In Vivo Assessment of Vesicular Monoamine Transporter Type 2 in Dementia With Lewy Bodies and Alzheimer Disease

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Objective: To assess the diagnostic potential of imaging striatal monoaminergic terminal integrity with the vesicular monoamine transporter type 2 (VMAT2) radioligand 18F 9-fluropropyl- (+)-dihydrotetrabenazine ([18F]AV-133) and positron emission tomography to distinguish dementia with Lewy bodies (DLB) from Alzheimer disease (AD).

Design, Setting, and Participants: Nine patients with DLB, 10 patients with AD, 20 patients with Parkinson disease (PD), and 10 healthy age-matched control subjects underwent [18F]AV-133 positron emission tomography studies. VMAT2 density was calculated through normalized tissue uptake value ratios at 120 to 140 minutes postinjection using the primary visual cortex as the reference region.

Main Outcome Measure: Comparison of the tissue ratio for [18F]AV-133 between the different clinical diagnostic groups.

Results: Lower VMAT2 densities were observed in patients with DLB when compared with patients with AD especially in the posterior putamen (caudate: mean [SD], 1.24 [0.6] vs 2.83 [0.9]; P < .001; effect size = 2.1; anterior putamen: mean [SD], 0.90 [0.5] vs 3.01 [0.9]; P < .001; effect size = 2.9; posterior putamen: mean [SD], 0.62 [0.5] vs 2.87 [0.8]; P < .001; effect size = 3.4). Compared with healthy controls, [18F]AV-133 tissue ratios were significantly lower by 88% and 74% in the posterior putamen, 74% and 65% in the anterior putamen, and 53% and 51% in the caudate nucleus of patients with PD and DLB, respectively. In contrast to patients with PD and DLB, no reductions were observed in patients with AD.

Conclusions: [18F]AV-133 allows assessment of nigrostriatal degeneration in Lewy body diseases. [18F]AV-133 can robustly detect reductions of dopaminergic nigrostriatal afferents in patients with DLB and assist in the differential diagnosis from AD.

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While Alzheimer disease (AD) is the most common cause of dementia in elderly individuals, postmortem studies have found dementia with Lewy bodies (DLB) to account for 20% of cases. The pathological hallmark of DLB is the presence of α-synuclein–containing Lewy bodies within the neocortical, limbic, and paralimbic regions, but as with idiopathic Parkinson disease (PD), there is also substantial loss of pigmented dopaminergic neurons in the substantia nigra and the consequent marked dopaminergic terminal loss in the striatum. The noninvasive evaluation of nigrostriatal dopaminergic integrity by positron emission tomography (PET) and single-photon emission computed tomography (SPECT) has provided useful clinical information for early and differential diagnosis of PD and for diagnosis of DLB from AD. The evaluation of nigrostriatal dopaminergic integrity was achieved by either assessing presynaptic dopamine synthesis or dopamine transporter (DAT) or vesicular monoamine transporter type 2 (VMAT2) densities. VMAT2 is the transporter responsible for uptake and storage of monoamines (dopamine, serotonin, and norepinephrine) into vesicles in monoamine-containing neurons. VMAT2 is mainly located on synaptic vesicles at the nerve terminals but also on dense core vesicles in nerve cell bodies and dendrites. [11C]-labeled dihydrotetra benazine ([11C]DTBZ) has been successfully used to quantify VMAT2 in PD as well as in the differential diagnosis between DLB and AD. These PET studies have shown decreased [11C]DTBZ binding to VMAT2 in the striatum of patients with PD and DLB. A reduction of VMAT2 reflects the degeneration of nigrostriatal dopaminergic neurons and is less suscept-
A novel 18F-labeled tetrabenazine derivative, 9-fluoropropyl(-)+dihydrotetrabenazine ([18F]AV-133), that selectively binds with high affinity to VMAT2 has been developed to assess VMAT2 density in vivo with PET.22-24 [18F]AV-133 PET has been shown to detect VMAT2 reductions in PD. 25 To assess the integrity of monoaminergic innervation as a differentiating feature in neurodegenerative diseases, a PET study was performed to compare [18F]AV-133 binding in patients with DLB, PD, AD as well as healthy controls (HCs).

