Clinical utility of dopaminergic imaging in Parkinson disease and parkinsonism

Nicolaas I. Bohnen, MD, PhD
University of Michigan
& Ann Arbor VAMC
Investigational use:

- $[^{18}F]DOPA$
- $[^{11}C]DTBZ$
- $[^{18}F]FP-DTBZ$
- $[^{11}C]MPH$
- $[^{123}I] \beta-CIT$
- $[^{123}I]FP-CIT$
- $[^{123}I] \text{Altropane}$
- $[^{99m}Tc]TRODAT$
- $[^{11}C] \text{Raclopride}$
- $[^{123}I] \text{I BF}$
- $[^{123}I] \text{I BZM}$
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.

*Slides are not to be reproduced without permission of author.*
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.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Ligand</th>
<th>n</th>
<th>Clinical examination medication</th>
<th>Target region**</th>
<th>Correlation of DAT binding with symptoms ***</th>
<th>Axial Tremor Rigidity Bradykinesia symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seibyl et al., 1995[2]</td>
<td>(^{[123]}\text{I}\beta\text{-CIT})</td>
<td>28</td>
<td>off</td>
<td>n-l-Caudate</td>
<td>NS</td>
<td>-0.46</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>n-c-Caudate</td>
<td>NS</td>
<td>-0.47</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>n-l-Putamen</td>
<td>NS</td>
<td>-0.52</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>n-c-Putamen</td>
<td>NS</td>
<td>-0.46</td>
</tr>
<tr>
<td>Brücke et al., 1997[6]</td>
<td>(^{[123]}\text{I}\beta\text{-CIT})</td>
<td>61</td>
<td>on</td>
<td>av Striatum</td>
<td>NS</td>
<td>0.38</td>
</tr>
<tr>
<td>Rinne et al., 1999[22]</td>
<td>(^{[18]}\text{F}\text{CFT})</td>
<td>27</td>
<td>off</td>
<td>av-Caudate</td>
<td>NS</td>
<td>-0.55</td>
</tr>
<tr>
<td>Benamer et al., 2000[19]</td>
<td>(^{[123]}\text{I}\text{FP-CIT})</td>
<td>41</td>
<td>off</td>
<td>av-Putamen</td>
<td>NS</td>
<td>-0.61</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>i-Caudate</td>
<td>NS</td>
<td>-0.44</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>c-Caudate</td>
<td>NS</td>
<td>-0.46</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>i-Putamen</td>
<td>-0.38</td>
<td>-0.34</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>c-Putamen</td>
<td>-0.32</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>av-Striatum</td>
<td>NS</td>
<td>-0.50</td>
</tr>
<tr>
<td>Present study</td>
<td>(^{[123]}\text{I}\beta\text{-CIT})</td>
<td>59</td>
<td>off</td>
<td>n-av-Striatum</td>
<td>NS</td>
<td>-0.42</td>
</tr>
</tbody>
</table>

† Superscript numbers correspond to the list of References.
* Medication off, at least 12 hours after withdrawing antiparkinsonian medication; de novo, naive for antiparkinsonian medication.
** For target region av, averaged over right and left hemisphere; n, normalized for age; c/l, contralateral/ipsilateral to clinically more affected body side.
*** Significant correlation, r or r\(_2\) values.
NS, no significant correlation.
Frey and colleagues reported striatal losses of about 9% per year, with greater losses in Parkinson disease patients with the most preserved binding on the initial scan (Frey et al. 2000).
Dopaminergic Synapse

**Imaging Targets:**

- **AADC** - $[^{18}F]{DOPA}$
- **VMAT2** - $[^{11}C]{DTBZ}$, $[^{18}F]{FP-DTBZ}$
- **DAT** - $[^{11}C]{MPH}$, $[^{123}I]{β-CIT}$, $[^{123}I]{FP-CIT}$, $[^{123}I]{Altropane}$, $[^{99m}Tc]{TRODAT}$
- **D₂ Receptor** - $[^{11}C]{RAC}$, $[^{123}I]{IBF}$, $[^{123}I]{IBZM}$

*Courtesy Kirk Frey*

*Slides are not to be reproduced without permission of author.*
FDOPA $K_l$ is a measure of AADC activity

AADC is widely distributed, but concentrated in catecholaminergic neurons

AADC activity is regulated by cAMP-PK phosphorylation; role of presynaptic dopamine D2 autoreceptors

