Dopamine Transporter Loss Visualized With FP-CIT SPECT in the Differential Diagnosis of Dementia With Lewy Bodies

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Background: Dementia with Lewy bodies (DLB) is a common form of late-life dementia that can be difficult to differentiate from other disorders, especially Alzheimer disease (AD), during life. At autopsy the striatal dopaminergic transporter is reduced.

Objectives: To examine the extent and pattern of dopamine transporter loss using iodine I 123–radiolabeled 2β-carbomethoxy-3β-(4-iodophenyl)-N-(3-fluoropropyl) nortropane (FP-CIT) with single-photon emission computed tomography (SPECT) in DLBs compared with other dementias and to assess its potential to enhance a differential diagnosis.

Design: Cohort study comparing FP-CIT with criterion standard of consensus clinical diagnosis.

Setting: General hospital.

Participants: One hundred sixty-four older subjects (33 healthy older control subjects, 34 with NINCDS/ADRDA [National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association]-confirmed AD, 23 with consensus guideline–confirmed DLB, 38 with United Kingdom's Parkinson Disease Society Brain Bank–confirmed Parkinson disease [PD], and 36 with PD and dementia).

Interventions: Injection of 123I-2β-carbomethoxy-3β-(4-iodophenyl)-N-(3-fluoropropyl) nortropane with SPECT scan performed at 4 hours.

Main Outcome Measures: Visual ratings of scans and region of interest analysis.

Results: Significant reductions (P<.001) in FP-CIT binding occurred in the caudate and anterior and posterior putamens in subjects with DLB compared with subjects with AD and controls. Transporter loss in DLBs was of similar magnitude to that seen in PD, but with a flatter rostrocaudal (caudate-putamen) gradient (P=.001), while the greatest loss in all 3 areas was seen in those who had PD and dementia. Both region of interest analysis and visual ratings provided good separation between DLBs and AD (region of interest: sensitivity, 78%; specificity, 94%; positive predictive value, 90%) but not among subjects with DLB, PD, and PD with dementia.

Conclusions: Dopamine transporter loss can be detected in vivo using FP-CIT SPECT in DLB. Further studies, especially of subjects with DLB without PD, are required to fully establish use in clinical practice.

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Parkinson disease is a major risk factor for subsequent dementia, but it is unclear whether the same neurobiological changes underpin PD with dementia (PDD) and DLB. Current diagnostic criteria do not allow the diagnosis of DLB in those who have had PD for longer than 12 months (such cases are classified as having PDD). To our knowledge, there have been no previous FP-CIT studies of PDD, yet information about patterns of dopaminergic loss may shed important light on understanding the relationship between DLB and PDD, while dopaminergic changes in the caudate may contribute to cognitive impairments in PDD.

This study sought to investigate FP-CIT changes in subjects with DLB compared with subjects with AD and healthy control subjects and to examine possible differences among subjects with DLB, cognitively intact subjects with PD, and subjects with PDD. Our main aims were to (1) determine the pattern and clinical correlates of dopamine transporter loss in DLB as assessed using 123I–FP-CIT SPECT compared with controls and subjects with PD, AD, or PDD; and (2) to examine whether FP-CIT changes might be a useful diagnostic discriminator between DLB and AD. We hypothesized that (1) FP-CIT reductions would occur in subjects with DLB but not in subjects with AD; (2) that these would be as marked as those in PD but that subjects with PDD would have even greater changes, particularly in the caudate; and (3) that there would be an association between caudate uptake and dementia severity in DLB and PDD.

PATIENTS AND HEALTHY CONTROLS

We studied 164 subjects (33 healthy older control subjects, 34 with NINCDS/ADRDA [National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer’s Disease and Related Disorders Association]–confirmed AD, 23 with consensus guideline–confirmed DLB, 38 with United Kingdom’s Parkinson Disease Society Brain Bank criteria–confirmed PD, and 36 with established PD who subsequently developed dementia with the neuropsychiatric features of DLB [PDD]). Patients meeting study criteria were obtained by screening all existing cases and new referrals seen by old age psychiatric and neurological outpatient hospital services between January 1, 1999, and December 31, 2002. Healthy controls were recruited from friends and spouses of patients included in this and other research studies. The study was approved by the local research ethics committee and the United Kingdom’s Department of Health’s Administration of Radioactive Substances Advisory Committee. All participants and the nearest relative for patients gave informed written consent.