### METHODS

#### PARTICIPANTS

Written informed consent was obtained from all participants. Approval for the study was obtained from the Austin Health Human Research Ethics Committee. Nine patients with DLB (mean [SD] age, 68.9 [7.9] years; range, 56-80 years), 10 patients with PD (mean [SD] age, 69.3 [13.3] years; range, 56-88 years), 20 patients with AD (mean [SD] age, 67.0 [9.1] years; range, 53-82 years), and 10agematched HCs (mean [SD] age, 67.5 [6.6] years; range, 57-83 years) were included in the study. The HCs were recruited by advertisement, while participants with AD and DLBL were recruited from the Austin Health Memory Disorders Clinic. All patients with AD met National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer’s Disease and Related Disorders Association criteria for probable AD.26 All patients with DLBL met consensus criteria for probable DLBL27 including progressive cognitive impairment with at least 2 of the 3 core features of (1) persistent visual hallucinations, (2) parkinsonian signs, and (3) fluctuation in cognitive performance. These criteria have a specificity of 90% for postmortem diagnosis of DLBL.28 Participants fulfilling clinical criteria for PD were recruited from Movement Disorders Clinics. All HCs performed within (<1.5 SD) the published norms for their age group on neuropsychological tests. Data from most of the HCs and patients with PD have appeared in a previous report.23 All subjects underwent neurological and neuropsychological examinations. In regard to dopaminergic medication, 15 patients with PD were receiving carbidopa-levodopa; 2 were receiving selegiline; 2, levodopa and benserazide; and 1, pramipexole. In regard to dopaminergic medication among patients with DLBL, 3 were receiving carbidopa-levodopa and 2, levodopa and benserazide. Six patients with DLBL were receiving anticholinesterase medication. Seven patients with AD were receiving anticholinesterase medication, 1 was receiving risperidone, and 1 was taking Ginkgo biloba. Two patients, 1 with DLBL and 1 with a diagnosis of AD, were taking no medication. The neurological evaluation of participants included the assessment of duration of illness, the Hoehn-Yahr score, and the motor subscale (Section III) of the Unified Parkinson’s Disease Rating Scale (UPDRS3) both “off” (24 hours after the last medication dosage) and “on” parkinsonian medication for the PD cohort and “on” medication only for the patients with DLBL. Treatment was resumed just before the PET scan. The neuropsychological evaluation included the Mini-Mental State Examination, Clinical Dementia Rating, the Hospital Anxiety and Depression Scale Fluctuating Assessment Scale, logical memory score, and verbal fluency score (Table 1). Clinical laterality of symptoms was assigned scores as previously described23 to allow correlation analysis with the [18F]AV-133 PET results.

