Parkinson disease and parkinsonism:
Clinical Questions

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University of Michigan
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Case II. The subject of the case which was next noticed was casually met with in the street. It was a man sixty-two years of age; the greater part of whose life had been spent as an attendant at a magistrate's office. He had suffered from the disease about eight or ten years. All the extremities were considerably agitated, the speech was very much interrupted, and the body much bowed and shaken. He walked almost entirely on the fore part of his feet, and would have fallen every step if he had not been supported by his stick. He described the disease as having come on very gradually, and as being, according to his full assurance, the consequence of considerable irregularities in his mode of living, and particularly of indulgence in spirituous liquors. He was the inmate of a poor-house of a distant parish, and being fully assured of the incurable nature of his complaint, declined making any attempts for relief.
CARDINAL SYMPTOMS OF PD

- **Tremor:**
  - 4-6 Hz, pill-rolling, asymmetric resting tremor
- **Rigidity**
  - Increased resistance to passive movement, often w/cogwheeling
- **Bradykinesia/Hypokinesia**
  - Loss of automatic movements (i.e. arm swing), masked facies, festinating gait, freezing
- **Postural Instability**
  - Difficulty rising from a chair
  - Falling backwards

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PD Videos

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Traditional paradigm of PD: Nigrostriatal dopaminergic denervation

The pars compacta region of the substantia nigra in the normal brain appears dark because dopamine-producing neurons are highly pigmented; as neurons die from Parkinson’s disease, the color fades.

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NIGROSTRIATAL DOPAMINERGIC DENERVATION IS CONSIDERED A KEY PATHOBIIOLOGICAL EVENT IN PD

- PET or SPECT imaging can demonstrate presynaptic dopaminergic denervation in PD. Striatal reductions are asymmetrically more prominent in the posterior and dorsal putamen.

- The greater the neuronal loss in the substantia nigra, the lower the concentration of dopamine in the striatum is and the more severe the parkinsonian symptoms, esp. bradykinesia.

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Clinical Diagnosis of PD

• Traditional diagnosis: >2-3 out of 4 cardinal symptoms (tremor, rigidity, bradykinesia, imbalance)

• Problem: 30% of patients with such symptoms have atypical parkinsonism (PSP, MSA, CBD, NPH)
Clinical PD Dx

Ex Vivo

N=100

76 IPD

30 pure IPD
46 IPD & comorbid path

24 not IPD

6 PSP
5 MSA
3 AD
3 lacunes
1 p-encephalitic
1 ET

19 IPD + striatal vasc
7 IPD + striatal plaques
1 IPD + caudate atrophy
9 IPD + typical AD
1 IPD + AD-pathology
7 IPD + vascular path
1 IPD + abscess
1 IPD / DLBD

Pure IPD

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## DDx PARKINSONISM

<table>
<thead>
<tr>
<th></th>
<th>IPD</th>
<th>MSA</th>
<th>PSP</th>
<th>CBD</th>
<th>FTD</th>
<th>DLB</th>
<th>Vasc PD</th>
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<td>+/-</td>
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<td>+++</td>
<td>+/-</td>
<td>+/-</td>
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<tr>
<td>L-DOPA response</td>
<td>+++</td>
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<td>👇</td>
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<td>👇</td>
<td>👇</td>
<td>mild</td>
<td>+/-</td>
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<td>+</td>
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<tr>
<td>Supranuclear gaze palsy</td>
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<td>+++</td>
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<td>Visual hallucinations</td>
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<td>+++</td>
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<tr>
<td>Apraxia</td>
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Improvement in clinical diagnosis from 2-3/4 cardinal symptoms

UKPDSBB Diagnostic Criteria for PD

United Kingdom Parkinson's Disease Society Brain Bank Diagnostic Criteria for Parkinson’s Disease

Step 1: Diagnosis of Parkinsonism
Bradykinesia and at least one of the following:

- Muscular rigidity
- 4–6 Hz resting tremor
- Postural instability not caused by primary visual, vestibular, cerebellar or proprioceptive dysfunction