Subjects underwent detailed physical, neurological, and neuropsychiatric examinations, including history, mental state, and physical examination and, for subjects with dementia, a standard dementia blood screen. Standardized schedules administered included the Mini-Mental State Examination, the Cambridge Cognitive Examination, and the motor function subsection of the Unified Parkinson’s Disease Rating Scale (UPDRS III). Diagnosis was made by consensus between experienced clinicians using the NINCDS/ADRDA criteria for AD, the consensus guidelines for DLB, and the United Kingdom’s Parkinson Disease Society Brain Bank criteria for PD. Parkinson disease with dementia was diagnosed when the consensus guidelines for DLB were fulfilled but when the duration of motor function symptoms preceded the cognitive impairment by more than 1 year. Diagnosis was made blind to FP-CIT SPECT imaging. All subjects with AD met criteria for probable AD, 17 subjects with DLB fulfilled probable DLB criteria, and 6 subjects with DLB fulfilled possible DLB criteria, while all subjects with PD and PDD met the clinical diagnostic criteria for PD. No subject was receiving medication that was suspected to affect the dopamine transporter including antiparkinsonian medication (except levodopa), central nervous system stimulants (eg, cocaine, amphetamine, or methylphenidate), and other agents (eg, fenfluramine, amoxapine, or buspirone).

SPECT DATA ACQUISITION

Subjects were imaged using a triple-detector rotating gamma camera (model 3000XP; Picker, Philips Medical Systems, Amsterdam, the Netherlands) with a high-resolution fan-beam collimator, 4 hours (SD, 15 minutes) after a bolus intravenous injection of 150 MBq of 123I-FP-CIT (DaTSCAN; Amersham Health, London, England). One hundred twenty-eight 15-second views over a 360° orbit were acquired on a 128×128-pixel matrix with a square pixel dimension of 3.3 mm. Imaging time was 30 minutes. Image reconstruction was performed without attenuation correction using filtered back projection with a 3-dimensional constructed Butterworth filter (order 13, cutoff 0.3 cycles/cm⁻¹). Axial resolution using these parameters was measured using an 123I line source and was 12.2 mm at full-width half-maximum setting. Scans were reoriented manually in the axial and transverse planes to ensure that left and right striatum were aligned. The reconstructed images were subsequently transferred to a personal computer for further analysis.

SPECT DATA ANALYSIS

Semiquantitative region of interest (ROI) analysis was performed using the ANALYZE 4.0 (Mayo Clinic, Rochester, Minn) biomedical imaging software by a single operator (S.C.) blind to all clinical information and diagnosis. Striatal binding was determined from the specific to nonspecific activity ratios, with specific binding calculated from ROIs in coronal sections and nonspecific from an occipital ROI from the transverse section containing maximum striatal intensity. Square ROIs of a fixed size (16×16 mm) were positioned at 3 distinct locations within the striatum to obtain measurements of the caudate, anterior putamen, and posterior putamen. Optimal size for the size and location of the ROIs was determined from a standard stereotactic brain atlas and then verified prior to the current analysis using the same software analysis on 40 T1-weighted whole-brain magnetic resonance images (8 from each study group) from the same subjects included in this study. For the caudate, the second coronal section after the one that initially showed striatal activity was chosen (section 2) and the square ROI was centred on caudate activity. The anterior and posterior putamen ROIs were then placed in the appropriate anatomical position; a further 2 (ie, on section 4) and 6 (ie, on section 8) coronal sections, respectively, in a posterior direction away from the section defining the caudate, that is, the relative positions between each ROI along the long axis of the striatum, remained constant for each subject (Figure 1). Nonspecific uptake was calculated from an ROI in the occipital lobe from a transaxial section that included most of the primary and secondary visual cortices. Specific–nonspecific activity ratios
for the 3 ROIs (in caudate and in the anterior and posterior putamens) for each hemisphere were determined using the following formula:

\[ \text{\textsuperscript{123}I–FP-CIT Binding}_{\text{Caudate, Anterior Putamen, Posterior Putamen}} = \frac{\text{Specific Uptake}_{\text{Caudate, Anterior Putamen, Posterior Putamen}}}{\text{Nonspecific Uptake}_{\text{Occipital}}} \]

Mean left and right values for each subject for each ROI were calculated. Intrarater reliability was assessed by repeating 5 measurements on 3 randomly selected blinded images. Mean coefficients of variation were 0.14% for the caudate, 2.00% for the anterior putamen, and 4.75% for the posterior putamen.

