was used (sensitivity and specificity, 100%).

CONCLUSION: The MR parkinsonism index can help distinguish patients with PSP from those with PD and MSA-P on an individual basis.

RSNA, 2007

Sensitivity and specificity were 100%

Diffusion weighted and diffusion tensor imaging

- Diffusivity in midbrain SN not very helpful in differentiating PD from healthy controls
- Decreased FA in SN can help distinguish PD from healthy controls
- Decreased FA values can be seen in frontal lobes in PD patients
- Increased putaminal diffusivity (ADC value) can help differentiate MSA-P from PD in early stage of the disease
- Increased putaminal diffusivity failed to differentiate MSA-P from PSP

Proton MRS

- Decreased NAA/Cr and NAA/Cho ratios in putamen and at the pontine base on a 3 T MRI scanner, can help differentiate MSA-C/MSA-P from PD and healthy controls

question

- What is diagnostic accuracy of clinical criteria in the diagnosis of PD

~75%

- Potential role of DAT SPECT

Early diagnosis of parkinsonism due to nigro-striatal cell loss and hence differentiating it from mimics

Potential role of 18F-FDOPA PET

Assess IPD progression

- Role of MRI

To differentiate IPD from APD

?may help differentiate parkinsonism from mimics

- Appropriate imaging as per the ACR-AC for

- PD with typical features and levodopa responsive: **MRI head without contrast (7)**
- PD with atypical features and levodopa resistant: **MRI head without contrast (8)**

Thank you for your attention

Dopaminergic Receptor Studies for Parkinson Syndromes

Yuyang Zhang

NM UW

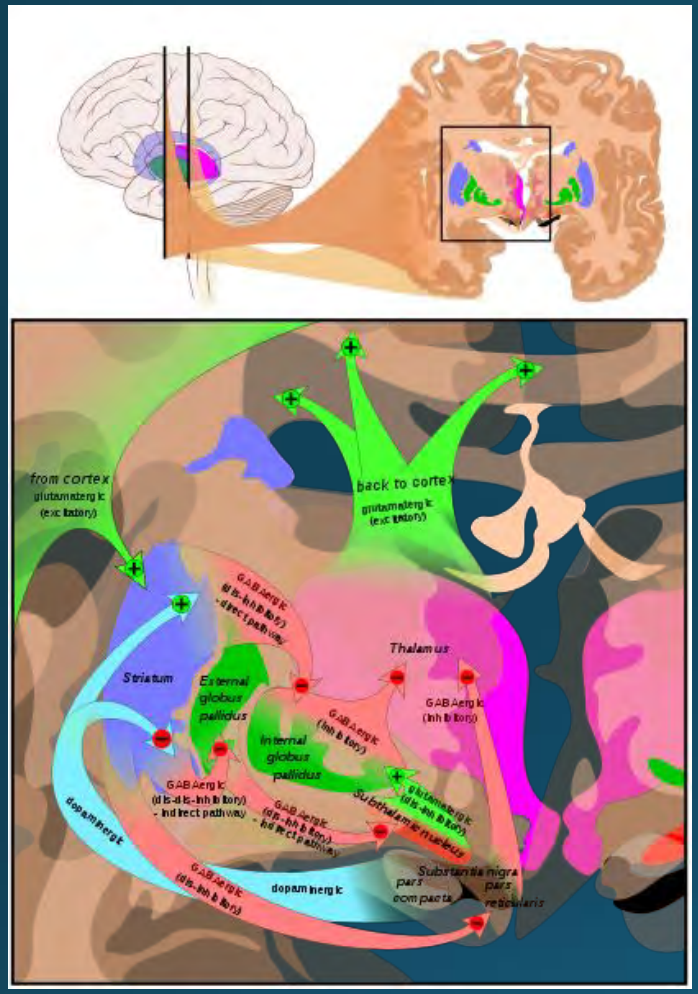
9/2/2010

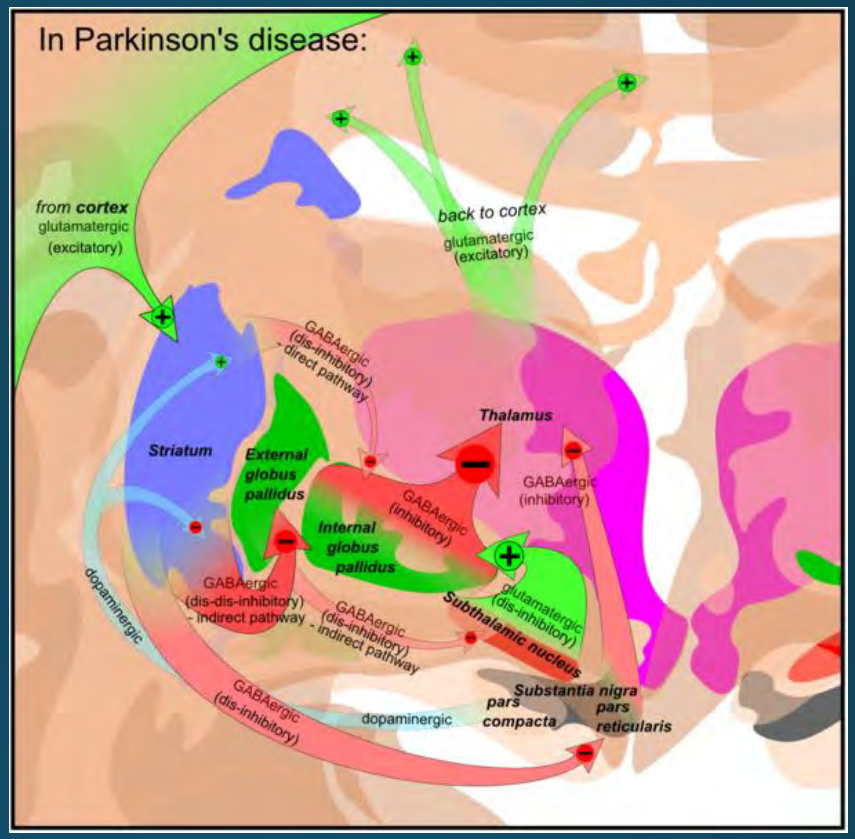
Definition:

- A neurological syndrome characterized by tremor, hypokinesia, rigidity and postural instability

The neurodenegerative condition parkinson's disease (PD) is the most common cause of parkinsonism. A wide-range of other etiologies can lead to a similar symptoms. Like:

- -AIDS
- -Corticobasal degeneration
- -Diffuse lewy body disease
- -Medication, such as antipsychotics, metoclopramide, MPTP
- -Encephalitis lethargical
- -Multiple system atrophy
- -Pantohenate kinase-associated neurodegeneration
- -Progressive supranuclear palsy
- -Toxicity, such as CO, carbon disulfide, manganese, paraquat, mercury, hexane, ---totenone and toluene
- -Vascular parkinsonism
- -Wilson's
- -Pareneoplastic syndrome
- -Genetic





cell death in the substantia nigra result in the greatly reduced activity of pigmented dopamine-secreting cells in the substantia nigra(black substance). These neurons project to the striatum and their loss leads to alterations in the activity of the neural circuits within the basal ganglia that regulate movement. In essence, GABA/ Substance P of the direct pathways diminish, leading to less inhibition of the pars reticulata and an inhibition of the indirect path way by way of GABA.

Dilemma of Diagnosis:

- Typically, the diagnosis is based on medical history and neurological examination. The physician interviews and observes the patient in the search of the cardinal motor symptoms of the disease, while also attending to other symptoms that would exclude the diagnosis of PD. Response to levodopa is another sign pointing towards PD. However there is no definitive test for diagnosis although finding lewy bodies during autopsy has been traditionally considered the gold standard for diagnosis.
- CT and MRI brain scans of people with PD usually appear normal, but useful for diagnosis to rule out other diseases which can be secondary causes of parkinsonism such as basal ganglia tumors, vascular pathology and hydrocephalus.

PD vs benign process like essential tremor vs neurodegenerative diseases

Need to differentiate

Presynaptic radiotracers for PD studies:

1.Dopamine transporter (DAT): Most common ones are TRODAT-1, FP-CIT, beta-CIT for SPECT and beta-CFT, FE-CIT for PET

↑(+)underlying degenerative mechanism; (-)r/o degenerative PD

↓no info. On postsynaptic level of the nigro-striatal circuity

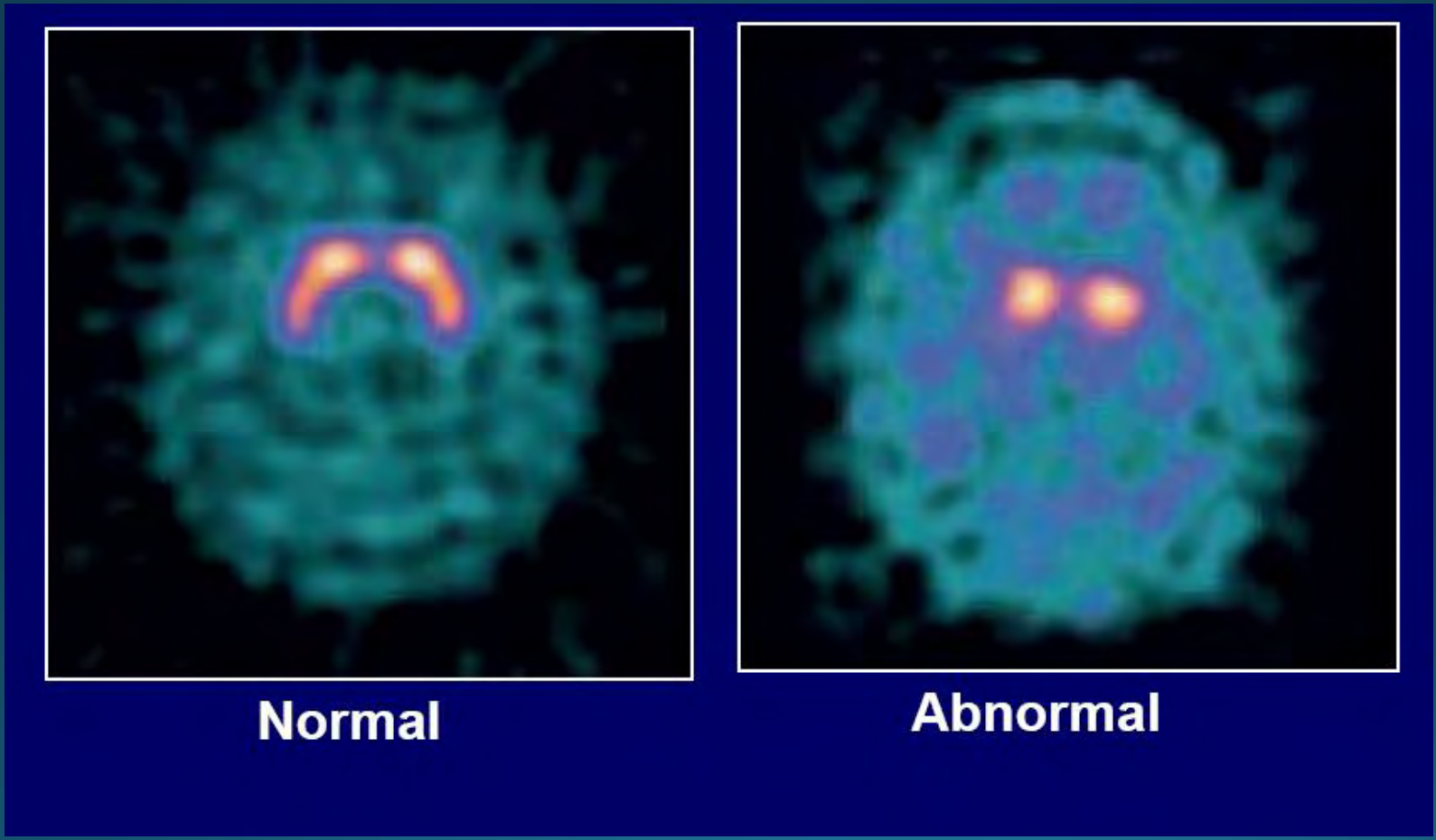
studies with DAT tracers discriminate PD patients from healthy subjects with ***100% sensitivity and specificity*.