Early PD: AADC is upregulated because of compensation
DAT BINDING TRACERS

- More specific for dopaminergic terminals
- Quantified by PET or SPECT ligand binding
- DAT cycles from cell surface to endosomes; directed by differential phosphorylations
- Internalized DAT does not bind to cocaine-analog ligands

- Examples: $^{123}\text{I-}\beta\text{-CIT}$, $^{123}\text{I-FP-CFT}$, $^{123}\text{I-Altropane (E-IACFT)}$, $^{99m}\text{Tc-TRODAT SPECT}$ & $^{11}\text{C-Altropane}$, $^{11}\text{C-}\beta\text{-CFT}$, $^{11}\text{C-MPH PET}$
$^{11}C-\beta$-CFT DOPAMINE TRANSPORTER PET

Healthy control  PD

Slides are not to be reproduced without permission of author.
11C-DTBZ / 18F-FP-DTBZ: VESICULAR MONOAMINE TRANSPORTER-2 PET

Striatal VMAT2:

- Binding site shared by all monoamine neurons; Over 95% dopaminergic
- Linearly related to integrity of dopaminergic innervation
- May be grossly unaffected/unregulated by drug treatments

Slides are not to be reproduced without permission of author.
### COMPARISON OF PRESYNAPTIC STRIATAL DOPAMINERGIC MARKERS

<table>
<thead>
<tr>
<th>STRIATAL PRE-SYNAPTIC DOPAMINE MARKERS</th>
<th>SUBSTRATE</th>
<th>REGULATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDOPA</td>
<td>Monoaminergic</td>
<td>Heavily regulated (Upregulated)</td>
</tr>
<tr>
<td>DAT</td>
<td>More specific for DA</td>
<td>Downregulated</td>
</tr>
<tr>
<td>VMAT-2</td>
<td>Monoaminergic</td>
<td>Minimal to no definite evidence of regulation</td>
</tr>
</tbody>
</table>
HOW DO THE 3 TYPES OF TRACERS COMPARE?

Evidence for FDOPA upregulation & DAT downregulation

Table 4: Symptomatic Threshold of PD

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal control</td>
<td>0.01047 ± 0.00119</td>
<td>0.957 ± 0.091</td>
<td>1.299 ± 0.223</td>
</tr>
<tr>
<td>H+</td>
<td>0.00648 ± 0.00147</td>
<td>0.466 ± 0.169 (48.7%)</td>
<td>0.576 ± 0.151 (44.3%)</td>
</tr>
<tr>
<td>Asymptomatic side</td>
<td>(61.9%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptomatic side</td>
<td>0.0097 ± 0.00213</td>
<td>0.362 ± 0.190 (37.8%)</td>
<td>0.379 ± 0.186 (29.2%)</td>
</tr>
<tr>
<td>H+&lt;sub&gt;23&lt;/sub&gt;</td>
<td>0.0048 ± 0.00161</td>
<td>0.368 ± 0.105 (38.5%)</td>
<td>0.435 ± 0.135 (35.3%)</td>
</tr>
<tr>
<td>Less affected side</td>
<td>(46.6%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>More affected side</td>
<td>0.0360 ± 0.00120</td>
<td>0.259 ± 0.064 (27.1%)</td>
<td>0.302 ± 0.088 (23.2%)</td>
</tr>
</tbody>
</table>

*Based on unilateral PET measurements in the putamen (mean ± SD).

All 3 tracers show reductions in striatal uptake in PD but reductions were:

- Largest for DAT
- Intermediate for VMAT2
- Least for F-DOPA

Presynaptic regulation may therefore reflect compensation

(From Lee et al. 2000)
ESTIMATES OF NIGROSTRIATAL DENERVATION USING DIFFERENT RADIOLIGANDS IN THE SAME PATIENT (Lee et al., 2000)

<table>
<thead>
<tr>
<th>Stage I Hoehn &amp; Yahr PD patients</th>
<th>$^{18}$F-FDOPA (fluorodopa)</th>
<th>$^{11}$C-DTBZ (VMAT2 ligand)</th>
<th>$^{11}$C-MP (DAT ligand)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic putamen</td>
<td>-52%</td>
<td>-62%</td>
<td>-71%</td>
</tr>
</tbody>
</table>

Because of its downregulation a DAT ligand may be a preferred choice for a screening or early diagnostic biomarker of PD.
Clinical diagnosis of PD

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

• 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)

• Diagnostic accuracy improves with longer duration of clinical follow-up
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

Slides are not to be reproduced without permission of author.