**VISUAL RATING OF SCANS**

Visual qualitative assessment of scans blind to diagnosis was undertaken by 5 raters (J.T.O., S.C., J.F., E.D.W., and M.F.) following a brief training session using transverse sections displayed on a computer screen (available at: http://www.psychology.nottingham.ac.uk/staff/cr1/mricro.html). Scans were rated independently by each panel member, with consensus taken when there was disagreement, using the following 4-point scale developed for previous investigations of FP-CIT in PD\textsuperscript{15}:

- 0 indicates normal;
- 1, a putamen reduction on 1 side;
- 2, a bilateral putamen reduction;
- 3, a bilateral caudate and putamen reduction.

**STATISTICAL ANALYSIS**

Data were analyzed using the Statistical Package for Social Sciences (SPSS for Windows, version 10.0; SPSS Inc, Chicago, Ill) using analysis of variance with the Gabriel post hoc tests for normally distributed data and the nonparametric Mann-Whitney test. The degree of agreement between observers (intersubject variability) was assessed using the Cohen weighted \( k \) test. Correlations between clinical and SPECT variables were examined using the Pearson \( r \) or Spearman \( \rho \) as appropriate. All statistical tests were reported as significant if \( P \leq .05 \). Diagnostic accuracy of FP-CIT in relation to the clinical diagnosis was determined by calculating sensitivity, specificity, positive predictive value, and likelihood ratio for visual ratings (0 being normal; 1-3, abnormal) and the posterior putamen ROI (uptake within 1.5 SDs of control mean being considered normal, a cutoff that correctly identified all but 2 controls).

**RESULTS**

**SUBJECT CHARACTERISTICS**

Table 1 summarizes the group characteristics. Groups were matched for sex and broadly matched for age, although the AD group were slightly older than both the controls (\( P = .04 \)) and subjects with PDD (\( P < .001 \)). Groups with dementia had similar degrees of cognitive impairment. As expected, those with DLB, PD, and PDD had significantly higher UPDRS III scores than subjects with AD and controls (\( P < .001 \)), with patients with AD having higher scores than controls (\( P < .001 \)). There were no significant differences in UPDRS III scores between those with DLB and those with PD. Only 2 subjects with DLB were receiving levodopa.