Step 2: Features tending to exclude Parkinson’s disease as the cause of Parkinsonism

- History of repeated strokes with stepwise progression of parkinsonian features
- History of repeated head injury
- History of definite encephalitis
- Neuroleptic treatment at onset of symptoms
- >1 affected relatives
- Sustained remission
- Strictly unilateral features after 3 years
- Supranuclear gaze palsy
- Cerebellar signs
- Early severe autonomic involvement
- Early severe dementia with disturbances of memory, language and praxis
- Babinski's sign
- Presence of a cerebral tumour or communicating hydrocephalus on computed tomography scan
- Negative response to large doses of levodopa (if malabsorption excluded)
- 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) exposure

Step 3: Features that support a diagnosis of Parkinson’s disease (three or more required for diagnosis of definite Parkinson’s disease)

- Unilateral onset
- Rest tremor present
- Progressive disorder
- Persistent asymmetry affecting the side of onset most
- Excellent (70–100%) response to levodopa
- Severe levodopa-induced chorea
- Levodopa response for ≥5 years
- Clinical course of ≥10 years

Clinical diagnosis of PD

• Clinical diagnosis can be improved by requiring asymmetry in limb symptoms, good l-DOPA response, and exclusion of “red” flags for non-IPD diagnosis (UK Brain Bank Diagnostic PD criteria).

• After application of UKBBPDS criteria improved diagnostic accuracy to 82% & diagnostic accuracy further improves with longer duration of clinical follow-up.

• However, the real diagnostic challenge is with the early diagnosis.
OTHER DIAGNOSTIC PROBLEMS: Is PD over-diagnosed even by neurologists?

ELLDOPA TRIAL ($^{123}$I-β-CIT SPECT): 11% of clinically diagnosed PD patients participating in drug study had normal DAT scan (Fahn et al. 2005)

REAL-PET STUDY ($^{18}$F-FDOPA PET): 9% of clinically diagnosed PD patients participating in ropinirole drug study had normal FDOPA scan (Whone et al. 2003)

Subjects Without Evidence of Dopaminergic Deficits

SWEDDs
Parkinson’s Disease is Overdiagnosed Clinically at Baseline in Diagnostically Uncertain Cases: A 3-Year European Multicenter Study with Repeat $[^{123}\text{I}]$FP-CIT SPECT

| TABLE 5. $T = 0$ clinical on-site diagnosis versus $T = 0$ baseline $[^{123}\text{I}]$FP-CIT SPECT |
|---------------------------------|-------------------------|
| $T = 0$ $[^{123}\text{I}]$FP-CIT SPECT | Abnormal 57 | Normal 42 |
| $T = 0$ On-site clinical diagnosis PD: Non-PD | 55 : 2 | 26 : 16 |

- 26/99 (26.2%) of early clinical diagnosis of PD had normal DAT SPECT scan when diagnosed by PCP.

What is the clinical significance or prognosis of a normal DAT scan in subjects with tremor or gait problems?

- 2-yr FU in 152 subjects with tremor (75%) and gait abnormality (12%): non-degenerative parkinsonism or tremor present in 97%.
- No significant worsening upon dopaminergic drug withdrawal (25/27)
- The clinical profile and therapy response during follow-up of patients with normal presynaptic dopamine imaging supports the diagnosis of a non-degenerative movement disorder in nearly all cases.
- ET: 50%

Fig. 1 Final diagnosis in 150 patients with normal 123I-FP-CIT SPECT.