In Vivo DA imaging vs. clinical diagnosis of PD

ELLDOPA TRIAL (\(^{123}\text{I-}\beta\text{-CIT SPECT})\): 11% of clinically diagnosed PD patients participating in drug study (Fahn et al. 2005)

REAL-PET STUDY (\(^{18}\text{F-FluoroDOPA PET})\): 9% of clinically diagnosed PD patients participating in ropinirole drug study (Whone et al. 2003)

Subjects Without Evidence of Dopaminergic Deficits

SWEDDs

\(\text{Slides are not to be reproduced without permission of author.}\)
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:
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

Slides are not to be reproduced without permission of author.
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

<table>
<thead>
<tr>
<th>T = 0 $[^{123}\text{I}]$FP-CIT SPECT</th>
<th>Abnormal</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>57</td>
<td><img src="#" alt="Arrow" /></td>
<td><img src="#" alt="Arrow" /></td>
</tr>
</tbody>
</table>

| 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.


*Slides are not to be reproduced without permission of author.*
• **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%)

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-degenerate 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-degenerate movement disorder in nearly all cases.
- ET: 50%

Fig. 1 Final diagnosis in 150 patients with normal 123I-FP-CIT SPECT.
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 $[^{123}]$-β-CIT. An asymmetric striatal binding reduction, more pronounced in the putamen, is evident in PD. By contrast, striatal β-CIT binding in the VP patient is not obviously reduced.

Pirker et al. Mov Disord 2002;17:518-523
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 $[^{123}\text{I}]$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 $[^{123}\text{I}]$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.
Model for the progression of loss of neuronal function in neurodegenerative disorders

ESTIMATES OF NIGROSTRIATAL DENERVATION USING DIFFERENT RADIOLIGANDS IN THE SAME PATIENT
(Lee et al., 2000)

<table>
<thead>
<tr>
<th>Stage I Hoehn &amp; Yahr PD patients</th>
<th>$^{18}\text{F-FDOPA}$ (fluorodopa)</th>
<th>$^{11}\text{C-DTBJ}$ (VMAT2 ligand)</th>
<th>$^{11}\text{C-MP}$ (DAT ligand)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic putamen</td>
<td>-38%</td>
<td>-51%</td>
<td>-56%</td>
</tr>
<tr>
<td>Symptomatic putamen</td>
<td>-52%</td>
<td>-62%</td>
<td>-71%</td>
</tr>
</tbody>
</table>

Conclusion: Clinical threshold for motor symptoms is at about >50% loss of nigrostriatal dopaminergic nerve terminals.
How can DA imaging help with the differential diagnosis of parkinsonism?

Pre-synaptic ([\(^{11}\)C]DTBZ) in idiopathic PD

**PRE-SYNAPTIC DA**

↓↓↓

Idiopathic PD (early)

↓↓

Idiopathic PD (advanced)

↓↓

ATYPICAL PARKINSONISM (MSA, PSP)

Post-synaptic D2 receptor PET ([\(^{11}\)C] Raclopride)

**POST-SYNAPTIC DA RECEPTOR**

↑ (early upregulation)

↓

↓

Slides are not to be reproduced without permission of author.
**Figure 2.** Iodine-123-2β-carbomethoxy-3β-(4-iodophenyl) tropane ([123I]β-CIT; dopamine transporter) scans (upper row) and [123I]iodobenzofuran ([123I]IBF; D2 receptor) scans (lower row) of a 64-year-old normal control, a 63-year-old woman with dopa-untreated Parkinson's disease, a 65-year-old man with dopa-treated Parkinson's disease, a 74-year-old man with MSA, and a 63-year-old man with PSP. Image intensity has been adjusted so that striatal activity roughly reflects the relative differences in the mean striatal $R$ values between the individuals.

Kim et al.. Mov Disord 2002;17:303-312.
Does combined imaging of the pre- and postsynaptic dopaminergic system increase the diagnostic accuracy in the differential diagnosis of parkinsonism?