**\textsuperscript{123}I–FP-CIT SPECIFIC TO NONSPECIFIC BINDING RATIOS**

Table 2 lists the mean specific–nonspecific activity ratios for each of the 3 ROIs across each group and Figure 2 shows representative \textsuperscript{123}I–FP-CIT SPECT scans of a control and subjects with AD, DLB, PD, and PDD. There were no sex differences in FP-CIT binding. Groups with DLB, PD, and PDD demonstrated a significant bilateral reduction in uptake in all 3 striatal areas compared with both subjects with AD and controls (\( P < .001 \)). The greatest reductions were seen in subjects with PDD who had sig-
Table 1. Demographic and Neuropsychological Data of Subjects Studied Using 123I–FP-CIT SPECT*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control (n = 33)</th>
<th>With AD (n = 34)</th>
<th>With DLB (n = 23)</th>
<th>With PD (n = 38)</th>
<th>With PD and DLB (n = 36)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, M/F</td>
<td>17/16</td>
<td>15/19</td>
<td>15/8</td>
<td>28/10</td>
<td>25/11</td>
<td>.06</td>
</tr>
<tr>
<td>Age, y</td>
<td>74.8 (6.3)</td>
<td>78.9 (5.6)</td>
<td>75.9 (7.1)</td>
<td>75.6 (5.1)</td>
<td>72.1 (5.4)</td>
<td>.04‡</td>
</tr>
<tr>
<td>MMSE score (maximum score, 30)</td>
<td>28.2 (1.5)</td>
<td>17.3 (4.9)</td>
<td>16.3 (5.8)</td>
<td>26.5 (2.1)</td>
<td>19.1 (5.6)</td>
<td>&lt;.001‡</td>
</tr>
<tr>
<td>CAMCOG score (maximum score, 107)</td>
<td>94.4 (3.9)</td>
<td>57.0 (17.9)</td>
<td>58.7 (14.2)</td>
<td>88.1 (8.3)</td>
<td>64.0 (16.6)</td>
<td>&lt;.001§</td>
</tr>
<tr>
<td>UPDRS III score (maximum score, 108)</td>
<td>1.2 (1.9)</td>
<td>5.6 (4.9)</td>
<td>26.1 (13.1)</td>
<td>24.9 (10.5)</td>
<td>37.8 (11.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>No. (%) of subjects with parkinsonism†</td>
<td>0</td>
<td>4 (12)</td>
<td>19 (83)</td>
<td>38 (100)</td>
<td>36 (100)</td>
<td>NA</td>
</tr>
<tr>
<td>No. (%) of subjects receiving levodopa therapy‡</td>
<td>0</td>
<td>0</td>
<td>2 (9)</td>
<td>27 (71)</td>
<td>31 (88)</td>
<td>NA</td>
</tr>
<tr>
<td>Duration of illness, mo</td>
<td>NA</td>
<td>39.6 (39.5)</td>
<td>29.5 (20.9)</td>
<td>63.5 (87.4)</td>
<td>88.5 (69.5)</td>
<td>.009#</td>
</tr>
</tbody>
</table>

Abbreviations: AD, Alzheimer disease; CAMCOG, Cambridge Cognitive Examination; DLB, dementia with Lewy bodies; 123I–FP-CIT, iodine I 123–radiolabeled 2β-carbomethoxy-3β-(4-iodophenyl)–N-(3-fluoropyrrolidone); MMSE, Mini-Mental State Examination; NA, not applicable; NS, not significant; PD, Parkinson disease; SPECT, single-photon emission computed tomography; UPDRS III, Unified Parkinson’s Disease Rating Scale subsection 3: motor function.

*Data are expressed as mean (SD) unless otherwise indicated.
†Subjects with AD greater than controls using the Gabriel post hoc tests.
‡Subjects with AD greater than subjects with PD and DLB using the Gabriel post hoc tests.
§Controls and subjects with PD greater than subjects with AD, DLB, and PD and DLB using the Gabriel post hoc tests. Note that the values for subjects with AD vs subjects with DLB and controls vs subjects with PD were not statistically significant.
¶Defined as a UPDRS III score higher than 10.
#Subjects with PD and DLB greater than subjects with PD, DLB, and AD using the Mann-Whitney post hoc tests.

Figure 3 shows the mean and 95% confidence intervals for normalized FP-CIT uptake. Compared with controls, the mean magnitude of activity reduction in the caudate and anterior and posterior putamens was 30%, 38%, and 40% for subjects with DLB; 26%, 33%, and 47% for subjects with PD; and 47%, 58%, and 59% for subjects with PDD, respectively. To determine rostrocaudal gradients of transporter loss between caudate and putamen, we calculated the striatal gradient (ratio) of FP-CIT uptake for each subject (ie, caudate activity/posterior putamen activity). Mean (SD) gradients were as follows: controls, 1.20 (0.15); subjects with AD, 1.17 (0.18); subjects with PD, 1.46 (0.27); subjects with PDD, 1.77 (0.43); and subjects with PDD, 1.44 (0.30). Gradients were significantly different between groups (F[4,139] = 26.97, P < .001) with DLB, PD, and PDD all having lower binding in the putamen compared with the caudate than subjects with AD and the controls. However, the gradient was significantly steeper in those with PD than in those with DLB (P = .001) or those with PDD (P = .01), indicating relatively greater selective reduction in putamen uptake in PD compared with DLB and PDD.