### Table 1. Demographics

<table>
<thead>
<tr>
<th></th>
<th>HC</th>
<th>DLBL</th>
<th>PD</th>
<th>AD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sample size</strong></td>
<td>10</td>
<td>9</td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td><strong>Age, y, mean (SD)</strong></td>
<td>67.5 (6.6)</td>
<td>68.9 (7.9)</td>
<td>67.0 (8.1)</td>
<td>69.3 (13.3)</td>
</tr>
<tr>
<td><strong>Sex (M/F), No.</strong></td>
<td>3/7</td>
<td>7/2</td>
<td>18/2</td>
<td>7/3</td>
</tr>
<tr>
<td><strong>Symptoms onset, y</strong></td>
<td>...</td>
<td>3.03 (1.9)</td>
<td>6.11 (4.4)</td>
<td>3.22 (1.5)</td>
</tr>
<tr>
<td><strong>Disease duration, y</strong></td>
<td>...</td>
<td>0.87 (1.9)</td>
<td>4.18 (4.0)</td>
<td>0.72 (0.4)</td>
</tr>
<tr>
<td><strong>MMSE score</strong></td>
<td>29.7 (0.7)</td>
<td>24.4 (2.9)</td>
<td>29.0 (1.2)</td>
<td>22.2 (4.1)</td>
</tr>
<tr>
<td><strong>CDR</strong></td>
<td>0</td>
<td>0.7 (0.4)</td>
<td>0.2 (0.5)</td>
<td>1.0 (0.4)</td>
</tr>
<tr>
<td><strong>Hoehn-Yahr score</strong></td>
<td>...</td>
<td>1.93 (0.9)</td>
<td>1.60 (0.6)</td>
<td>...</td>
</tr>
<tr>
<td><strong>UPDRS3, score</strong></td>
<td>0</td>
<td>...</td>
<td>1.63 (0.6)</td>
<td>0.33 (1.0)</td>
</tr>
<tr>
<td><strong>UPDRS3, subscale</strong></td>
<td>0.25 (0.5)</td>
<td>11.7 (5.4)</td>
<td>13.9 (7.4)</td>
<td>22.2 (5.4)</td>
</tr>
<tr>
<td><strong>Bradykinesia</strong></td>
<td>0.0</td>
<td>0.9 (0.9)</td>
<td>2.1 (0.9)</td>
<td>0.0</td>
</tr>
<tr>
<td><strong>Rigidity</strong></td>
<td>0.0</td>
<td>1.0 (0.5)</td>
<td>1.8 (0.6)</td>
<td>0.0</td>
</tr>
<tr>
<td><strong>Fluctuating Assessment Scale score</strong></td>
<td>0.0</td>
<td>1.2 (1.2)</td>
<td>0.6 (1.4)</td>
<td>1.2 (1.6)</td>
</tr>
<tr>
<td><strong>Logical memory score</strong></td>
<td>12.9 (5.4)</td>
<td>7.9 (3.1)</td>
<td>11.9 (4.1)</td>
<td>4.3 (2.2)</td>
</tr>
<tr>
<td><strong>Verbal fluency score</strong></td>
<td>41.1 (10.5)</td>
<td>29.1 (10.9)</td>
<td>33.5 (10.8)</td>
<td>31.6 (12.7)</td>
</tr>
<tr>
<td><strong>HADS score</strong></td>
<td>9.0 (7.2)</td>
<td>11.3 (5.2)</td>
<td>12.5 (5.1)</td>
<td>8.0 (5.7)</td>
</tr>
<tr>
<td><strong>Aβ imaging (high/low), No.</strong></td>
<td>0/2</td>
<td>2/5</td>
<td>0/5</td>
<td>5/0</td>
</tr>
</tbody>
</table>

Abbreviations: AD, Alzheimer disease; CDR, Clinical Dementia Rating; DLBL, dementia with Lewy bodies; HADS, Hospital Anxiety and Depression Scale; HC, healthy control; MMSE, Mini-Mental State Examination; on, while not taking medication; off, while taking medication; PD, Parkinson disease; UPDRS3, motor subscale (Section III) of the Unified Parkinson’s Disease Rating Scale; [18F]AV-133, 9-fluoropropyl(-)+dihydrotetrabenazine.

a Symptoms onset: years lapsed between onset of symptoms and [18F]AV-133 scan.
b Disease duration: years lapsed between clinical diagnosis and [18F]AV-133 scan.
c Significantly different from PD (P<.05).
d Significantly different from HC (P<.05).
**IMAGING PROCEDURES**

[18F]AV-133 was synthesized using previously described methods. Each subject received about 250 MBq of [18F]AV-133 by intravenous injection over 1 minute. Imaging was performed with a Philips Allegro PET camera (Philips Healthcare, Best, the Netherlands). A rotation transmission sinogram acquisition in 3-dimensional (3D) mode with a single [18F]Cs point source was performed before each emission acquisition for attenuation correction purposes. Thirty-six participants (17 with PD, 8 HCs, 7 with DLB, and 4 with AD) underwent an initial 90-minute dynamic list-mode emission acquisition in 3D mode after injection of [18F]AV-133. Further static images were obtained at 120 to 140 and 180 to 200 minutes after injection. Thirteen participants (3 with PD, 2 HCs, 2 with DLB, and 6 with AD) underwent only the 120- to 140-minute static image acquisition. The sorted sinograms were reconstructed using a 3D row-action maximum likelihood algorithm. All subjects, except 1 patient with DLB, received a magnetic resonance imaging (MRI) scan for screening of other diseases. Seven patients with DLB, 5 patients with AD, and 5 patients with PD as well as 2 HCs had previous amyloid scans.