Idiopathic PD vs. atypical parkinsonism

*Slides are not to be reproduced without permission of author.*
<table>
<thead>
<tr>
<th></th>
<th>IPD</th>
<th>MSA- P (SND)</th>
<th>MSA- P (SDS)</th>
<th>MSA- C (OPCA)</th>
<th>PSP</th>
<th>CBD</th>
<th>FTD</th>
<th>DLB</th>
<th>Vasc PD</th>
<th>Drug - PD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parkinsonism</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
<td>+/-</td>
<td>+++</td>
<td>++</td>
<td>+/-</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Asymmetry</td>
<td>+++</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+++</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>L-DOPA response</td>
<td>+++</td>
<td>-</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>mild</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>Dysautonomia</td>
<td>+/-</td>
<td>+/-</td>
<td>+++</td>
<td>+/-</td>
<td>+/-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Supranuclear gaze palsy</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+++</td>
<td>+/-</td>
<td>-</td>
<td>-</td>
<td>+/</td>
<td>-</td>
</tr>
<tr>
<td>Ataxia</td>
<td>-</td>
<td>+/-</td>
<td>-</td>
<td>+++</td>
<td>+/-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+/-</td>
<td>-</td>
</tr>
<tr>
<td>Dementia</td>
<td>late</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>++</td>
<td>+/-</td>
<td>++</td>
<td>+++</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>Visual hallucinations</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
<td>+</td>
<td>+</td>
<td>+/</td>
<td>+/-</td>
</tr>
<tr>
<td>Apraxia</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+++</td>
<td>+/-</td>
<td>-</td>
<td>+</td>
<td>+/-</td>
<td>-</td>
</tr>
</tbody>
</table>

*Slides are not to be reproduced without permission of author.*
CHALLENGE D2 RECEPTOR IMAGING IN DIFFERENTIAL DIAGNOSIS OF PD AND PARKINSONISM

• Combined presynaptic and postsynaptic dopaminergic imaging may not be able to distinguish atypical parkinsonian disorders from each other or from advanced idiopathic Parkinson disease.

• Sometimes, glucose metabolic or cerebral blood flow studies may provide additional diagnostic information about atypical parkinsonian syndrome.

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).
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

Slides are not to be reproduced without permission of author.
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

Slides are not to be reproduced without permission of author.
Parkinsonism & dementia: Is there a role for DA imaging?
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

Slides are not to be reproduced without permission of author.
11C-DTBZ in DEMENTIA

K1

NC  AD  DLB  PD

DVR

Courtesy Kirk Frey

Slides are not to be reproduced without permission of author.
DAT SPECT IMAGING CAN ALSO DISTINGUISH DLB FROM AD ON THE BASIS OF STRIATAL DENERVATION

(O’Brien et al. 2004)

I-123 FP-CIT

Slides are not to be reproduced without permission of author.
### Table 3 Sensitivity and specificity of $^{123}$I–FP–CIT SPECT v. follow-up clinical diagnosis

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Reader</th>
<th>Participants with rateable scans, $n$</th>
<th>Participants with abnormal scans, $n$</th>
<th>Accuracy, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>A</td>
<td>80</td>
<td>65</td>
<td>81.3 (71.0–89.1)</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>80</td>
<td>59</td>
<td>73.8 (62.7–83.0)</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>80</td>
<td>63</td>
<td>78.8 (68.2–87.1)</td>
</tr>
<tr>
<td>Specificity</td>
<td>A</td>
<td>121</td>
<td>115</td>
<td>95.0 (89.5–98.2)</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>122</td>
<td>112</td>
<td>91.8 (85.4–96.0)</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>120</td>
<td>111</td>
<td>92.5 (86.2–96.5)</td>
</tr>
</tbody>
</table>

SPECT, single photon emission computed tomography.