Two-year follow-up in 150 consecutive cases with normal dopamine transporter imaging.
Marshall, Vicky; Patterson, Jim; Hadley, Donald; Grosset, Katherine; Grosset, Donald

Nuclear Medicine Communications. 27(12):933-937, December 2006.
DOI: 10.1097/01.mnm.0000243374.11260.5b

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## PD Tremor vs. Essential Tremor (ET)

<table>
<thead>
<tr>
<th></th>
<th>PD</th>
<th>ET</th>
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<tbody>
<tr>
<td><strong>Prevalence</strong></td>
<td>1% elderly</td>
<td>1-10% elderly</td>
</tr>
<tr>
<td><strong>Age of onset</strong></td>
<td>60-70</td>
<td>Peaks 15-20 &amp; 50-70</td>
</tr>
<tr>
<td><strong>M/F</strong></td>
<td>M&gt;F</td>
<td>M=F</td>
</tr>
<tr>
<td><strong>Tremor</strong></td>
<td>Resting&gt;Postural&gt;Kinetic</td>
<td>Kinetic&gt;Postural&gt;Resting</td>
</tr>
<tr>
<td></td>
<td>(&quot;rest&quot; tremor) 4-6 Hz</td>
<td>(&quot;action&quot; tremor) (8-10 Hz)</td>
</tr>
<tr>
<td><strong>Rx (drugs)</strong></td>
<td>Dopaminergic; anti-</td>
<td>Beta-blockers; primidone;</td>
</tr>
<tr>
<td></td>
<td>cholinergic</td>
<td>topiramate; gabapentin;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>benzodiazepine</td>
</tr>
<tr>
<td><strong>Surgery (DBS)</strong></td>
<td>STN, Gpi, (Vim Thalamus)</td>
<td>Vim Thalamus</td>
</tr>
</tbody>
</table>

*Mixed resting/action tremor, esp. when asymmetric, represent a diagnostic challenge*

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Tremors & tremors:
Mixed action & resting tremor syndromes represent a clinical diagnostic challenge

- ET
- Primary cerebellar tremor
- Holmes’ or midbrain tremor
- Wilson disease
- Dystonic tremor
- Exaggerated physiological tremor
- Drug-induced tremor (valproic acid, lithium, neuroleptics etc)
- Neuropathic/myopathic tremor
- Pseudo-athetosis
- PD
- DLB
A FREQUENT CLINICAL PROBLEM
Drug-induced parkinsonism: IS IT THE DRUG OR IS IT PD?

Basal ganglia STRESS TEST

Action tremor in the elderly:  
Is it DLB or ET?

• ET has a bimodal distribution with a second peak in the elderly.

• Recent post-mortem studies show that a subset of elderly ET patients have Lewy body pathology in the brainstem.

• Tremor in dementia with Lewy bodies (DLB) can sometimes present more as an action tremor rather than a typical parkinsonian resting tremor.

• Given the increasing frequency of cognitive impairment as well as (action) tremor in the elderly the differential diagnosis between DLB vs Alzheimer disease (with ET) can be clinically challenging.
The Clinical Problem:
Early diagnosis & DDx of parkinsonism

- Misdiagnosis 9-30% in the early stage
  - 9-30% clinically diagnosis with PD may not have PD as defined by nigrostriatal denervation and may have ET, dystonia, drug-induced or vascular parkinsonism
  - “ET” in the elderly, esp. when having cognitive impairment, may be a sign of DLB rather than “pure” ET.

- Why bother?
  - Prognostic information for patient & family
    - Career/Retirement/Disability planning
  - Decide on treatment
    - Pharmacological (PD vs. ET drugs)
    - Surgical (choice of DBS surgical target: STN, Gpi,Vim thal)
    - (Future) Pathobiology-specific treatments that will be especially relevant for early diagnosis.
  - Recruitment for clinical trials (sample enrichment)
The Clinical Problem:
Early diagnosis & DDx of parkinsonism

- **DA imaging** can be of clinical utility to answer some of these clinical diagnostic dilemmas
The Clinical Problem: 
Early diagnosis & DDx of parkinsonism

• Misdiagnosis 9-30% in the early stage
  ➢ Controversy remains whether findings of normal DAT or FDOPA scans in subjects clinically diagnosed with Parkinson disease by movement disorders specialists may represent misdiagnoses, tremor-variant syndromes, or limitations of the imaging techniques