**IMAGE ANALYSIS**

The dynamically acquired PET images of the 36 participants were converted into binding potential (BP) parametric images through Logan graphical analysis, with the PMOD software (version 3.0; PMOD Technologies, Zurich, Switzerland), using the primary visual cortex, a region relatively devoid of monoaminergic terminals, as input function. The static images of all participants acquired between 120 and 140 minutes were transformed into tissue ratio (RT) parametric images using the primary visual cortex as the reference region. Parametric [18F]AV-133 PET images were spatially normalized into the Montreal Neurological Institute MRI brain template standard stereotactic space using statistical parametric mapping software (SPM5; Wellcome Trust Centre for Neuroimaging, London, England). Volumes of interest were placed over the standard-space MRI over the cortical areas as well as over the caudate nucleus, anterior and posterior putamen, and midbrain by an operator blind to clinical diagnosis. Volumes of interest were then transferred onto the individual parametric [18F]AV-133 PET images, and regional BP or RT values were obtained. For establishing unsigned asymmetry, indexes between right (R) and left (L) were calculated as follows: (|R−L|)/(R+L)/2). A striatal anterior to posterior ratio was calculated as the caudate nucleus R to posterior putamen R ratio. Finally, to determine the diagnostic accuracy in distinguishing DLB from AD, parametric [18F]AV-133 PET images of all participants acquired between 120 and 140 minutes were visually rated by 2 independent raters, blind to the clinical diagnosis, using a 3-level scale to characterize [18F]AV-133 striatal binding: 1=normal binding; 2=slight decrease; and 3=marked decrease.

**STATISTICAL ANALYSIS**

Correlations between the striatal [18F]AV-133 BP and RT values in 36 participants were performed using Pearson correlation analysis. Subsequently, statistical comparison of regional R and L values between groups was performed using a Tukey-Kramer honestly significant difference test to establish differences between group means and a Dunnet test to compare each group with controls. Effect size was measured with Cohen d. Statistical comparison of clinical data was performed using the Mann-Whitney U test. Statistical significance for each analysis was defined as P<.05. Given the age decline in VMAT2, all comparisons and correlations were corrected for age effects. Receiver operating characteristic curve analysis was applied to assess the robustness of the different parameters to discriminate between the clinical groups. SPM5 was additionally used to evaluate intergroup [18F]AV-133 R differences on a voxelwise basis. Group comparisons between patients with DLB, AD, and PD and HCs were performed by voxel-by-voxel t tests, accepting only voxels surviving false discovery rate correction for the entire volume at a P value <.05 to avoid false-positive results.

**RESULTS**

Demographic and clinical data are summarized in Table 1. All patient groups contained a higher proportion of men than the HC group. Both patients with AD and DLB were considered to have mild to moderate dementia (mean [SD] Mini-Mental State Examination score of 22.2 [4.1] and 24.4 [2.9] with a mean [SD] Clinical Dementia Rating of 1.0 [0.4] and 0.7 [0.4] for patients with AD and DLB, respectively). As a group, patients with AD presented with significantly lower logical memory scores than the other groups. Patients with PD were considered to have mild to moderate PD (off-medication state Hoehn-Yahr scores 1-3: stage 1: n=9; stage 1.5: n=2; stage 2: n=6; stage 2.5: n=2; and stage 3: n=1). Patients with DLB presented with a similar distribution of scores (on-medication state Hoehn-Yahr scores 1-3: stage 1: n=3; stage 1.5: n=1; stage 2: n=5; stage 2.5: n=3; and stage 3: n=1). The Hoehn-Yahr and UPDRSmotor scores in an off-medication state were significantly higher in patients with PD than patients with AD and HCs. The Hoehn-Yahr and UPDRSmotor scores in the off-medication state were unavailable in 1 patient in the PD group and 1 patient in the DLB group, respectively. The Hoehn-Yahr and the UPDRSmotor scores in the on-medication state were significantly higher in patients with PD and DLB compared with HCs and patients with AD. There was no difference between the patients with PD and HCs in Clinical Dementia Rating, Fluctuating Assessment Scale score, logical memory score, and verbal fluency score.