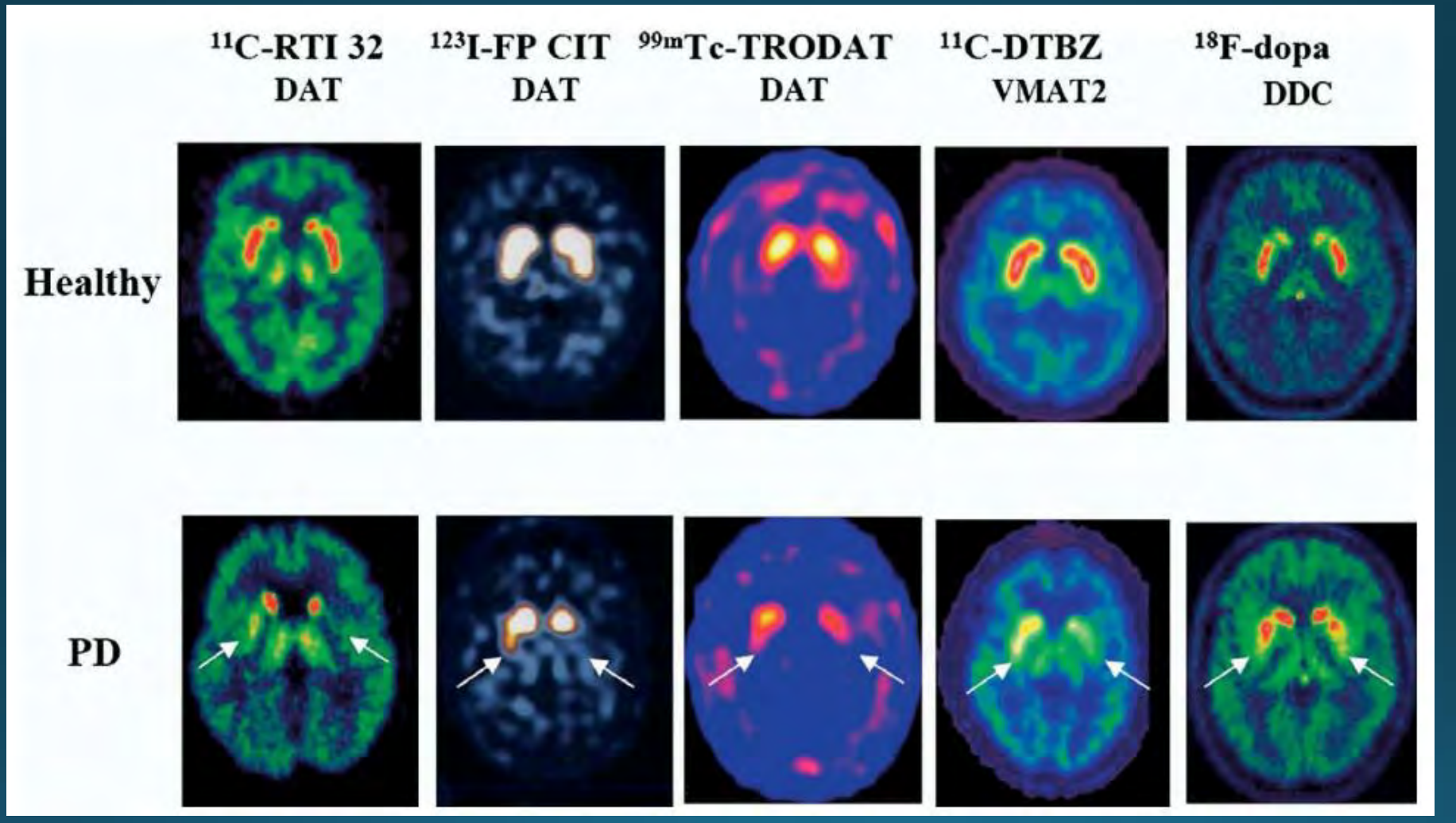
** A DAT named DATscan has been approved by FDA recently.

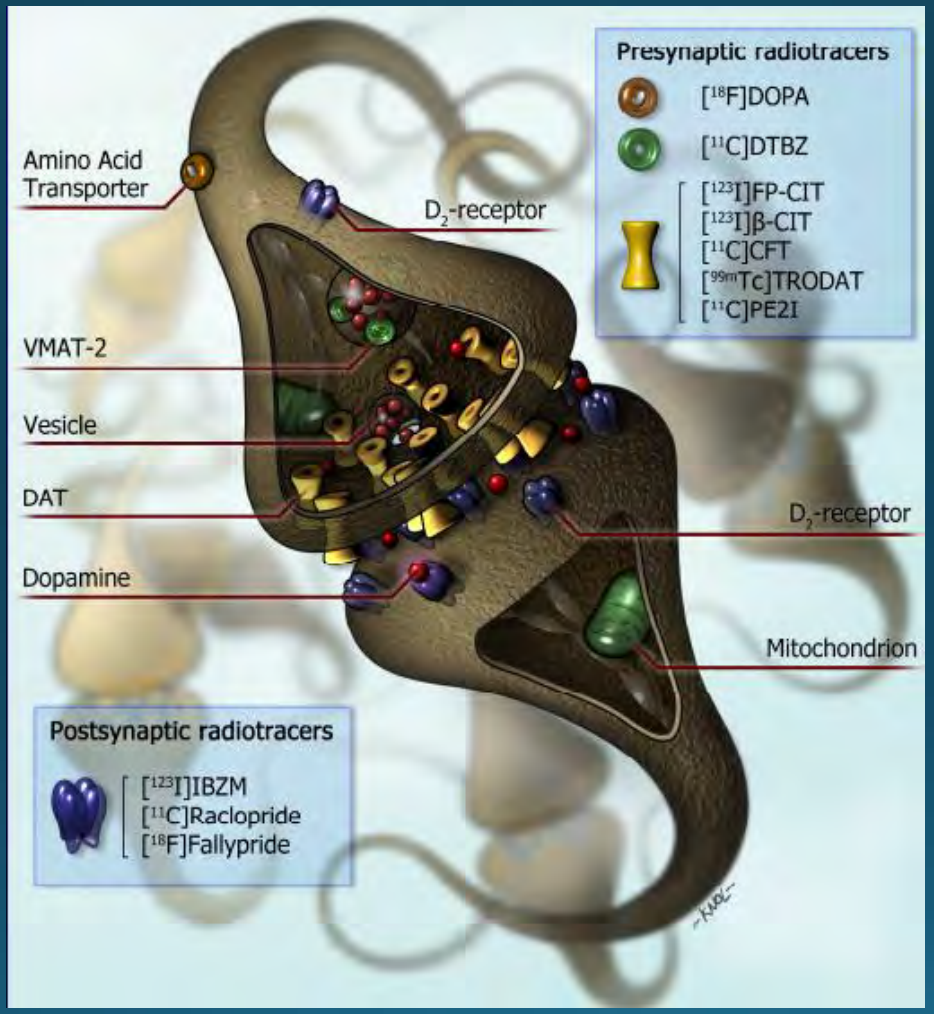
2.vesicular monoamine transporters(VMAT): DTBZ for PET

3.Dopa-decarboxylase(DDC): F18-dopa to estimate dopamine synthesis

DATscan: 1. for use with SPECT imaging; 2. contains I-123 labeled ioflupane
Images DaT in the stiatum of the brain
Approved in Europe since 2000 and other 31 countries
Estimated exposure of 216000 patients as of june, 2009




^{11}C-RTI 32
DAT
^{123}I-FP CIT
DAT
^{99m}Tc-TRODAT
DAT
^{11}C-DTBZ
VMAT2
^{18}F-dopa
DDC
Healthy
PD



Booij and Kemp. EJNMMI 2008

Rationale of D2 receptor binding tracer research

- **Presynaptic tracers** is a reliable criterion to distinguish *PD from healthy subjects or essential tremor or other forms not characterized by loss of presynaptic DA cells*.
- For therapeutic and prognostic reasons it is necessary to differentiate between PD and atypical PD due to other neurodegenerative diseases.Post-mortem shows 20% of clinical dx PD have atypical syndrome.
- Presynaptic tracer can not differentiate PD and atypical PD syndrome.
- Patients with PD show a normal or upregulated **postsynaptic D2 receptor,** whereas patients with atypical PD show reduced binding indicating *decreased receptor density*.

Table 3	Radiotracers of postsynaptic dopaminergic function
Imaging techniques	**Radiotracers**
PET	D1 receptor probes
	[^{11}C]-R-(+)-8-chloro-2,3,4,5-tetrahydro-3-methyl-5-phenyl-1H-3-benzazepine-7-ol ([^{11}C]-SCH- 23390)
	[^{11}C]-(+)-8-chloro-5-(7-benzofuranyl)-7-hydroxy-3-methyl-2,3,4,5-tetra-hydro-lH-3-benzazepine ([^{11}C]-NNC-112)
	D2/3 receptor probes
	[^{11}C]-raclopride
	[^{18}F]-fallypride
	[^{18}F]-desmethoxyfallypride
	[^{11}C]-*N*-methylspiperone
	[^{18}F]-benperidol
	[^{11}C]-FLB-457
	[^{11}C]-norpropylapomorphine (NPA) [^{11}C](+)propyl-9-hydroxynaphthoxazine (PHNO)
	[^{11}C]-epidepride
SPECT	D2/3 receptor probes [^{123}I]IBZM [^{123}I]epidepride

Nandhagopal, R. et al. Neurology 2008;70:1478-1488

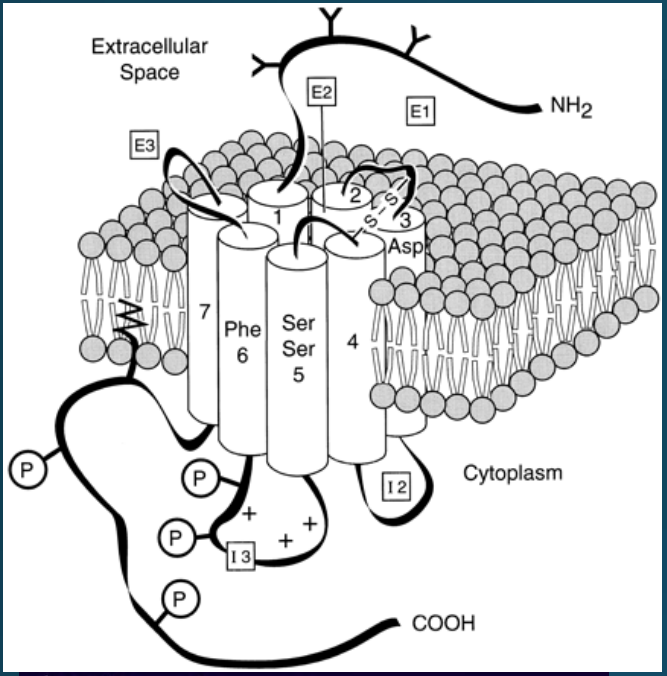
4.D2 dopamine receptors: on clinical research IBZM for SPECT and raclopride for PET

postsynaptic, dopaminergic involvement, help with unclear PD(PD vs atypical parkinsonism)

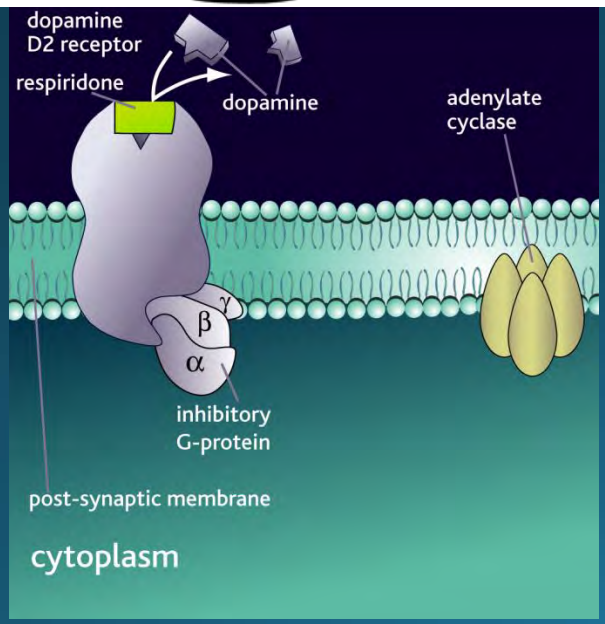
-a class of metabotropic G protein-coupled receptors that are prominent in the vertebrate central nervous system (CNS). The neurotransmitter dopamine is the primary endogenous ligand.

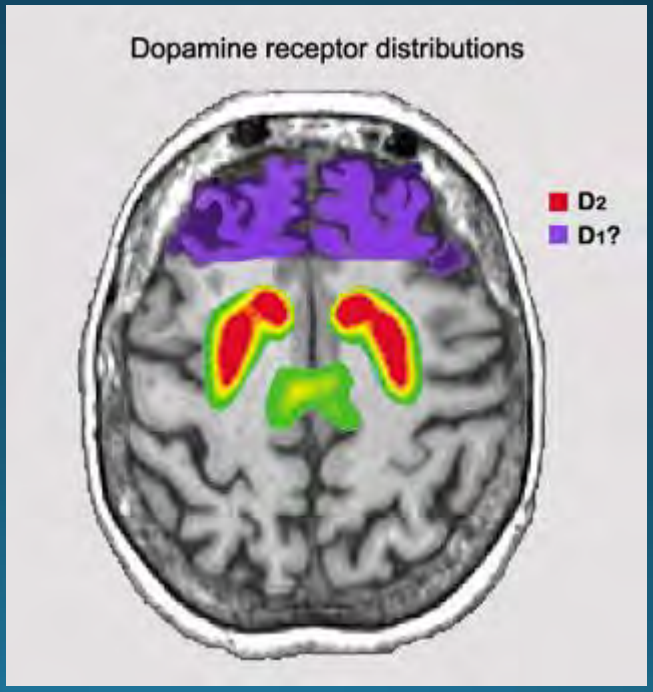
-dopamine receptors are common neurologic drug targets; antipsychotics are often dopamine receptor antagonists while psychostimulants are typically indirect agonists of dopamine receptors.

-Activation of D2-like family receptors is coupled to the G protein Gαi, which directly inhibits the formation of cAMP by inhibiting the enzyme adenylate cyclase.