• Why bother?
  ➢ Prognostic information for patient & family
    ➢ Career/Retirement/Disability planning
  ➢ Decide on treatment
    ➢ Pharmacological (PD vs. ET drugs)
    ➢ Surgical (choice of DBS surgical target: STN, Gpi, Vim thal)
  ➢ Recruitment for clinical trials (sample enrichment)
  ➢ Preclinical/prodromal diagnosis (patient or family member in case of available effective neuroprotective or neuroregenerative therapy)
Hughes et al. 1994

• Clinical diagnosis correct in 76%
• After application of UKBBPDS criteria improved diagnostic accuracy to 82%.
DISCUSSION

• Most of the tremor manifestations have sufficient clinical presentation to allow distinction between PD and ET.

• A simple DA treatment challenge still remains a solid and cheap clinical approach to aid in the diagnosis of idiopathic PD and if positive, would equate a pharmacological equivalent of nigrostriatal denervation in idiopathic PD.

• Therefore, a DA scan should not be a first line of diagnostic testing. Patient should see a movement disorders neurologist first and for, remaining uncertain subjects a DA scan should be considered.

• If general practitioners prefer to order a DA scan, consideration should be given to use cheaper screening tests, such as smell tests, first.
INDICATION DA IMAGING

• 1. PD
  • 1.1. Early and/or preclinical/prodromal diagnosis to allow identification of “at risk” populations for neuroprotective agents (when available) to delay or prevent the onset of symptoms.
  • 1.2. More accurate PD diagnosis to allow more pure subjects recruitment for clinical trials
  • 1.3. Assessment of severity of disease (?)
  • 1.4. Measuring PD disease progression
  • 1.5. Monitoring neuroprotection/neuroregeneration
• 2. Differential diagnosis of parkinsonian syndromes (?)
• 3. Diagnosis of DLB vs AD
  • Imaging of the dopamine transporter may help to identify subjects with DIP secondary to a loss of dopamine nerve terminals.
  • Diagnostic accuracy improves with longer duration of clinical follow-up but challenge remains in early diagnosis
  • A positive DA scan will not significantly help to identify these subjects with idiopathic PD and comorbid brain disease (AD, vascular, striatal plaques) and a normal DA scan does not help with the DDx of a non-PD tremor syndrome.
15/99 (15.1%) of three-year clinical “gold” standard diagnosis of PD had normal DAT SPECT scan.

Although 3-yr clinical “gold” standard diagnosis had high sensitivity (93%) specificity was low (46%)

Progressive Supranuclear Palsy (imbalance-predominant parkinsonism, gaze palsy) :
MRI & FDG PET IMAGING

MRI: Midbrain atrophy ("hummingbird" sign)

FDG PET: Striatal, thalamic, pontine, (frontal) cortical hypometabolism but not in the cerebellum (Foster et al. 1988).

FTD cortical pattern on FDG PET

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Corticobasal degeneration (asymmetric rigidity, apraxia & alien limb): FDG PET & MRI IMAGING

FDG PET: Focal asymmetric cortical (frontoparietal) and subcortical (thalamic, striatal hypometabolism)

MRI: Focal and asymmetric cortical (frontal/parietal) atrophy

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Multiple System Atrophy (MSA; parkinsonism, ataxia, dysautonomia): MRI & FDG PET IMAGING

MSA-P: Putaminal atrophy & hyperintense signal in the posterolateral portions of the putamen

MSA-C: MRI pontine atrophy (hot-cross-bun sign) & cerebellar atrophy

MSA-P: Putaminal hypometabolism

MSA-C: Cerebellar & pontine hypometabolism

Kwon et al. Mov Disord 2008
DEMENTIA WITH LEWY BODIES (DLB)

- DLB may be the second most common degenerative dementia after AD

- Differential diagnostic criteria recommended by the International Consortium on DLB:
  
  *Visual Hallucinations, Fluctuating Mental Status, Parkinsonism, Neuroleptic Drug “Sensitivity”*