In the 36 participants with dynamic PET scans, the degree of association between striatal BP and striatal RT values was explored. Correlation analysis showed very high association (r=0.99; P < .001) between [18F]AV-133 BP, obtained through graphical analysis of dynamic scans, and [18F]AV-133 RT, calculated from 20-minute static scans at 120 minutes postinjection (eFigure, http://www.archneurol.com). Given the high correlation observed between BP and RT, all reported results are [18F]AV-133 R.

Visually, lower [18F]AV-133 striatal binding was observed in the putamen, caudate, and midbrain of patients with DLB and PD, while patients with AD showed [18F]AV-133 striatal and midbrain binding similar to those observed in HCs. Blinded reading of the images obtained at 120 to 140 minutes postinjection correctly distinguished DLB from AD in all cases except for 2 cases and with a high intrarater agreement (κ=0.79). The sensitivity of [18F]AV-133 PET for distinction of AD from DLB against diagnosis based on clinical criteria was 90% with a specificity of 100%. Representative [18F]AV-133
Voxel-based group comparison of \(^{18}\)F]AV-133 RT images showed a significantly lower \(^{18}\)F]AV-133 RT in patients with DLB and PD than in patients with AD and HCs in the striatum (Figure 1B). Significantly lower \(^{18}\)F]AV-133 RT values were also observed in the anterior midbrain of patients with DLB and PD compared with HCs.

Volumes of interest–based analysis similarly indicated significantly lower RT values in the caudate nucleus and putamen of patients with DLB and PD (Table 2). No overlap was observed between the \(^{18}\)F]AV-133 RT values in the putamen of patients with DLB and PD and those of HCs and patients with AD (Figure 2). Similarly, as previously reported for PD,\(^{25}\) in DLB the greatest \(^{18}\)F]AV-133 RT reduction was observed in the posterior putamen (−74%), followed by the anterior putamen (−65%) and the caudate nuclei (−51%) (Figure 2). In the posterior putamen, mean \(^{18}\)F]AV-133 RT values in patients with DLB were more than 3 SDs below patients with AD and HCs. There was a significant lower \(^{18}\)F]AV-133 RT in the midbrain (−36%) of patients with DLB when compared with HCs and patients with AD. There were no significant differences in striatal or midbrain \(^{18}\)F]AV-133 RT values between patients with AD and HCs (Table 2). The striatal \(^{18}\)F]AV-133 RT values clearly distinguished DLB from AD.
with effect sizes of 2.1, 2.9, and 3.4 for the caudate and anterior and posterior putamen, respectively.

While there were no significant differences in the asymmetry indices for the striatal regions between patients with DLB and PD, there was a significant correlation between \([18F]AV-133\) asymmetry indices in the striatum and the clinical laterality scores in the PD group but not in the DLB group. No striatal asymmetries were detected in the HC and AD groups. The striatal anterior to posterior ratio was significantly higher in patients with DLB compared with HCs and patients with AD (Table 2).

Analysis of extrastriatal VMAT2 \(R_T\) values showed no significant differences between HCs and the other groups. An apparent reduction in hippocampal and temporal \([18F]AV-133\) \(R_T\) values in AD disappeared after partial volume correction of the PET data for atrophy using the patient’s MRI.

In patients with DLB, there was a significant correlation between Hoehn-Yahr scores and the anterior putamen \(R_T\) \((r = -0.82; \ P = .02)\), but no significant correlations were observed between striatal \(R_T\) and the UPDRS\(_S\) score, nor with the bradykinesia or rigidity subscores. While there were no significant correlations between striatal \([18F]AV-133\) \(R_T\) and disease duration or duration from onset of symptoms to clinical diagnosis in patients with DLB, those with a high A\(_B\) burden in the brain had a 3.7 times shorter time from onset of symptoms to clinical diagnosis \((0.75\) years vs \(2.80\) years for patients with DLB with high and low A\(_B\) burden, respectively).