Extracellular Space
E2
E1
NH2
E3
1
2
3
S-S
Asp
7
Phe 6
Ser Ser 5
4
P
P
P
P
+
+
+
I3
I2
Cytoplasm
COOH

IC3
IC1
IC2
C
TM6
TM4
TM7
TM3
TM1
TM5
TM2
N

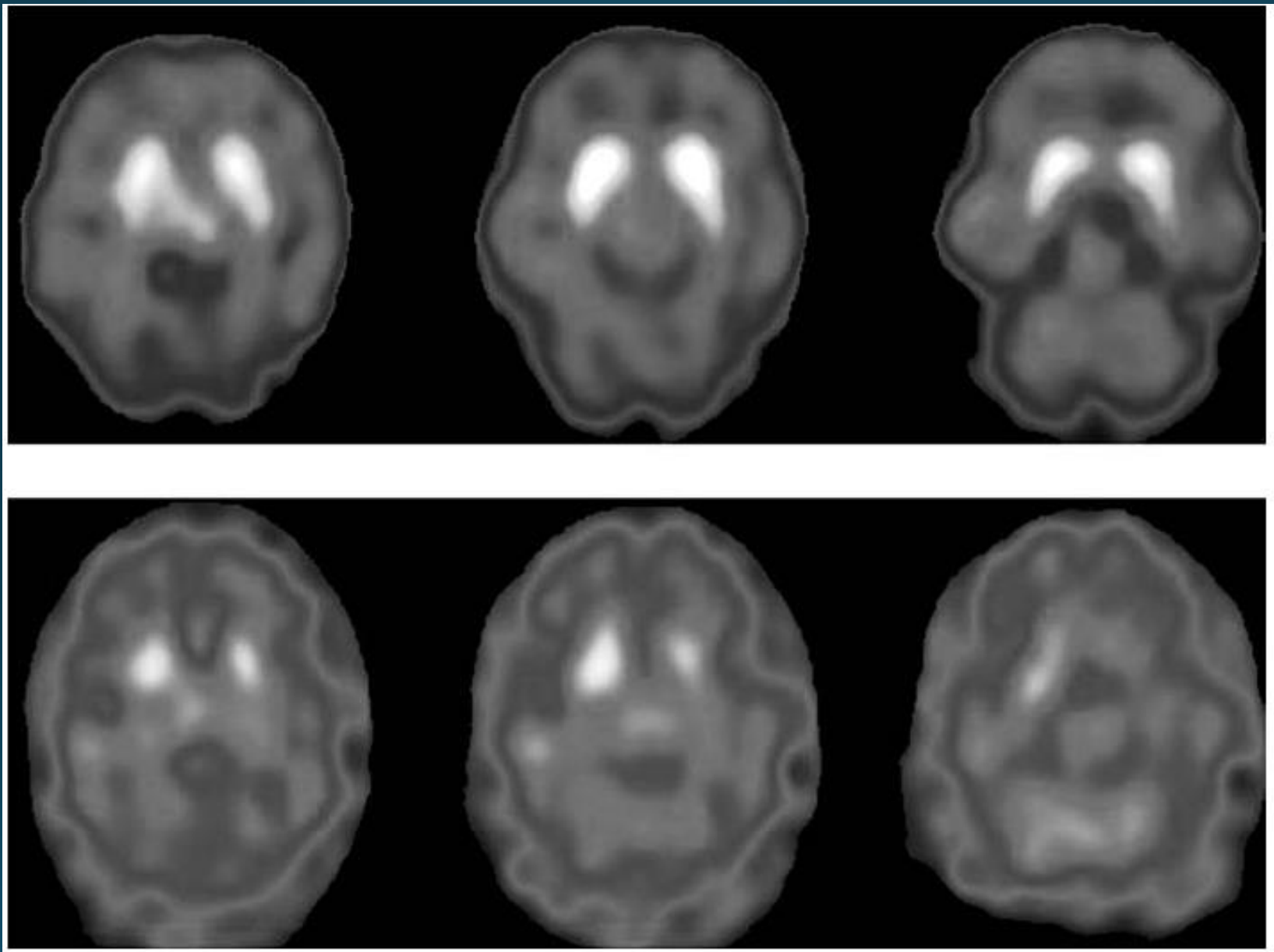

dopamine D2 receptor
respiridone
dopamine
adenylate cyclase
β
γ
α
inhibitory G-protein
post-synaptic membrane
cytoplasm

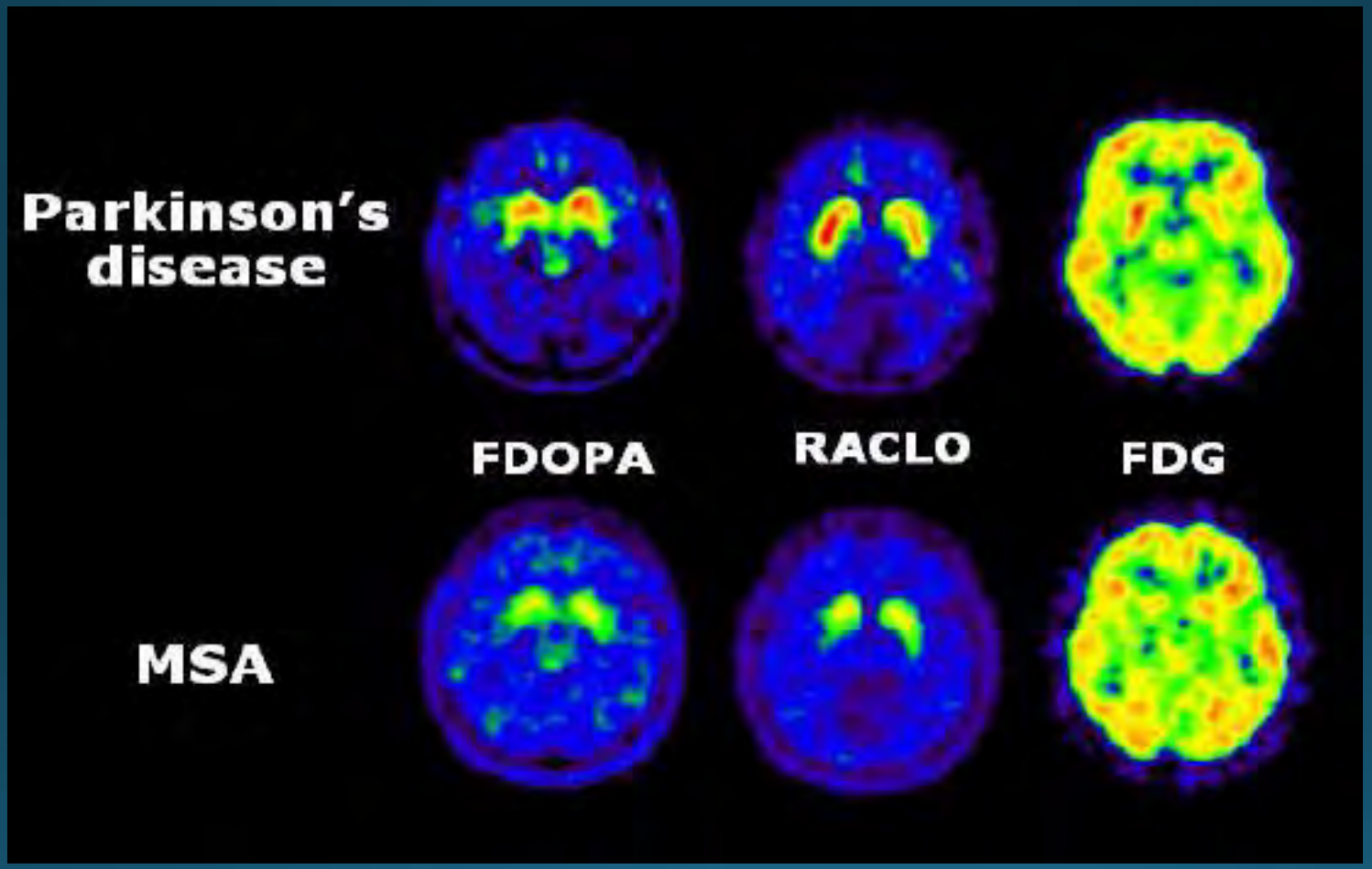

Dopamine receptor distributions
D2
D1?

D2 receptor

D2 receptor binding radiotracers

- **Raclopride** is a synthetic compound that acts as an antagonist on D2 dopamine receptors. It can be radiolabelled with the carbon-11 radioisotope and used in positron emission tomography (PET) scanning to assess the degree of dopamine binding to the D2 neuroreceptor
- **IBZM** (abbreviation for *iodobenzamide*) is a chemical substance. Pharmaceutically it is a dopamine antagonist and it can be used by as a radioactive tracer for SPECT where the radioactive isotope is iodine-123


PD
MSA



Antonini, 1997

syndromes	integrity nigrostriatal pathway	binding to D_2 receptors
	DAT SPECT	[^{123}I]IBZM SPECT
PD	loss	normal/increased
MSA	loss	reduced
PSP	loss	reduced
ES	no loss	normal

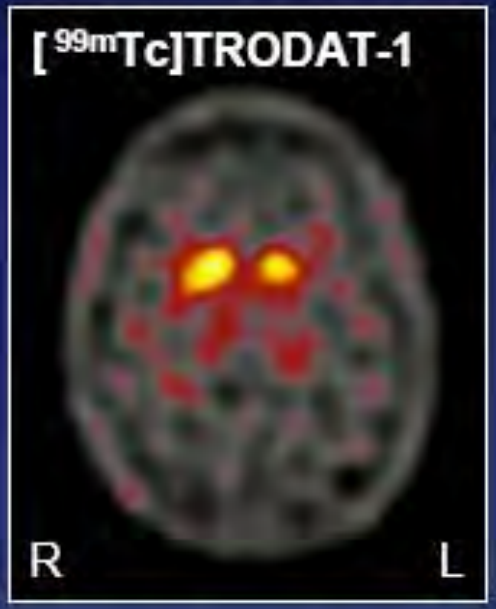
Comparison of SPECT IBZM and PET Raclopride

- I123-IBZM: widespread clinical use; favorable half life(13.2 hr); comparably lower sensitivity and image quality

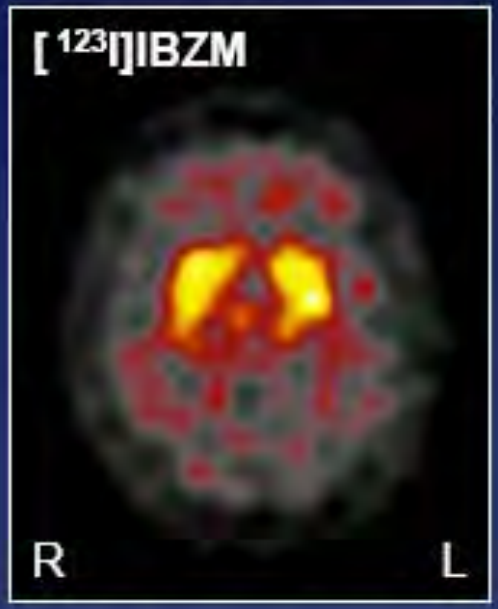
- C11-Raclopride: higher sensitivity and image quality; a spatial resolution of 3-5 mm; brief half life (20 min) need local cyclotron; a similar product F18-DMFP with half life of 110 min may be more favorable

Future

Simultaneous assessment of the pre- and postsynaptic dopaminergic system: IPS



rt: 0.72 lt: 0.48



rt: 0.86 lt: 0.89

What is the next??

- functional imaging can be enormously useful in **detecting preclinical disease**. Functional imaging studies will continue to provide substantial insights into the **mechanisms** that underlie both motor and neuropsychiatric complications of advanced disease and of therapy. Studies of natural history and using markers of aberrant cell function may shed light on disease pathogenesis. Perhaps most excitingly, functional imaging studies conducted in patients with PD provide an unparalleled opportunity to assess the multiple roles of dopamine in the brain,. Future advances in molecular imaging, perhaps allowing quantitative in vivo visualization of gene and protein expression, will result in even richer rewards.
- One of the major challenges facing all investigators interested in neurodegenerative diseases is the capacity to **assess the effects of disease-modifying therapies**, including neuroprotection and cell-based treatments designed to reverse disease. While functional imaging should be an ideal means by which to do this, existing methods have, for reasons that are not fully understood, proved highly unsatisfactory. Development and characterization of novel imaging markers to assess disease progression and the effects of therapeutic interventions is likely to form a major focus of research in the next decade.
- The benefits of imaging studies must be considered in the context of **challenges** that are both potential and already very real. PET is expensive and studies of dopaminergic function are available at only a minority of centers. Presymptomatic detection of disease, while potentially very useful in a research setting, is fraught with considerations of how one will use the resulting information, particularly as there is currently **no established therapy** to prevent the emergence or progression of disease

Thank you!