  - Neurology 65:1863-72; 2005

- Diagnostic Sensitivity (vs. autopsy) 30% - 80%

  - Arch Neurol 55:969-78, 1998
  - Arch Neurol 59:43-6, 2002
  - Int J Geriat Psychiat 14:526-33, 1999
  - Neurology 53:1974-82, 1999
  - Neurology 53:1292-9, 1999
PDD vs. DLB
The 1-year rule

1
Motor

2 (\ldots x \ldots) \text{yr}

Motor

\psi

DLB

\psi

Motor

\psi

PDD

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DLB vs. PDD

The 1-year rule & $\beta$-amyloid burden

$^{11}$C-PIB
CONCLUSIONS

• PET and SPECT measurements of dopaminergic pathways in the brain have confirmed the importance of dopamine in the pathophysiology of Parkinson disease.

• Presynaptic DA imaging may allow very early, even preclinical, diagnosis of PD.

• Dopaminergic studies may have a limited clinical role in the diagnosis of patients with symptoms suggestive of PD yet do not respond to typical dopaminergic drugs, such as patients with vascular parkinsonism or essential tremor with mild resting tremor.

• Nigrostriatal denervation is not specific for PD and has also been demonstrated in patients with atypical parkinsonism, such as MSA, or PSP. Combined presynaptic dopaminergic and postsynaptic DA receptor binding studies may aid in the distinction between early idiopathic PD and an atypical parkinsonian syndrome but may not be able to distinguish atypical parkinsonian disorders from each other or from advanced idiopathic PD. Glucose metabolic or rCBF flow studies may provide additional diagnostic information about atypical parkinsonian syndromes.

• Controversy remains whether findings of normal dopaminergic scans in subjects clinically diagnosed with PD by movement disorders specialists may represent misdiagnosis, overdiagnosis, tremor-variant syndromes, or limitations of the imaging techniques. However, in the absence of cognitive or behavioral symptoms, a normal dopaminergic imaging may support the diagnosis of a nondegenerative movement disorder.

• Presynaptic DA imaging may distinguish DLB from prototypical AD but not from PDD.
### Opportunities

- **Preclinical/prodromal PD Dx**
  - Select subjects for neuroprotective therapy, the early institution of which confers a better outcome

- **Clinical PD Dx**
  - May help with (early) diagnosis in clinically uncertain subjects
  - May help to unmask idiopathic PD in subset of “drug”-induced parkinsonism or “vascular” parkinsonism

- **Positive predictive value (PPV)**
  - Prognostication (infers non-degenerative movement disorder)

- **Clinical PD Dx**
  - Redirects diagnostic process
  - Justifies more aggressive anti-ET tremor therapy (pharmacologically & selection of DBS surgical target)

### Challenges

- **Preclinical/prodromal PD Dx**
  - It is unclear when, or indeed whether, clinically normal subjects will go on to develop parkinsonism.

- **Clinical PD Dx**
  - If subject has good l-DOPA response, confirmation of diagnosis does not alter management

- **Positive predictive value (PPV)**
  - Lacks specificity to DDx IPD from atypical parkinsonism
  - Concern about over-use general practitioner ($)$

- **Clinical PD Dx**
  - May not help with DDx of non-PD tremor syndromes (ET, Holmes, pure cerebellar etc)

- **Negative predictive value (NPV)**
  - Braakian model of IPD: the use of imaging to detect non-dopaminergic abnormalities representing disease caudal to the midbrain remains in its infancy
## DISCUSSION