Receiver operating characteristic analysis of the DLB and AD groups revealed an area under the curve of 0.91 for the anterior midbrain \([18F]AV-133\) \(R_T\), 0.95 for the caudate \([18F]AV-133\) \(R_T\), and 1.00 for the anterior and posterior putamen \([18F]AV-133\) \(R_T\), respectively (Table 3). An area under the curve of 1.00 was also obtained if all the striatal regions were grouped together. Areas under the curve of 0.71 and 0.86 were obtained for the striatal asymmetry index and the striatal anterior

### Table 2. Regional \(R_T\) Values for \([18F]AV-133\) PET

<table>
<thead>
<tr>
<th>Region</th>
<th>HC</th>
<th>DLB</th>
<th>PD</th>
<th>AD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caudate nuclei</td>
<td>2.53 (0.3)</td>
<td>1.24 (0.6)(^a)</td>
<td>1.20 (0.5)(^a)</td>
<td>2.83 (0.9)</td>
</tr>
<tr>
<td>R caudate nuclei</td>
<td>2.51 (0.3)</td>
<td>1.20 (0.6)(^a)</td>
<td>1.22 (0.5)(^a)</td>
<td>2.78 (0.9)</td>
</tr>
<tr>
<td>L caudate nuclei</td>
<td>2.56 (0.3)</td>
<td>1.27 (0.6)(^a)</td>
<td>1.18 (0.5)(^a)</td>
<td>2.88 (1.0)</td>
</tr>
<tr>
<td>Anterior putamen</td>
<td>2.56 (0.3)</td>
<td>0.90 (0.5)(^a)</td>
<td>0.66 (0.3)(^a)</td>
<td>3.01 (0.9)</td>
</tr>
<tr>
<td>R anterior putamen</td>
<td>2.61 (0.3)</td>
<td>0.88 (0.5)(^a)</td>
<td>0.68 (0.3)(^a)</td>
<td>2.99 (0.9)</td>
</tr>
<tr>
<td>L anterior putamen</td>
<td>2.52 (0.3)</td>
<td>0.93 (0.5)(^a)</td>
<td>0.64 (0.2)(^a)</td>
<td>3.04 (0.9)</td>
</tr>
<tr>
<td>Posterior putamen</td>
<td>2.53 (0.3)</td>
<td>0.62 (0.5)(^a, b)</td>
<td>0.30 (0.2)(^a)</td>
<td>2.87 (0.8)</td>
</tr>
<tr>
<td>R posterior putamen</td>
<td>2.36 (0.3)</td>
<td>0.60 (0.4)(^a)</td>
<td>0.33 (0.2)(^a)</td>
<td>2.83 (0.8)</td>
</tr>
<tr>
<td>L posterior putamen</td>
<td>2.43 (0.3)</td>
<td>0.64 (0.5)(^a, b)</td>
<td>0.28 (0.1)(^a)</td>
<td>2.90 (0.8)</td>
</tr>
<tr>
<td>Anterior midbrain</td>
<td>0.63 (0.1)</td>
<td>0.40 (0.2)(^a)</td>
<td>0.40 (0.2)(^a)</td>
<td>0.71 (0.2)</td>
</tr>
<tr>
<td>Frontal cortex</td>
<td>-0.03 (0.1)</td>
<td>-0.05 (0.1)</td>
<td>0.03 (0.1)</td>
<td>-0.09 (0.1)(^b)</td>
</tr>
<tr>
<td>Temporal cortex</td>
<td>-0.07 (0.1)</td>
<td>-0.09 (0.1)(^b)</td>
<td>-0.03 (0.1)</td>
<td>-0.10 (0.0)(^b)</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>0.05 (0.1)</td>
<td>-0.03 (0.1)(^a, b)</td>
<td>0.07 (0.1)</td>
<td>0.00 (0.1)(^b)</td>
</tr>
<tr>
<td>Striatal APR</td>
<td>1.06 (0.1)</td>
<td>2.40 (1.2)(^a)</td>
<td>5.12 (3.0)(^a)</td>
<td>0.98 (0.1)</td>
</tr>
</tbody>
</table>

Abbreviations: AD, Alzheimer disease; DLB, dementia with Lewy bodies; HC, healthy control; PD, Parkinson disease; PET, positron emission tomography; \(R_T\), tissue ratio; Striatal APR, striatal anterior to posterior ratio (caudate/posterior putamen); \([18F]AV-133\), 9-fluoropropyl- (+)-dihydrotetrabenazine.