Lauren K. Toney
Nuclear Medicine

Parkinson's Disease

Parkinson's Disease (PD)

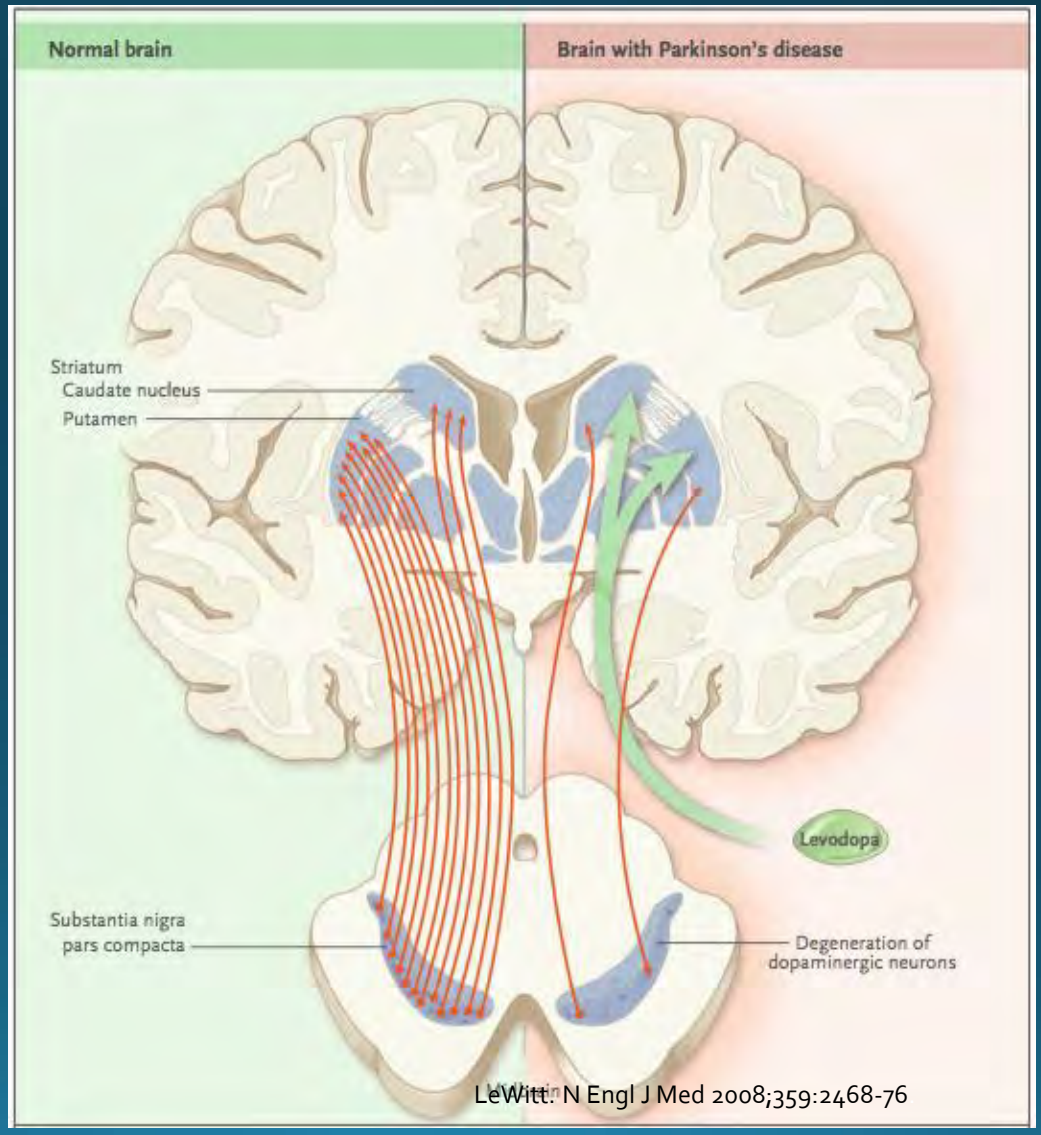
- PD is a neurodegenerative disorder
- Characteristic findings: resting tremor, rigidity, slowed movement, decreased dexterity, small handwriting, flexed posture, gait disorder, imbalance, dementia.
- Mean age of onset 57 years
- Affects 1-2% of population over age 60
- Highly varied collection of symptoms and pace of progression

Pathogenesis of PD

- 11 genetic forms identified (LRRK2)
- 10-15% affected have suggestive family history
- Unknown cause for sporadic cases (oxidative stress, Nrf2)

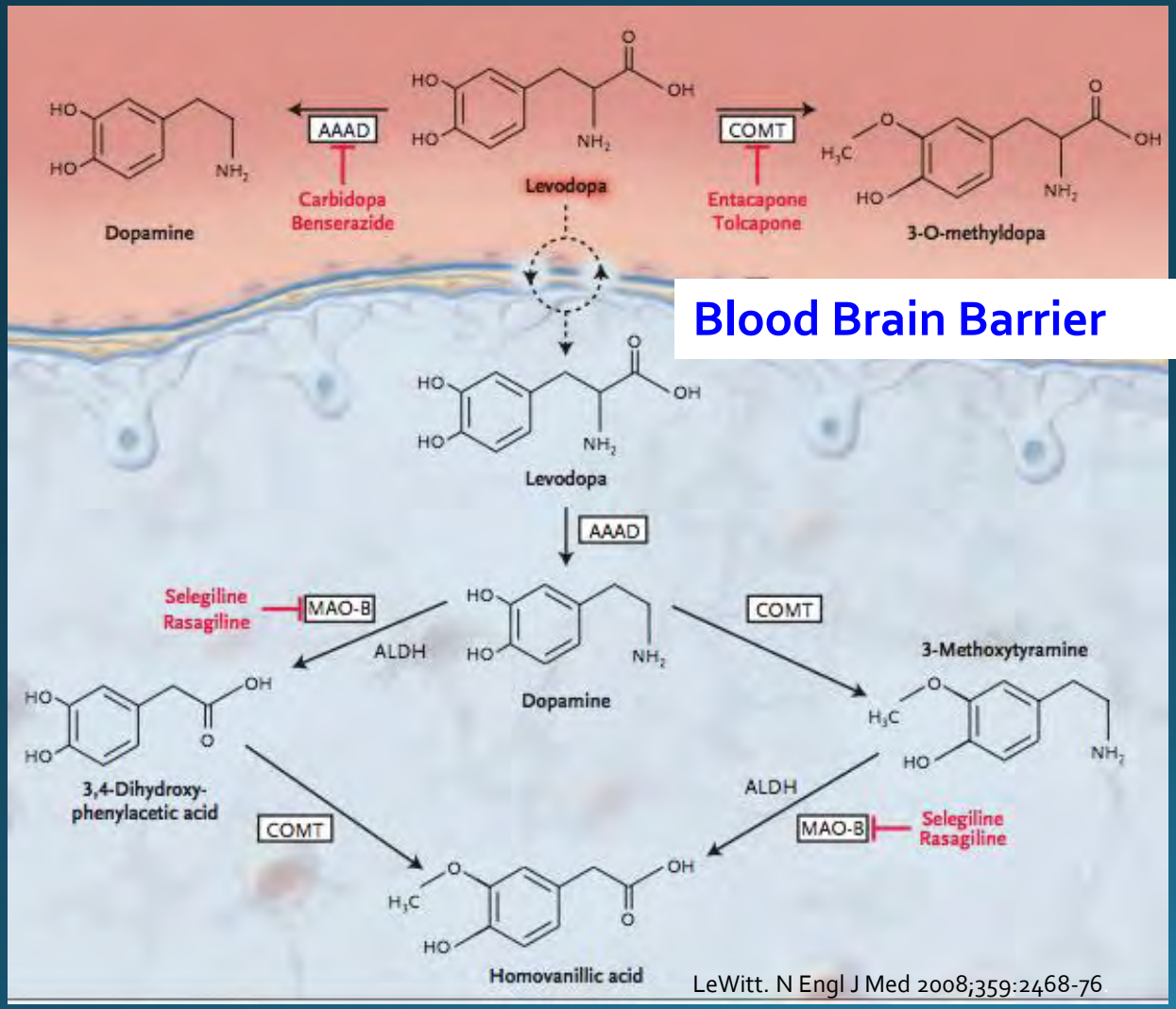
PD is neurodegenerative

- Motor impairments arise from loss of dopaminergic neurons arising from substantia nigra
- Nerve loss of ~50% required for symptoms



LeWitt. N Engl J Med 2008;359:2468-76

Treatments



LeWitt. N Engl J Med 2008;359:2468-76

1. Levodopa
2. Dopaminergic agents (ropinirole, pramipexole)
3. Inhibitors of peripheral metabolism (by AAAD, COMT)
4. Inhibitors of CNS metabolism (by MAO-B)

Clinical Use of Levodopa

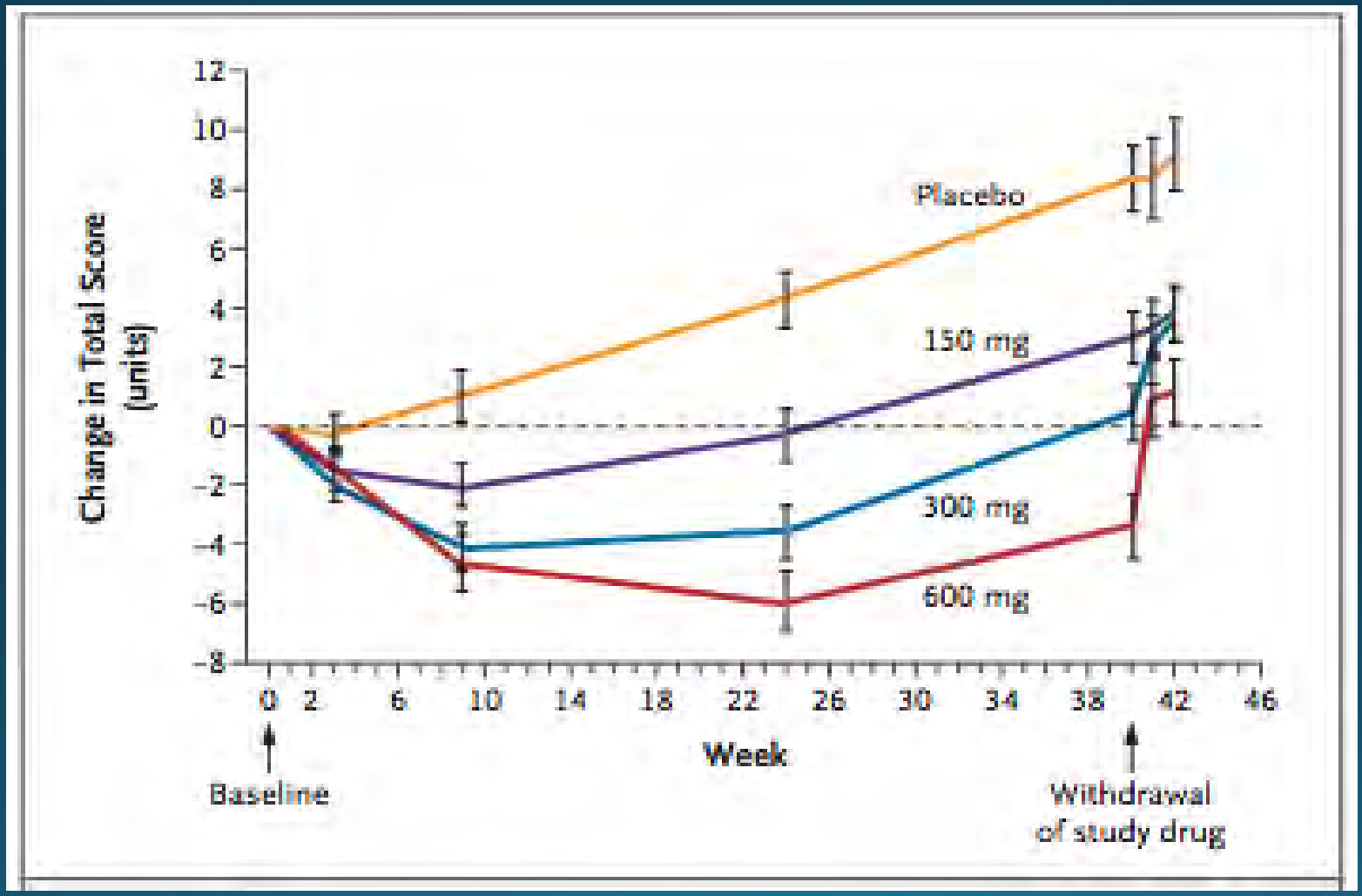
1. Diagnostic tool
2. Almost always combined with carbidopa
3. Does not always help all symptoms
4. Can have blunted response over time

   (use alternative monotherapy or use as polytherapy)
5. Significant side effects (dyskinesias)

Clinical Evidence for Levodopa

- Earlier versus Later Levodopa Therapy in Parkinson Disease (ELLDOPA NEJM 2004)
- Concern about levodopa hastening neurodegeneration despite symptomatic control.
- Randomized 361 patients with early PD to placebo or one of three doses of levodopa (with carbidopa)

ELLDOPA



LeWitt. N Engl J Med 2008;359:2468-76.

ELLDOPA Conclusions

1. Levodopa improves signs and symptoms in dose-dependent manner
2. Levodopa does not hasten progression of underlying disease
3. As part of study, subjects underwent B-CIT SPECT at baseline and week 40:

   slower decline in striatal uptake in placebo group compared with 3 treatment groups

Results

Change in dopaminergic binding from 0 to 40 weeks on B-CIT SPECT imaging:

	Placebo	Levodopa		
		150mg/d	300mg/d	600mg/d
Change (%)	-1.4	-6.0	-4.0	-7.2

- Does levodopa accelerates the loss of nigrostriatal dopamine nerve terminals?
- Does levodopa modify binding of β-CIT or down-regulate DAT?
- Does falling dopamine in placebo group lead to compensatory increase in DAT (hence increased β-CIT binding)?