### DIAGNOSTIC IMAGING IN DEMENTIA: DLB vs prototypical AD/FTD

<table>
<thead>
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<th>Opportunities</th>
<th>Challenges</th>
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<tr>
<td><strong>Clinical DLB Dx</strong></td>
<td><strong>At present, practical impact on clinical management still remains limited.</strong></td>
</tr>
<tr>
<td>Positive predictive value (PPV)</td>
<td>At present, practical impact on clinical management still remains limited.</td>
</tr>
<tr>
<td>May help with (early) diagnosis in clinically uncertain subjects</td>
<td>Even with potential advent of anti-amyloid therapy, benefit of diagnostic stratification remains uncertain.</td>
</tr>
<tr>
<td>May help with selection of pharmacotherapy: More aggressive cholinergic therapy &amp; avoidance of neuroleptics in DLB</td>
<td>FDG or β-amyloid PET may provide alternative strategy to aid with diagnostic process.</td>
</tr>
<tr>
<td>May help to better understand nature of parkinsonism in dementia i.e., redirects diagnostic process toward FTD, drug-induced or vascular etiology.</td>
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Figure 1. Axial SPECT images at the level of the striatum in a 67-year-old healthy subject (Control, left), a 60-year-old patient with Parkinson's disease in Hoehn and Yahr stage I (PD, middle), and a 76-year-old patient with vascular parkinsonism (VP, right) 20 hours after injection of $[^{123}I]$:CIT. An asymmetric striatal binding reduction, more pronounced in the putamen, is evident in PD. By contrast, striatal $\beta$-CIT binding in the VP patient is not obviously reduced.
Drug-induced parkinsonism:
DAT SPECT may help to identify subjects with DIP secondary to a loss of dopamine nerve terminals in the context of a progressive degenerative parkinsonism.

Putamen [$^{123}$I]FP-CIT SPET binding was reduced in 14 and normal in the remaining 18 patients. There was no difference between the two groups for age, duration of DRBAs treatment, UPDRS III, tremor, rigidity, and bradykinesia subscores for upper and lower limbs. Conversely, symmetry of parkinsonian signs and presence bucco-linguo-masticatory dyskinesias were more frequent in individuals with normal tracer binding.

Imaging of the dopamine transporter may help to identify subjects with DIP secondary to a loss of dopamine nerve terminals. Putamen [$^{123}$I]FP-CIT SPET binding was reduced in 14 and normal in the remaining 18 patients. There was no difference between the two groups for age, duration of DRBAs treatment, UPDRS III, tremor, rigidity, and bradykinesia subscores for upper and lower limbs. Conversely, symmetry of parkinsonian signs and presence bucco-linguo-masticatory dyskinesias were more frequent in individuals with normal tracer binding.

Imaging of the dopamine transporter may help to identify subjects with DIP secondary to a loss of dopamine nerve terminals.


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Model for the progression of loss of neuronal function in neurodegenerative disorders


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SWEDD

72 yo woman with 4 yr history of left >right arm resting tremor, decreased arm swing bilaterally, mild rigidity. No significant bradykinesia

UPDRS-m=12
OLFACITION=31/40

DAT PET normal for age:
**NIGROSTRIATAL DOPAMINERGIC DENERVATION IN PD vs. NORMAL AGING**

**FROM:**
*Positron emission tomography of monoaminergic vesicular binding in aging and Parkinson disease*
Nicolaas I Bohnen, Roger L Albin, Robert A Koepppe, Kristine A Wernette, Michael R Killbourn, Satoshi Minoshima and Kirk A Frey

**Figure 1.**

Posterior putamen DTBZ BP versus age in normal (filled circles = men; open circles = women) and PD subjects (filled squares = men, open squares = women). The line is the regression of PP DTBZ BP versus age in normal subjects using a declining exponential model (see Table 2). The shaded region indicates the subset of normal subjects used for group comparisons with PD. Within the normal group, there is a significant age-related decline in DTBZ BP. There is complete separation of normal and PD subject groups. There are no significant gender differences in normal or PD subjects.

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CARDINAL MOTOR SIGNS
PARKINSONISM

Rhythmic tremor often occurs at first in one hand, where it resembles the motion of rolling a pill between the thumb and forefinger.

Muscle rigidity shows itself in the cogwheel phenomenon: pushing on an arm causes it to move in jerky increments instead of smoothly.

Leaning forward or backward when upright reflects impairment of balance and coordination.

Difficulty rising from a sitting position is a common sign of disordered control over movement. Some patients report feelings of weakness and of being constrained by ropes or other forces.

Parkinson’s disease