---

DAT SPECT can accurately distinguish DLB from prototypical AD

but DA imaging may not be able to distinguish DLB from PDD (PD with dementia)
PDD vs. DLB
The 1-year rule

1  

Motor \( \psi \)  

2 (..\( x \)) yr

1  

Motor \( \psi \)  

DLB

Motor \( \psi \)  

PDD

Slides are not to be reproduced without permission of author.
## DLB vs. PDD

**The 1-year rule & \( \beta \)-amyloid burden**

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2 (( \ldots \times )) yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motor</td>
<td>( \psi )</td>
<td>DLB</td>
</tr>
<tr>
<td>( \psi )</td>
<td>Motor</td>
<td>DLB</td>
</tr>
<tr>
<td>Motor</td>
<td>( \psi )</td>
<td>PDD</td>
</tr>
</tbody>
</table>

\( ^{11} \text{C-PIB} \)

*Slides are not to be reproduced without permission of author.*
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 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.
## DISCUSSION DA DIAGNOSTIC IMAGING IN PD

<table>
<thead>
<tr>
<th>Opportunities</th>
<th>Challenges</th>
</tr>
</thead>
<tbody>
<tr>
<td>Select subjects for neuroprotective therapy, the early institution of which confers a better outcome</td>
<td>It is unclear when, or indeed whether, clinically normal subjects will go on to develop parkinsonism.</td>
</tr>
<tr>
<td>May help with (early) diagnosis in clinically uncertain subjects</td>
<td>If subject has good L-DOPA response, confirmation of diagnosis does not alter management</td>
</tr>
<tr>
<td>Prognostication (infers non-degenerative movement disorder)</td>
<td>Lacks specificity to DDx IPD from atypical parkinsonism</td>
</tr>
<tr>
<td>Redirects diagnostic process</td>
<td>Concern about over-use general practitioner ($)</td>
</tr>
<tr>
<td>Justifies more aggressive anti-ET tremor therapy (pharmacologically &amp; selection of DBS surgical target)</td>
<td>May not help with DDx of non-PD tremor syndromes (ET, Holmes, pure cerebellar etc)</td>
</tr>
<tr>
<td>Braakian model of IPD: the use of imaging to detect non-dopaminergic abnormalities representing disease caudal to the midbrain remains in its infancy</td>
<td></td>
</tr>
</tbody>
</table>

Preclinical/prodromal PD Dx
Clinical PD Dx
Positive predictive value (PPV)

Clinical PD Dx
Negative predictive value (NPV)
## DISCUSSION

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

<table>
<thead>
<tr>
<th>Opportunities</th>
<th>Challenges</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical DLB Dx</td>
<td>At present, practical impact on clinical management still remains limited.</td>
</tr>
<tr>
<td>Positive predictive value (PPV)</td>
<td>Even with potential advent of anti-amyloid therapy, benefit of diagnostic stratification remains uncertain.</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical PD Dx</td>
<td>FDG or β-amyloid PET may provide alternative strategy to aid with diagnostic process.</td>
</tr>
<tr>
<td>Negative predictive value (NPV)</td>
<td></td>
</tr>
</tbody>
</table>

May help with (early) diagnosis in clinically uncertain subjects

May help with selection of pharmacotherapy: More aggressive cholinergic therapy & avoidance of neuroleptics in DLB

May help to better understand nature of parkinsonism in dementia i.e., redirects diagnostic process toward FTD, drug-induced or vascular etiology.
Cost-effectiveness

Antonini et al. Mov Disord 2008;2202-2209

123I-FP-CIT SPECT is likely to be regarded as economically advantageous to differentiate ET from PD, increasing time on potentially beneficial therapy at a lower overall cost to the healthcare system.

Slides are not to be reproduced without permission of author.
Radionuclide scanning to diagnose Parkinson disease: is it cost-effective?

A Jon Stoessl

A recent study has concluded that the use of 123I-2β-carbomethoxy-3β-(4-iodophenyl)-N-(3-fluoropropyl)nortropane single-photon emission computed tomography (123I-FP-CIT SPECT) is cost-effective or cost-saving in patients in whom the diagnosis of Parkinson disease versus essential tremor is uncertain. This conclusion is based on numerous assumptions, not all of which are likely to be universally applicable. The economic advantages associated with the use of 123I-FP-CIT SPECT will vary depending on the prevalence of Parkinson disease in the group of patients with uncertain diagnosis, the cost of usual clinical evaluation including other diagnostic tests, and the consequences of either delaying or inappropriately instituting dopaminergic therapy. The cost-effectiveness of radionuclide scanning is likely to increase in the future if a therapy is developed with a convincing impact on disease progression, the early institution of which confers a better outcome.
Cost-effective multi-tiered screening approach for PD vs. ET diagnosis

1. Uncertain Dx ET vs PD
2. ET: nl smell
3. PD: ↓ smell

ET & equivocal l-DOPA challenge

*Slides are not to be reproduced without permission of author.*