VISUAL RATING OF 123I–FP-CIT SPECT IMAGES

The mean (SD) multirater κ statistic for agreement between the 5 raters was 0.88 (0.02), indicating excellent overall agreement. The degree of agreement between each

Table 2. Summary of Specific–Nonspecific Activity Ratios in Each Region of Interest Across Subject Groups*

<table>
<thead>
<tr>
<th>Binding Ratios</th>
<th>Control (n = 33)</th>
<th>With AD (n = 34)</th>
<th>With DLB (n = 23)</th>
<th>With PD (n = 38)</th>
<th>With PD and DLB (n = 36)</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean caudate</td>
<td>3.82 (0.46)</td>
<td>3.47 (0.49)</td>
<td>2.67 (0.56)</td>
<td>2.82 (0.57)</td>
<td>2.01 (0.48)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Mean anterior putamen</td>
<td>4.39 (0.54)</td>
<td>4.17 (0.73)</td>
<td>2.71 (0.81)</td>
<td>2.87 (0.75)</td>
<td>1.83 (0.53)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Mean posterior putamen</td>
<td>3.20 (0.49)</td>
<td>3.01 (0.49)</td>
<td>1.92 (0.66)</td>
<td>1.70 (0.63)</td>
<td>1.31 (0.28)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>L caudate</td>
<td>3.68 (0.51)</td>
<td>3.37 (0.49)</td>
<td>2.65 (0.58)</td>
<td>2.76 (0.56)</td>
<td>2.00 (0.47)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>R caudate</td>
<td>3.94 (0.51)</td>
<td>3.56 (0.63)</td>
<td>2.70 (0.68)</td>
<td>2.88 (0.66)</td>
<td>2.02 (0.55)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>L anterior putamen</td>
<td>4.46 (0.68)</td>
<td>4.14 (0.68)</td>
<td>2.79 (0.84)</td>
<td>3.00 (0.81)</td>
<td>1.87 (0.55)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>R anterior putamen</td>
<td>4.32 (0.53)</td>
<td>4.19 (0.86)</td>
<td>2.63 (0.81)</td>
<td>2.75 (0.78)</td>
<td>1.80 (0.54)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>L posterior putamen</td>
<td>3.20 (0.54)</td>
<td>3.00 (0.46)</td>
<td>1.93 (0.71)</td>
<td>1.72 (0.69)</td>
<td>1.33 (0.31)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>R posterior putamen</td>
<td>3.20 (0.55)</td>
<td>3.03 (0.57)</td>
<td>1.90 (0.65)</td>
<td>1.67 (0.62)</td>
<td>1.29 (0.30)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviations: AD, Alzheimer disease; DLB, dementia with Lewy bodies; L, left; PD, Parkinson disease; R, right.

*Data are expressed as mean (SD).
†Controls and subjects with AD greater than subjects with DLB, PD, and PD and DLB using Gabriel’s post hoc tests. All groups greater than subjects with PD and DLB using Gabriel’s post hoc tests. Note that the values for subjects with PD vs subjects with DLB are not statistically significant.

Significantly lower uptake in all areas than all of the other groups (P < .05). There were no differences in either hemisphere between controls and subjects with AD or between subjects with DLB and those with PD in any ROI. The mean and 95% confidence intervals for normalized FP-CIT uptake. Compared with controls, the mean magnitude of activity reduction in the caudate and anterior and posterior putamens was 30%, 38%, and 40% for subjects with DLB; 26%, 33%, and 47% for subjects with PD; and 47%, 58%, and 59% for subjects with PDD, respectively. To determine rostrocaudal gradients of transporter loss between caudate and putamen, we calculated the striatal gradient (ratio) of FP-CIT uptake for each subject (ie, caudate activity/posterior putamen activity). Mean (SD) gradients were as follows: controls, 1.20 (0.15); subjects with AD, 1.17 (0.18); subjects with PD, 1.46 (0.27); subjects with PDD, 1.77 (0.43); and subjects with PDD, 1.44 (0.30). Gradients were significantly different between groups (F[4,139] = 26.97, P < .001) with DLB, PD, and PDD all having lower binding in the putamen compared with the caudate than subjects with AD and the controls. However, the gradient was significantly steeper in those with PD than in those with DLB (P = .001) or those with PDD (P = .01), indicating relatively greater selective reduction in putamen uptake in PD compared with DLB and PDD.