Disparity between clinical outcomes and radiotracer imaging in PD

- ELLDOPA: levodopa controls symptoms and does not promote neurodegeneration, but B-CIT imaging shows less loss in binding with placebo groups.
- Two smaller studies comparing

  (1) Whone AL, et al. REAL-PET. Ann Neurol 2003
  levodopa vs. ropinirole

  (2) Parkinson Study Group. CALM-PD. JAMA 2002
  levodopa vs. pramipexole

Surrogate endpoints

- Clinical endpoint (CE) – how a patient feels, functions, or survives

  Unified Parkinson's Disease Rating Scale (UPDRS)

- Surrogate endpoint (SE) – a biomarker substitute for a CE

  cholesterol (death from heart disease)

  PSA (survival in prostate cancer)

  ? Radiotracer imaging in PD

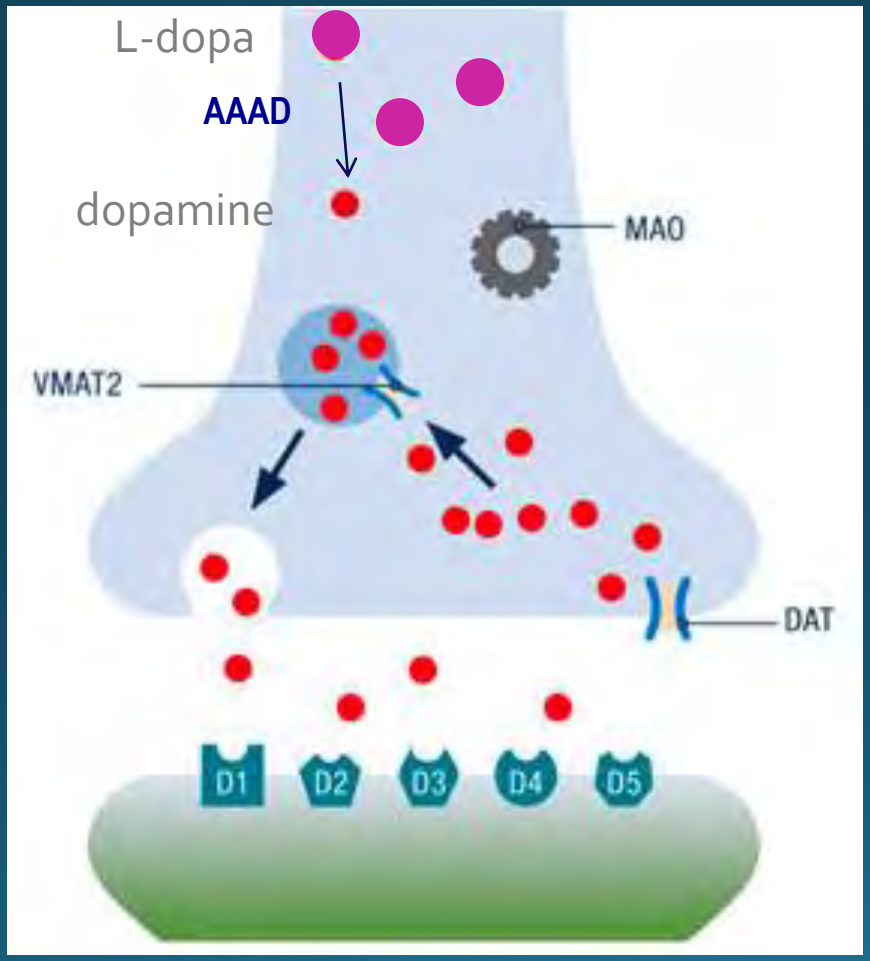
Surrogate endpoint failures

Advantage of SE's: save time and money, shorten clinical trial

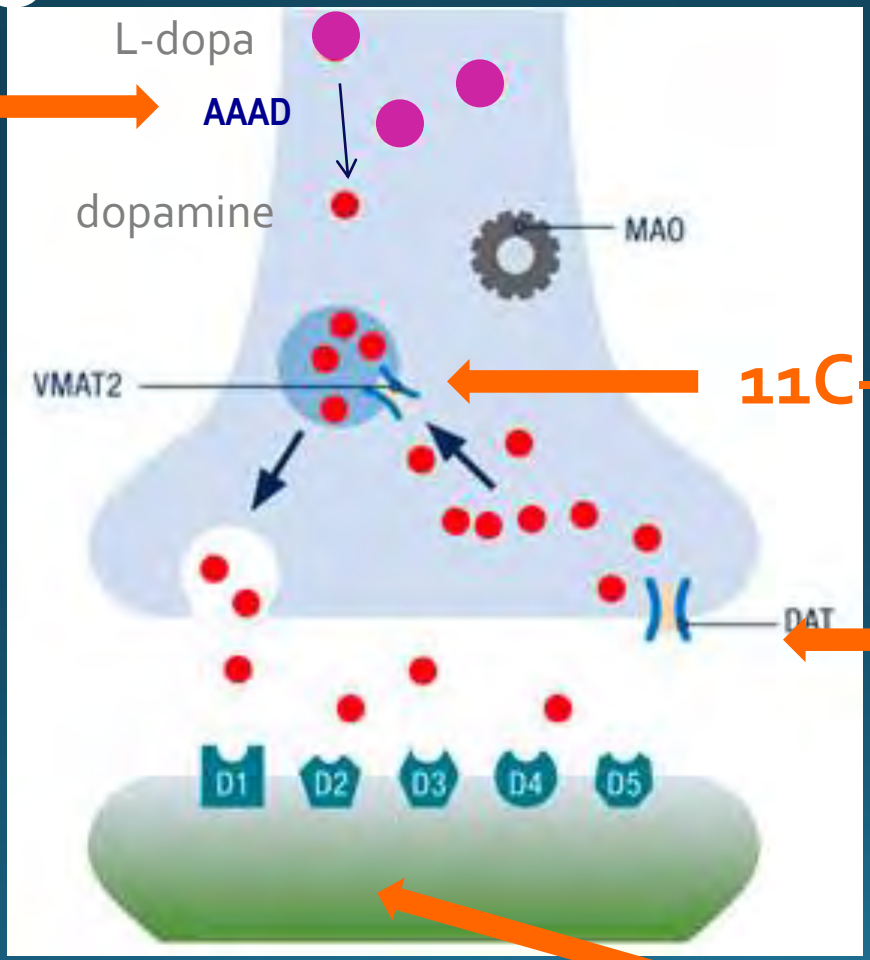
Disadvantage of SE's – one example
- CE= cardivascular mortality in post-MI patients
- SE = Ventricular arrythmias
- Encainide and flecainide approved on basis of reducing SE
- Subsequently shown to increase mortality (CAST Trial. NEJM. 1992).

Multiple trials needed to establish relationship between a SE and a CE.

Dopaminergic nerve terminal



Targets of radiotracers in PD imaging



18F-dopa

11C-DTBZ

123I-B-CIT

FDG-PET

123I-IBZM

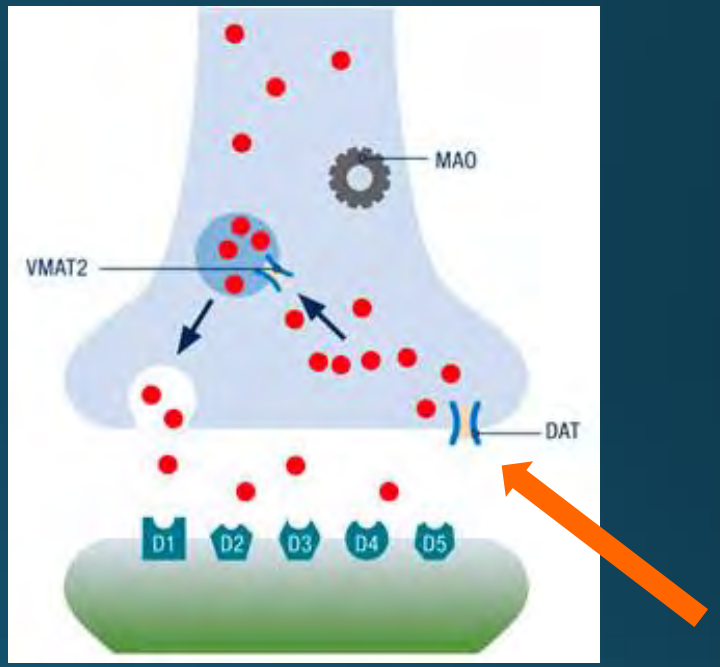
Uses of radiotracer imaging in PD

1. Exploring the biologic process (upregulation of D2 receptor)
2. Study diagnosis and prognosis (PD versus ET))
3. Therapy development and evaluation (early, late)
4. Primary outcome in clinical trials
5. Assisting in choosing and monitoring response to therapy

DAT imaging in PD

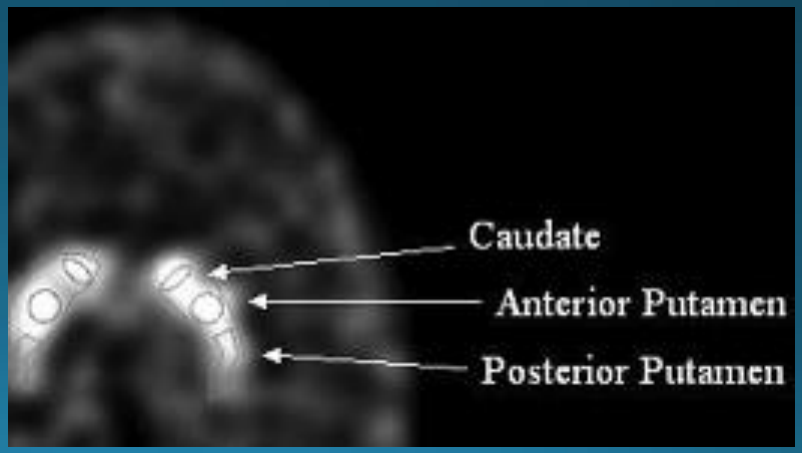
Radiotracers:

- 123I beta-CIT tropane (B-CIT)
- 123I FP-CIT ioflupane (DATSCAN)
  - Approved 1/20/11
- 99mTc-TRODAT-1 altropane (TRODAT)
- 18F FP-CIT

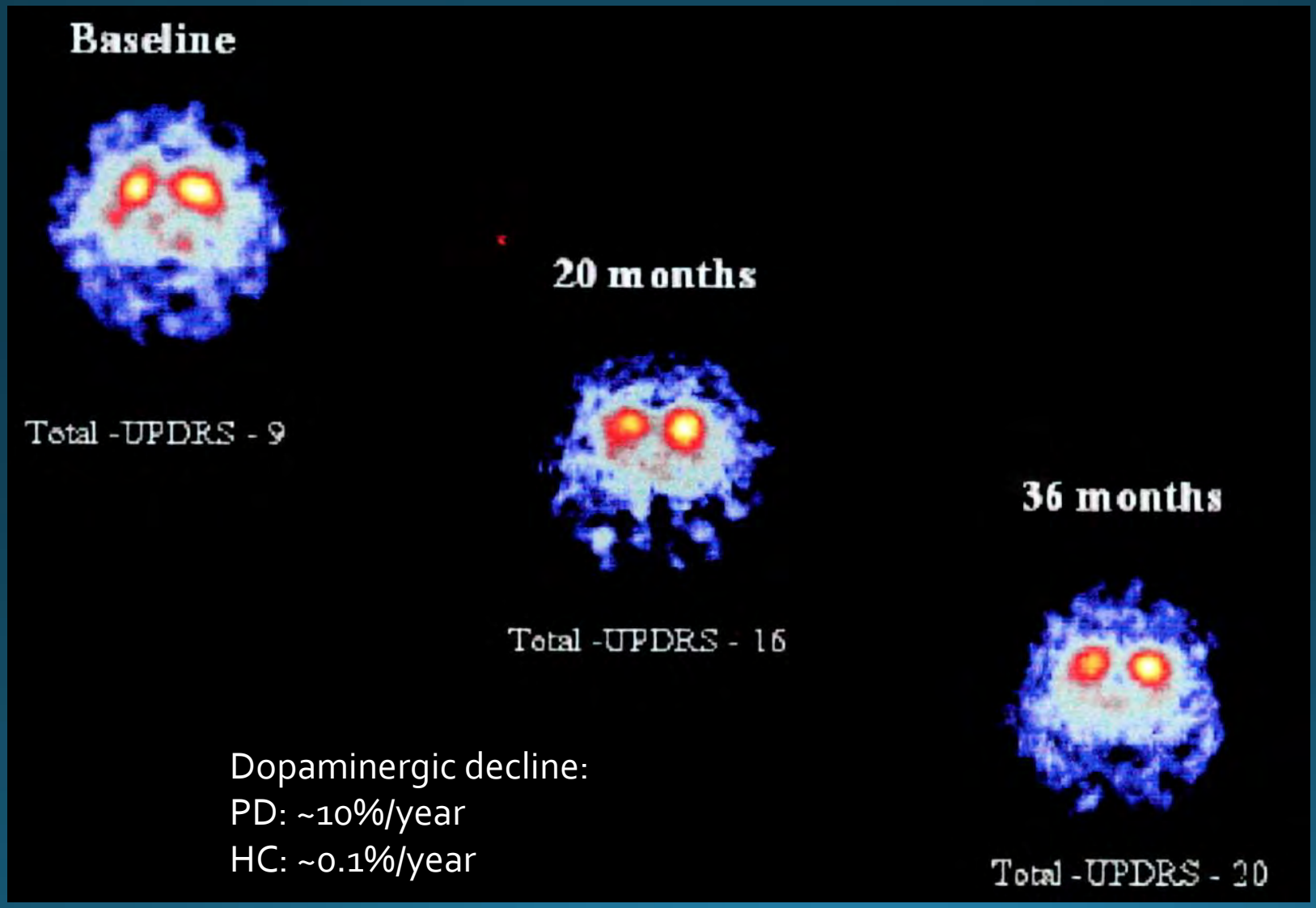


Findings:

1. Markedly reduced DAT density
2. Putamen > caudate
3. Asymmetric
4. Correlates with clinical severity



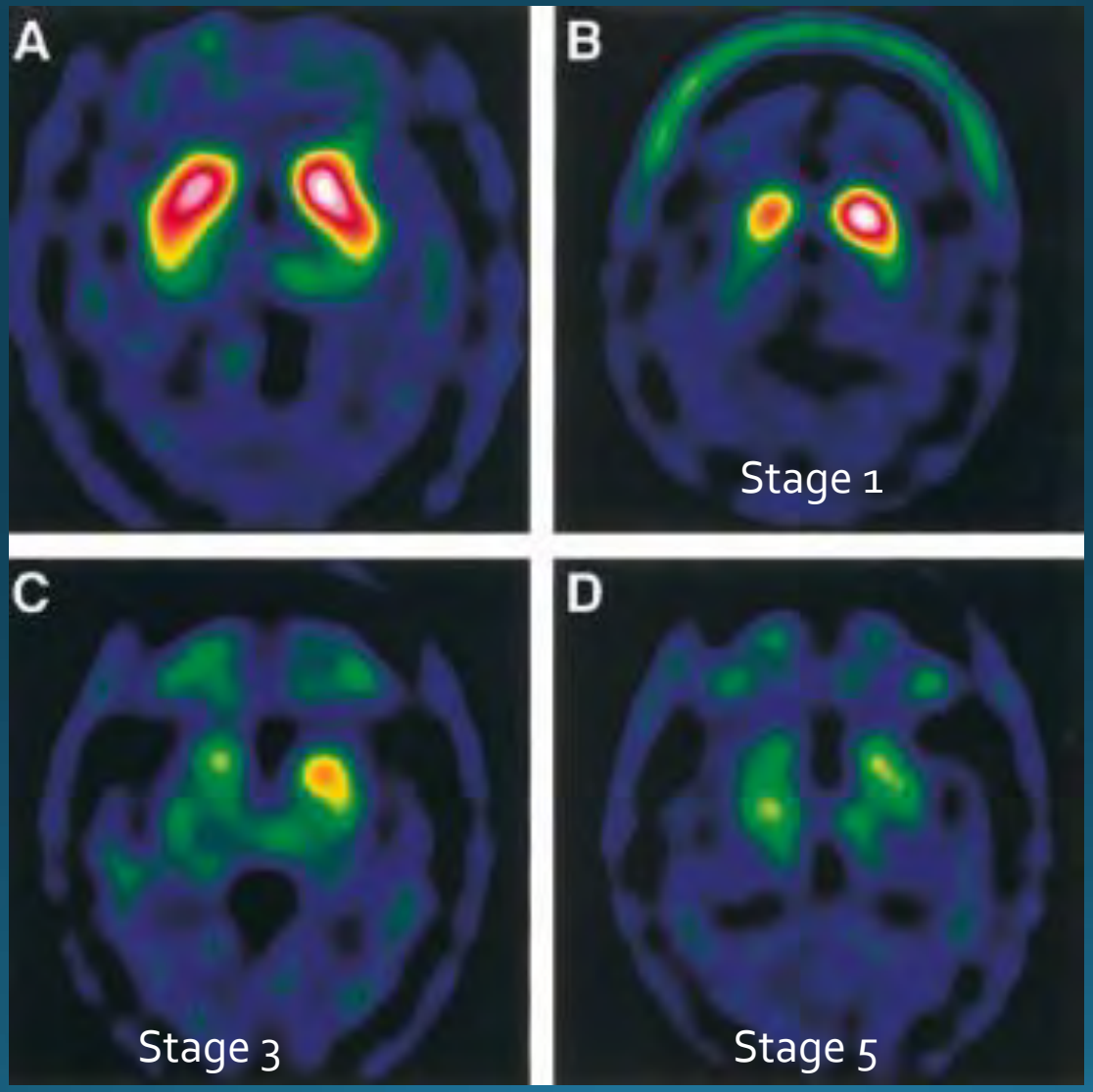
123I-β-CIT SPECT in PD progression over 3-year period



Dopaminergic decline:
PD: ~10%/year
HC: ~0.1%/year

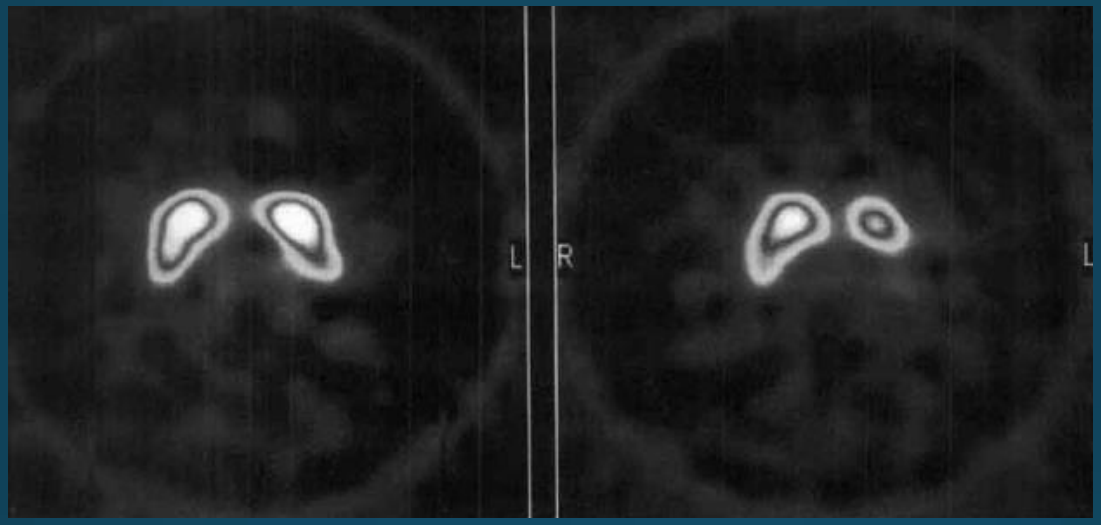
Marek K et al. Neurology 2001;57:2089-2094

Tc-99m-TRODAT-1 SPECT reflects symptom severity/side

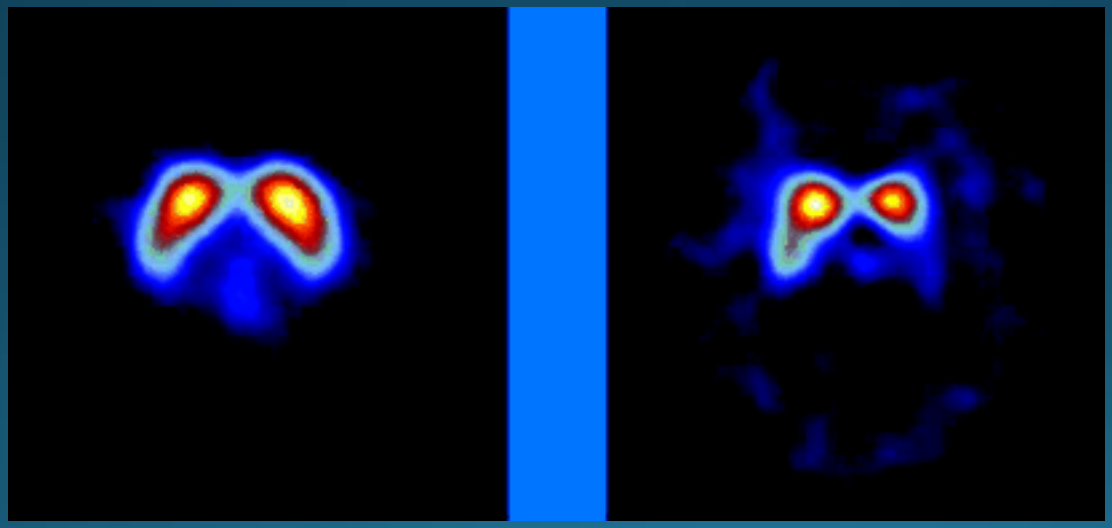


Weng, YH. Jnucl Med 2004. Marc 45(3).

I-123-B-CIT SPECT in Hemiparkinsonism



Marek KL. Neurology. 1996 Jan;46(1):231-7.

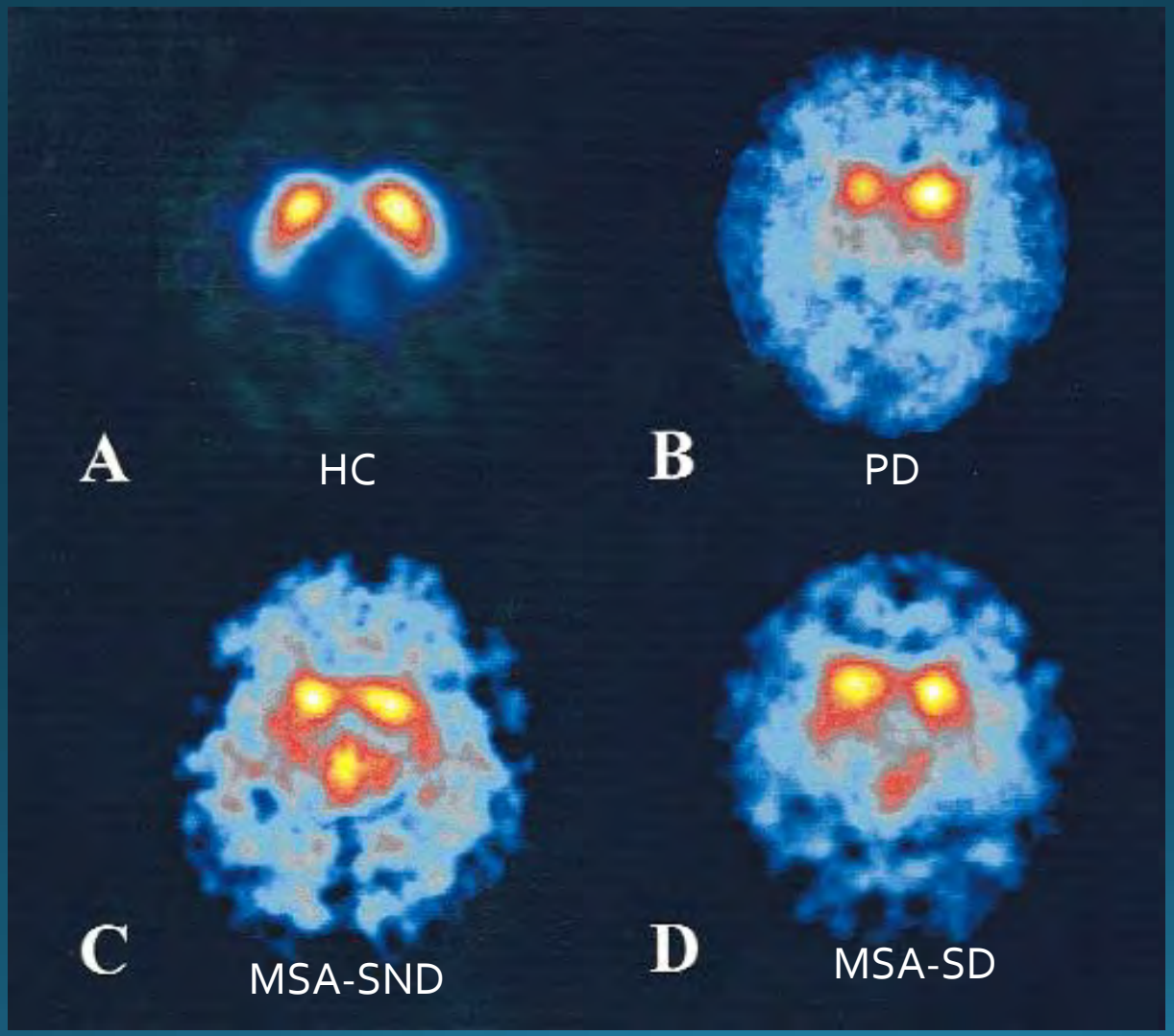


Seibyl J. Institute for Neurodegenerative Disorders.

Healthy control

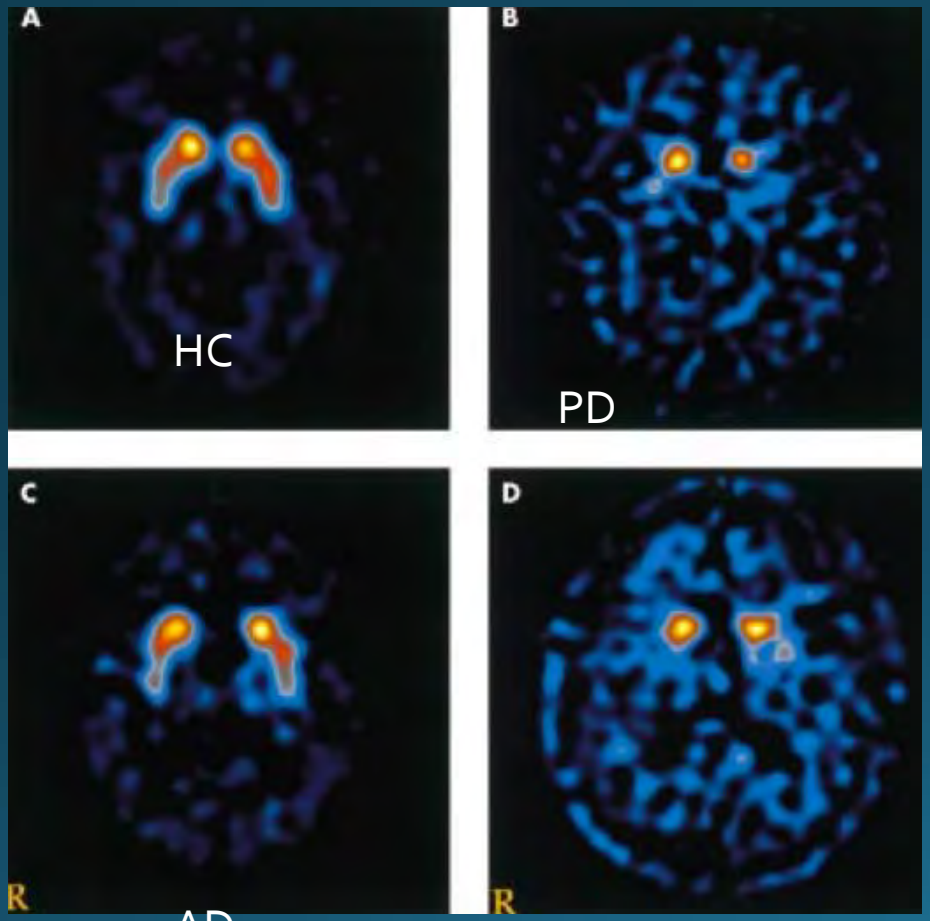
Right

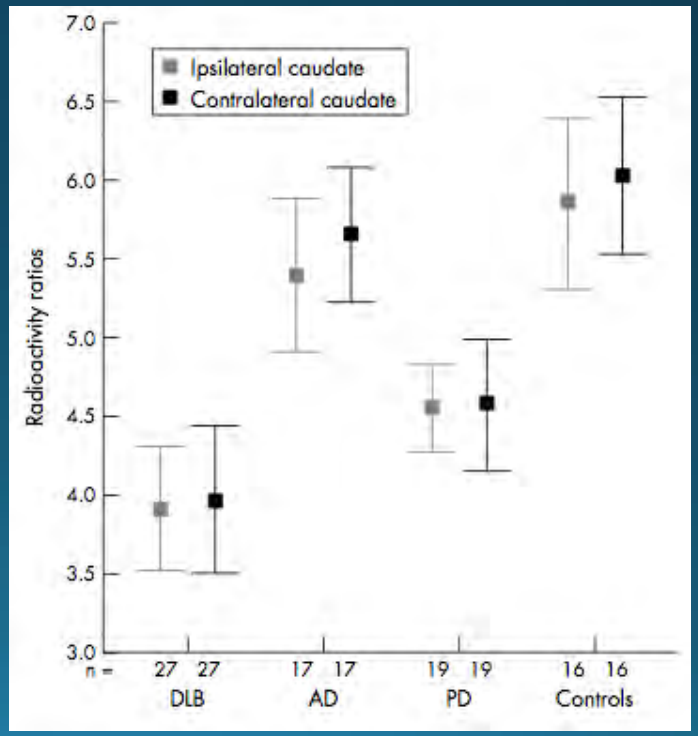
123I-B-CIT SPECT in may distinguish PD versus MSA subtypes via symmetry index