VISUAL RATING OF 123I–FP-CIT SPECT IMAGES

The mean (SD) multirater κ statistic for agreement between the 5 raters was 0.88 (0.02), indicating excellent overall agreement. The degree of agreement between each
rater and the final consensus rating was also calculated (κ values, 0.91, 0.94, 0.91, 0.91, and 0.93) that also demonstrated excellent concordance. Table 3 summarizes diagnostic discrimination of the consensus $^{123}$I–FP-CIT visual rating and ROI data from the posterior putamen. As can be seen, diagnostic discrimination was similar when
Using visual ratings and ROIs when comparing groups who have basal ganglia disease with controls, although the comparison with those with AD showed a higher specificity for ROI analysis. In the clinically important distinction between DLB and AD, visual ratings had a sensitivity of 78%, a specificity of 85%, and a positive predictive value of 78%, while ROIs analyses had a sensitivity of 78%, a specificity of 94%, and a positive predictive value of 89%. There was no difference in the proportion of abnormal scans between subjects taking and those not taking levodopa ($\chi^2 = 2.2, P = .19$). Of the 4 subjects with DLB who had low UPDRS III scores (<10), 3 had abnormal scans. Of the 12 subjects with AD who had some parkinsonism (UPDRS III score, >10), only 1 had an abnormal scan. Of the 5 subjects with DLB who were misclassified, 3 had a diagnosis of possible DLB and 2 had a diagnosis of probable DLB. The 2 subjects with AD who were misclassified were among the oldest participants in the study (aged 86 and 89 years; see “Correlations” subsection following).

### CORRELATIONS

Visual ratings negatively correlated with FP-CIT binding in all 3 ROIs (caudate, $r = -0.83, P < .001$; anterior putamen, $r = -0.86, P < .001$; and posterior putamen, $r = -0.88, P < .001$). There was a significant inverse correlation in subjects with AD only between age and FP-CIT uptake in the anterior putamen ($r = -0.46, P = .006$) and posterior putamen ($r = -0.50, P = .002$) but not in the caudate ($P = .16$). There was an inverse correlation between FP-CIT uptake in the posterior putamen and the UPDRS III score in subjects with AD ($r = -0.48, P = .004$) with trends toward a correlation in DLB ($r = -0.40, P = .06$) and PD ($r = -0.31, P = .06$) but not in PDD ($r = -0.18, P = .29$). However, in subjects with AD only age correlated with the UPDRS III score ($r = 0.55, P = .001$) and the partial correlation between the FP-CIT and UPDRS III score became nonsignificant when controlling for age. A significant correlation between caudate (but not putamen) uptake and Mini-Mental State Examination score was seen in subjects with PDD ($r = 0.33, P = .047$) but not in subjects with PD ($r = 0.1, P = .56$), DLB ($r = 0.32, P = .14$), or AD ($r = -0.016, P = .37$).

### COMMENT

We found a significant reduction at all levels of the striatum (caudate and anterior and posterior putamens) of FP-CIT binding on SPECT in subjects with DLB, PD, and PDD compared with similarly aged subjects with AD and healthy older controls. The reduction in binding in those with DLB was equivalent to that seen in those with PD, although there was a difference in the rostrocaudal distribution of loss, with selectively greater involvement of posterior putamen in subjects with PD and a more even reduction across the whole striatum (caudate and putamen) in subjects with DLB and PDD. Subjects with PDD had the greatest reduction in FP-CIT binding. The reduction demonstrated on semiquantitative ROIs analyses was apparent on visual inspection of scans using a simple 4-point scale that had excellent reliability and could be used after minimal training.

Our results confirm demonstration of reduced dopaminergic transporter using CIT in DLB and support the only other previous investigation of FP-CIT in DLB. In addition, we examined the rostrocaudal distribution of transporter loss and found the putamen to be selectively affected in PD but more global striatal involvement in DLB and PDD. An autopsy study of the transporter using tritiated methoxytetrabenazine found significant reductions of DLB in the caudate, similar in magnitude to the loss in the posterior putamen. Our results support and extend this finding, showing that such caudate involvement occurs in vivo at the mild to moderate stages of dementia. We found a significant although modest correlation between the Mini-Mental State Examination score and the FP-CIT uptake in PDD, providing some support for the view that dopaminergic loss here contributes to cognitive impairment in PDD, although no such correlation was seen in subjects with DLB. Accurate antemortem recognition of DLB is important for optimal clinical treatment. Imaging of the dopaminergic system, using ligands such as FP-CIT, may have

### Table 3. Diagnostic Discrimination of FP-CIT Between Groups*

<table>
<thead>
<tr>
<th>Variables</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive Predictive Value</th>
<th>Likelihood Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Visual Rating</td>
<td>ROIs</td>
<td>Visual Rating</td>
<td>ROIs</td>
</tr>
<tr>
<td>Compared with healthy older control subjects</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subjects with DLB (n = 23)</td>
<td>78</td>
<td>78</td>
<td>94</td>
<td>94</td>
</tr>
<tr>
<td>Subjects with PD (n = 38)</td>
<td>84</td>
<td>82</td>
<td>94</td>
<td>94</td>
</tr>
<tr>
<td>Subjects with PDD (n = 36)</td>
<td>97</td>
<td>97</td>
<td>94</td>
<td>94</td>
</tr>
<tr>
<td>Compared with subjects with AD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subjects with DLB (n = 23)</td>
<td>78</td>
<td>78</td>
<td>85</td>
<td>84</td>
</tr>
<tr>
<td>Subjects with PD (n = 38)</td>
<td>84</td>
<td>82</td>
<td>85</td>
<td>84</td>
</tr>
<tr>
<td>Subjects with PDD (n = 36)</td>
<td>97</td>
<td>97</td>
<td>85</td>
<td>94</td>
</tr>
</tbody>
</table>

Abbreviations: AD, Alzheimer disease; DLB, dementia with Lewy bodies; FP-CIT, 2β-carbomethoxy-3β-(4-iodophenyl)-N-(3-fluoropropyl) nortropane; PD, Parkinson disease; PDD, PD with dementia and DLB; ROIs, regions of interest.

*Data are given as percentages unless otherwise indicated. For the visual rating a score of 0 was considered normal and a score of 1 through 3 was considered abnormal. For ROIs data uptake in the mean posterior putamen was used (since this region showed the greatest changes in subjects with DLB, PD, and PDD) and a cutoff of 1.5 SDs from the control mean was used.
considerable potential to assist accurate antemortem recognition of DLB. Imaging is well tolerated by patients, particularly at the early stages of disease, SPECT is widely available, and analysis by visual scan rating is quick and simple, requiring minimal specific training. The reductions in FP-CIT have a clear and obvious relationship between one of the major neurobiological changes of DLB, that of dopaminergic loss. It is increasingly being used to assist in the in vivo recognition of PD and the current study showed similar diagnostic accuracy for DLB as for PD. Sensitivity for DLB was 78% and specificity 94% for both controls and subjects with AD when using a 1.5-SD cutoff from control mean on putamen uptake. While the study is confounded by the presence of parkinsonism, which was present in most subjects with DLB and absent in most subjects with AD, 3 of the 4 subjects with DLB who did not have parkinsonism had abnormal SPECT scans while only 1 of the 12 subjects with AD who had parkinsonism had an abnormal SPECT scan. In addition, there was no significant correlation between the FP-CIT uptake and the UPDRS III score in subjects with DLB.

Strengths of the current study include a large sample size, rigorous clinical diagnostic assessment according to a standardized protocol, use of a triple-detector gamma camera for accurate visualization of striatal uptake, and comparison of ROIs analyses with visual ratings. Visual ratings detected striatal degeneration and discriminated between groups almost as well as the more elaborate ROIs analyses. However, larger studies, including more subjects with DLB who did not have parkinsonism and with autopsy confirmation of diagnosis, are required to assess the usefulness of this technique in clinical practice. Further work is also needed to investigate whether these changes occur at early (presymptomatic) stages, the degree to which they might underpin specific cognitive impairments in DLB and PDD, and how they progress over time.

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REFERENCES