Varrone A. Movement Disorders, 16: 1023–1032

FP-CIT SPECT in PD versus AD and DLB

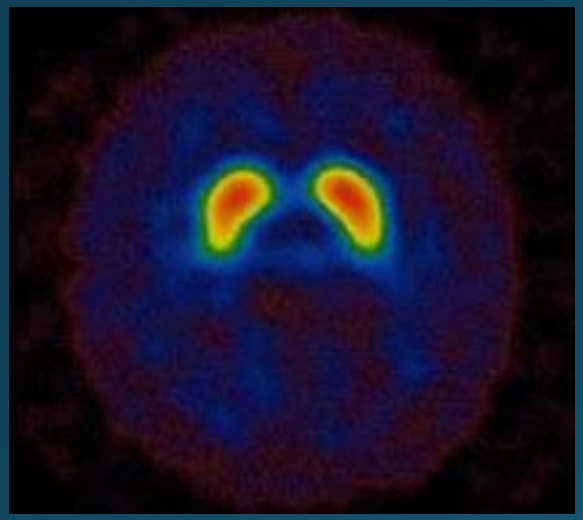




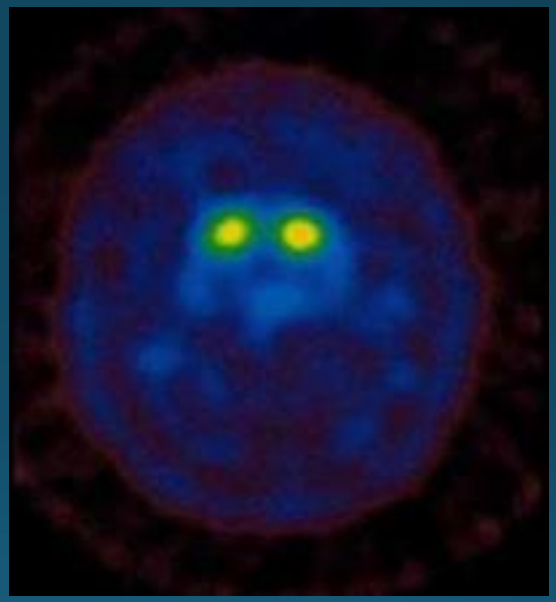
Walker Z. J Neurol Neurosurg Psychiatry. 2002 Aug;73(2).

FP-CIT in PD vs Essential Tremor

ET

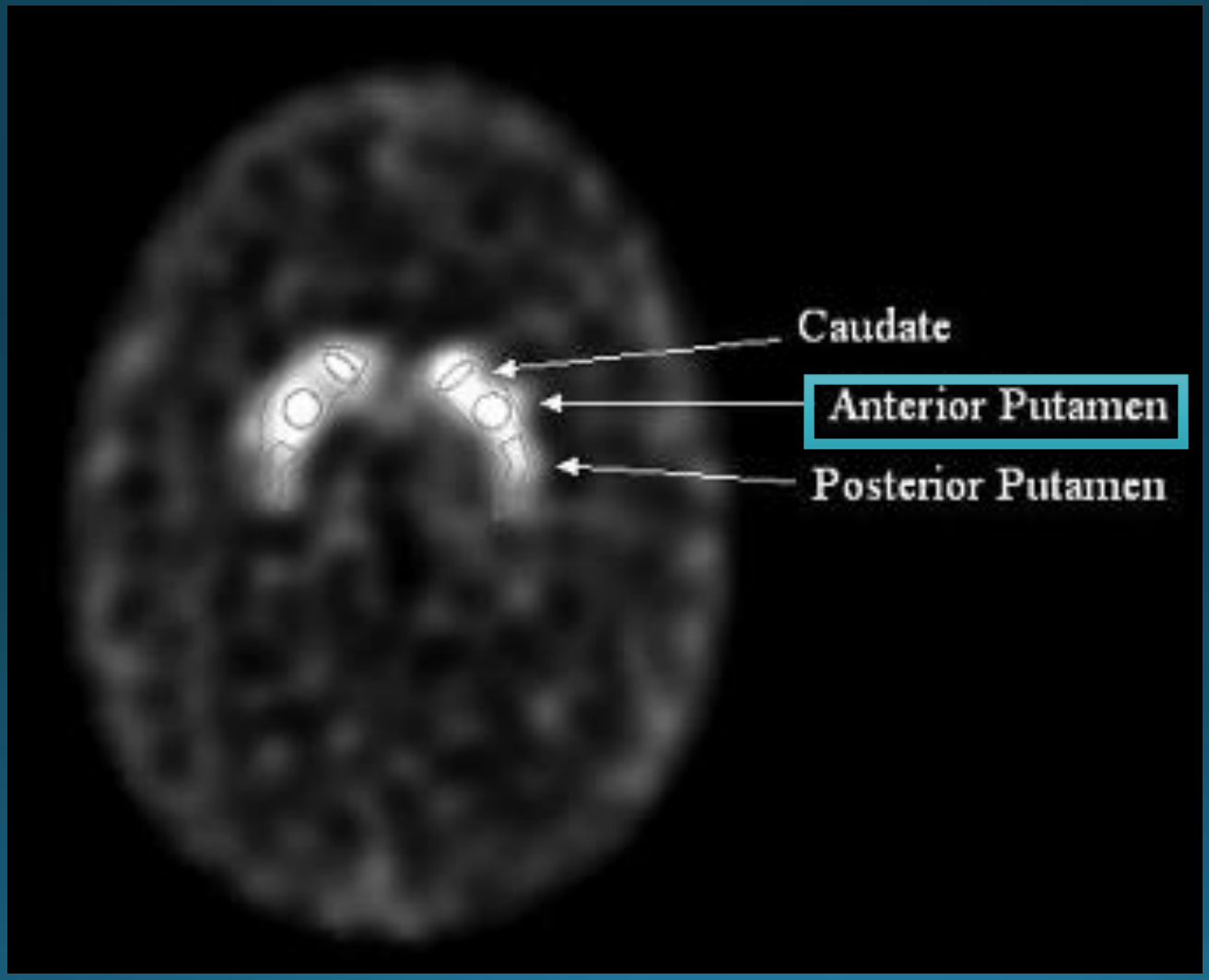


PD



Takada S. Ann Nucl Med. 2006 Aug;20(7

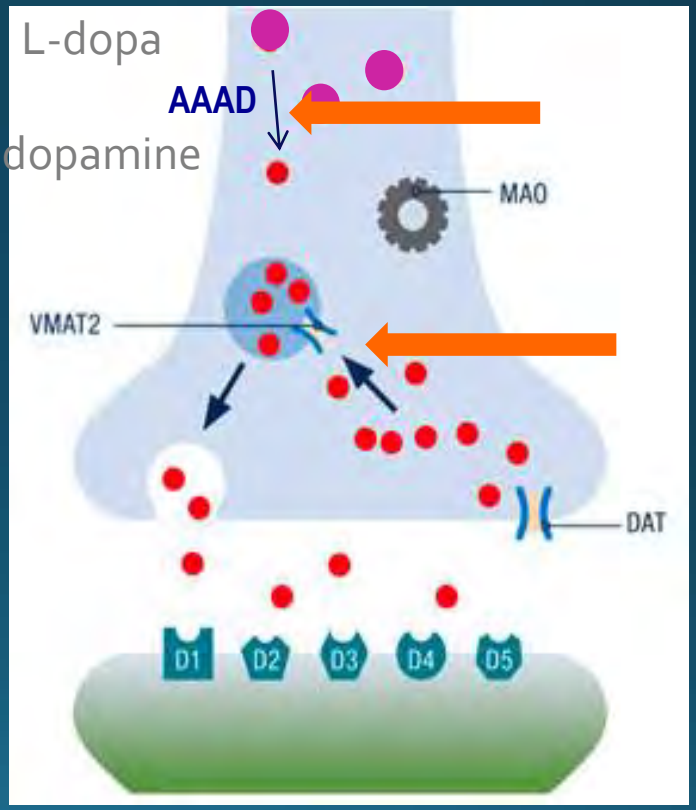
Tc-99m TRODAT SPECT in PD plus anxiety/depression



Weintraub B. J Nucl Med. 2005 Feb;46(2).

[^{18}F]fluorodopa (F-dopa) PET and (+)-[^{11}C]dihydrotetrabenazine (DTBZ) PET

- Generally same findings as DAT imaging



VMAT2 imaging confirms olfactory deficit mechanism

- Previously: PD odor dysfunction correlated with hippocampal dopamine loss
- Observed: Hyposmia in AD is related to hippocampal cholinergic loss
- Hypothesis: olfactory dysfunction in PD related to hippocampal cholinergic loss.
- PD diagnosis confirmed by VMAT2 PET (11C-DTBZ).
- AchE imaging with 11C-PMP (methyl-4-piperidinyl propionate) PET
- Dynamic imaging with kinetics models

Robust correlation between hippocampal cholinergic activity and odor identification scores in non-demented PD patients.

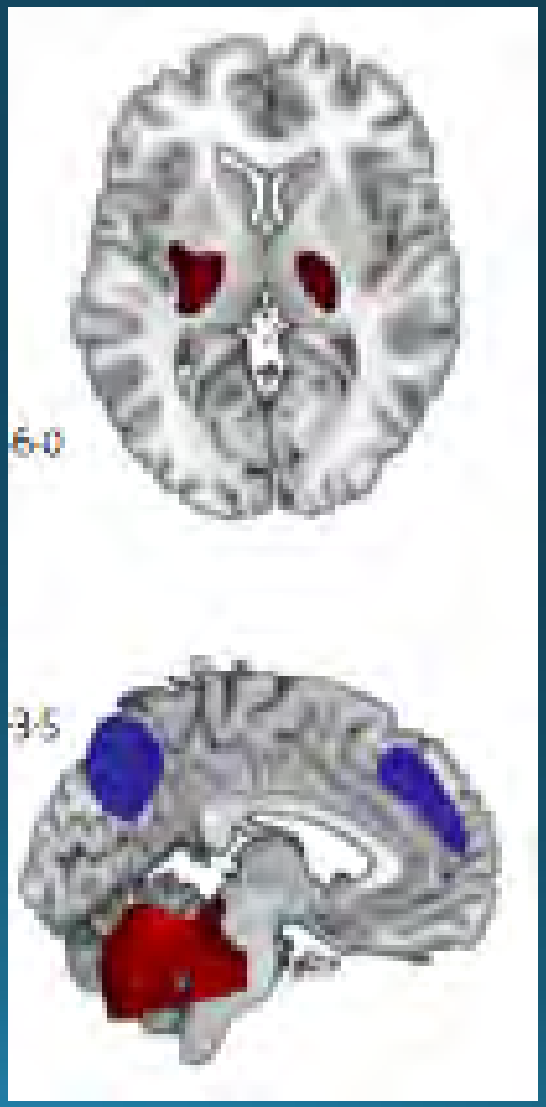
Bohnen NI. Brain. 2010 Jun;133(Pt 6):1747-54

[^{18}F]fluorodeoxyglucose (FDG) PET

Disease-related pattern in PD:

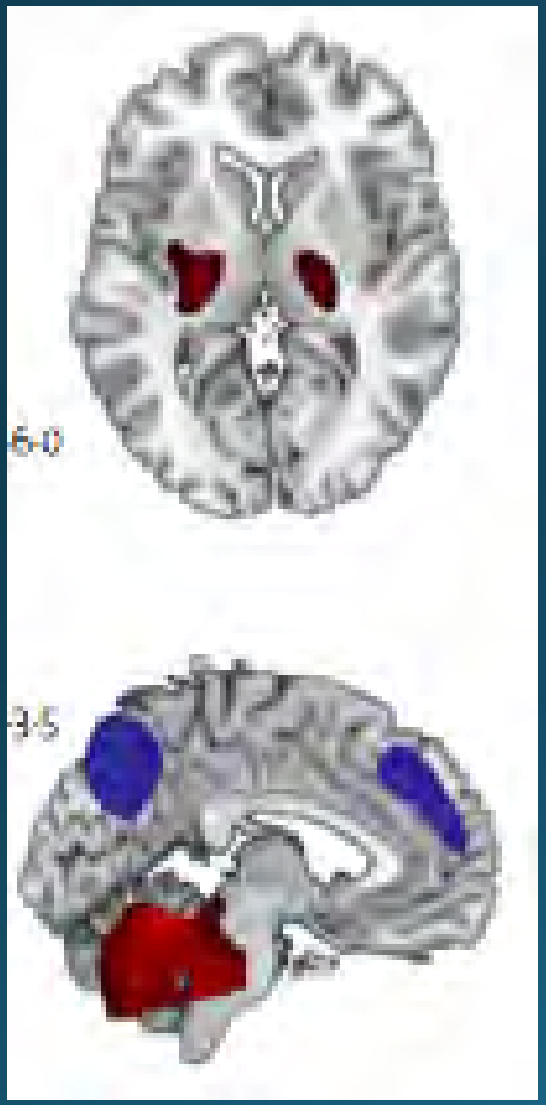
hypermetabolism: pallidothalamic, pontocerebellar

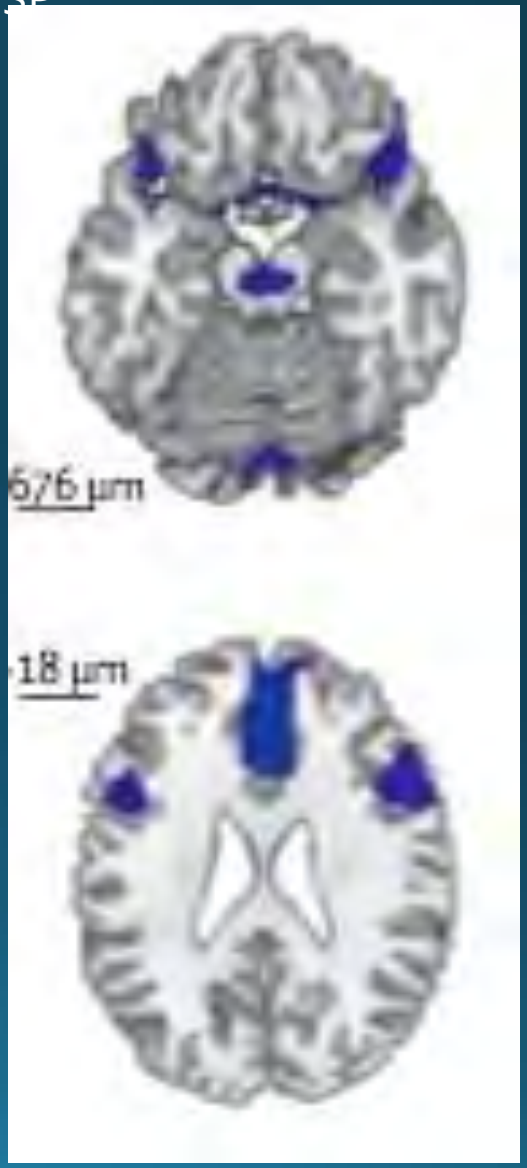
hypometabolism: lateral premotor cortex, supplementary motor area, parietooccipital association region



PD

MSA
PSP

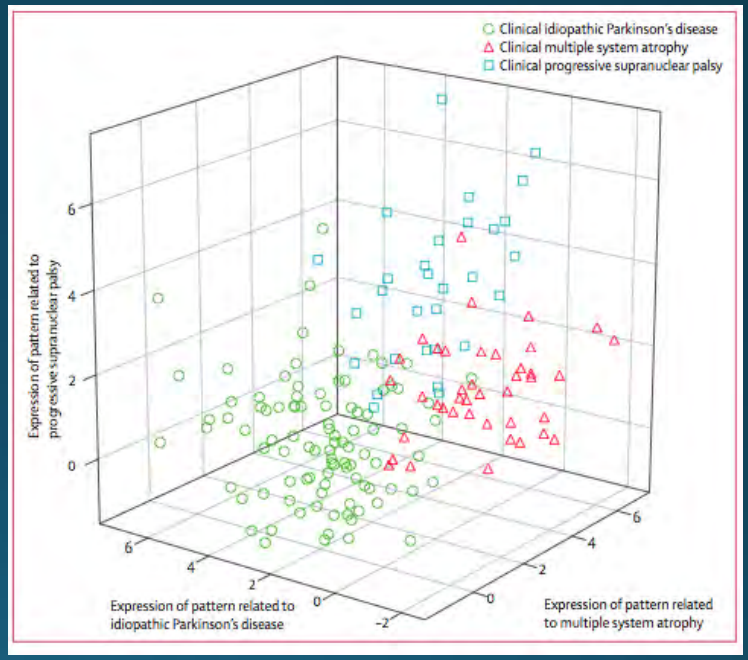




Red = increased metabolism
Blue = decreased metabolism

FDG-PET and PD vs MSA and PSP

- Disease-related pattern of FDG uptake in idiopathic PD, MSA, and PSP
- Developed automated classification procedure
- Diagnosed 3 diseases with Sn 84-88%, Sp 94-97%, PPV 91-98%, NPV 82-92%



Tang C. Lancet Neurol. 2010 Feb;9(2):

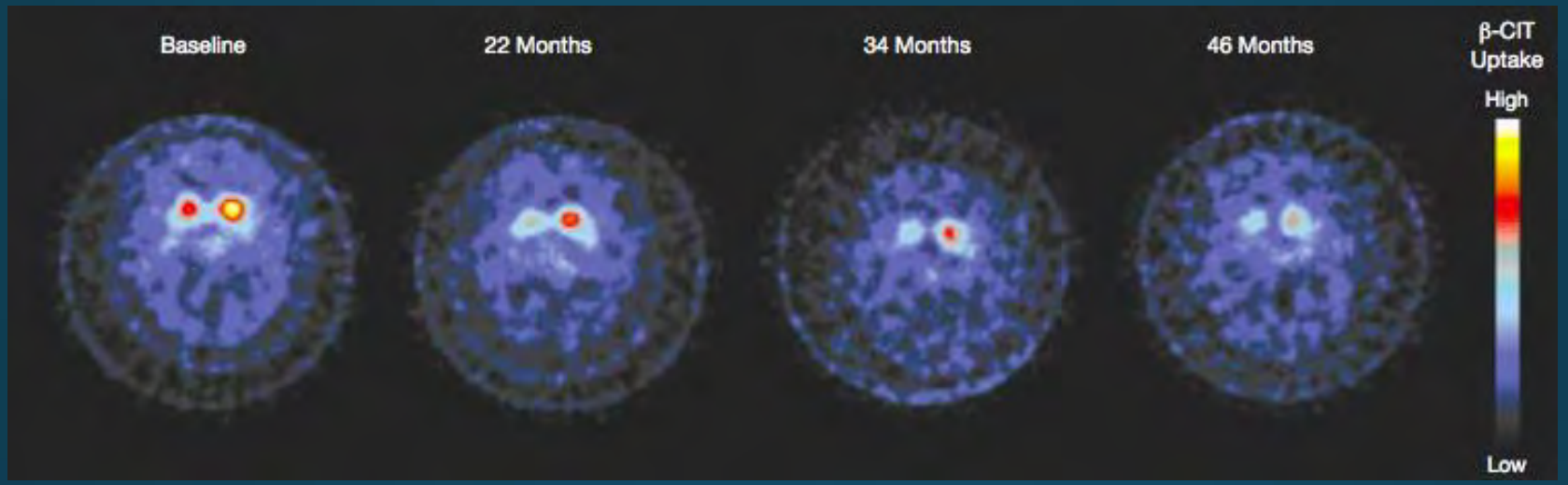
Can radiotracer imaging serve as surrogate endpoint in PD?

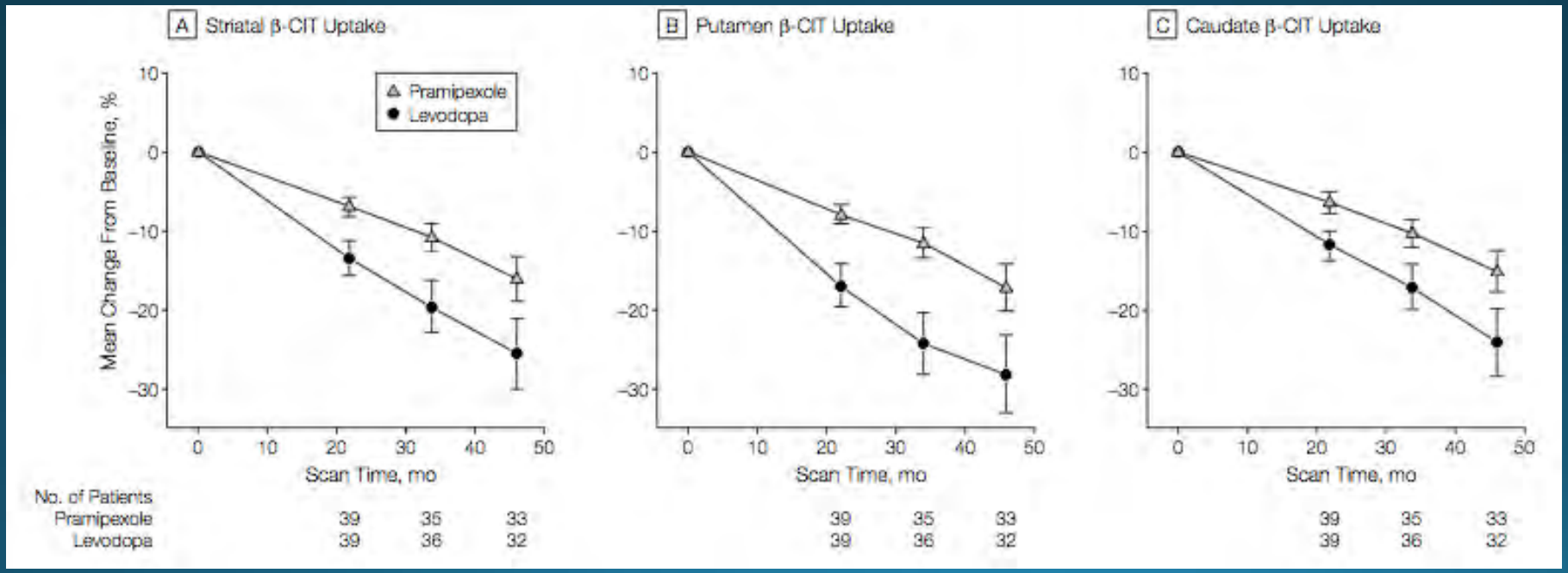
- ELLDOPA: levodopa controls symptoms and does not promote neurodegeneration, but B-CIT imaging shows less loss in binding with placebo groups.
- Two smaller studies comparing

  (1) Whone AL, et al. REAL-PET. Ann Neurol 2003
  levodopa vs. ropinirole

  (2) Parkinson Study Group. CALM-PD. JAMA 2002
  levodopa vs. pramipexole

CALM-PD


Baseline
22 Months
34 Months
46 Months
β-CIT Uptake
High
Low


A Striatal β-CIT Uptake
B Putamen β-CIT Uptake
C Caudate β-CIT Uptake
Pramipexole
Levodopa
Mean Change From Baseline, %
10
0
−10
−20
−30
0
10
20
30
40
50
Scan Time, mo
No. of Patients
Pramipexole 39 35 33
Levodopa 39 36 32

	REAL-PET (Levodopa vs Ropinirole)	CALM-PD (Levodopa vs Pramipexole)
Nuclear imaging	18F-DOPA PET (all)	123I-B-CIT SPECT (subset)
Group with better UPDRS scores	Levodopa	Levodopa
Group with fewer motor complications	Ropinirole	Pramipexole
Nuclear Imaging findings	1/3 less decline in uptake in Ropinirole group (at 24 months)	1/3 less decline in uptake in Pramipexole group (at 48 months, but not at 24 months)

***Table 2** Human Parkinson disease studies assessing direct pharmacologic effects on DAT tracers*

Drug	n	Duration	Measure	Findings
L-dopa 750 mg/d	8	4–6 wk	[^{123}I]β-CIT SPECT	No changes[51]
Selegiline 10 mg/d	8			
Pramipexole 1.5–4.5 mg/d	7	10 wk	[^{123}I]β-CIT SPECT	No changes[43,50]
L-dopa 300–600 mg/d	6			
L-dopa 200–400 mg/d	7	2–3 mo	[^{18}F]-CFT PET	No changes[51]
Pergolide 2.75 mg	12	4–6 wk	[^{123}I]β-CIT SPECT	Nonsignificant 12% increase in caudate[52]
L-dopa 300 mg/d	10	6 wk	[^{11}C]-RTI-32	Striatal DAT reduced as much as 21%, L-dopa, 20% pramipexole, 11% placebo[53]
Pramipexole 1.5 mg	10			
Placebo	10			

DAT = dopamine transporter; RTI = radiotracer imaging.

Ravina B, et al. Neurology 2005 Jan 25;64(2):208-215.

Summary

- Each of these neuroimaging techniques (except FDG-PET) measures one or more functions of dopaminergic neurons.
- They do not directly assess the # of dopaminergic neurons.
- Helpful in diagnosis, studying biology of disease, drug development.
- There are non-dopaminergic processes in PD (such as olfactory dysfunction) which will not be captured by dopamine-related tracers.

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