\(^a\)Significantly different from HC (corrected \(P < .05)\).

\(^b\)Significantly different from PD (corrected \(P < .05)\).
to posterior ratio, respectively (Table 3). Using a striatal \(^{18}F\)AV-133 RT threshold of 1.62, \(^{18}F\)AV-133 had 100% accuracy to distinguish participants with AD from participants with DLB.

### Table 3. AUCs From the ROC Curve Analysis for \(^{18}F\)AV-133 PET

<table>
<thead>
<tr>
<th></th>
<th>Caudate RT</th>
<th>Ant Putamen RT</th>
<th>Post Putamen RT</th>
<th>Ant Midbrain RT</th>
<th>Visual</th>
<th>Striatal RT</th>
<th>Striatal APR</th>
<th>Asymmetry Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>HC vs DLB</td>
<td>1.00 (^a)</td>
<td>1.00 (^a)</td>
<td>1.00 (^a)</td>
<td>0.86</td>
<td>1.00 (^a)</td>
<td>1.00 (^a)</td>
<td>0.83</td>
<td>0.80</td>
</tr>
<tr>
<td>HC vs AD</td>
<td>0.58</td>
<td>0.64</td>
<td>0.70</td>
<td>0.61</td>
<td>0.54</td>
<td>0.64</td>
<td>0.64</td>
<td>0.73</td>
</tr>
<tr>
<td>AD vs DLB</td>
<td>0.95 (^a)</td>
<td>1.00 (^a)</td>
<td>1.00 (^a)</td>
<td>0.91</td>
<td>0.95 (^a)</td>
<td>1.00 (^a)</td>
<td>0.86</td>
<td>0.71</td>
</tr>
<tr>
<td>AD vs PD</td>
<td>0.98 (^a)</td>
<td>1.00 (^a)</td>
<td>1.00 (^a)</td>
<td>0.92</td>
<td>0.98 (^a)</td>
<td>1.00 (^a)</td>
<td>0.94</td>
<td></td>
</tr>
<tr>
<td>DLB vs PD</td>
<td>0.54</td>
<td>0.62</td>
<td>0.82</td>
<td>0.55</td>
<td>0.55</td>
<td>0.64</td>
<td>0.85</td>
<td>0.71</td>
</tr>
</tbody>
</table>

Abbreviations: AD, Alzheimer disease; Ant, anterior; AUC, area under the curve; DLB, dementia with Lewy bodies; HC, healthy control; PD, Parkinson disease; PET, positron emission tomography; Post, posterior; ROC, receiver operating characteristic; RT, tissue ratio; Striatal APR, striatal anterior to posterior ratio (caudate/posterior putamen); \(^{18}F\)AV-133, 9-fluropropyl-(+)-dihydrotetrabenazine.

\(^a\) AUC > 0.95.

One of the diagnostic problems faced by clinicians, due to the overlap of cognitive symptoms early in the disease course, is the differential diagnosis between patients who will develop AD vs those who will ultimately develop DLB. While the introduction of amyloid imaging has been extremely useful in the early detection of A\(\beta\) deposition,\(^2,3,5,6\) it is not a useful tool in differentiating between AD and DBL as the majority of DBL cases also show extensive cortical A\(\beta\) deposition.\(^2,3,5,6\) Molecular imaging studies with fluorodeoxyglucose (FDG) have shown that occipital hypometabolism with parietal involvement\(^31-33\) and preservation of metabolic activity in the posterior cingulate\(^34,35\) are the most distinctive features of DBL, with FDG having a 75% to 85% accuracy in the differential diagnosis of DBL from AD.\(^20,35,36\)

Imaging studies with \(^{11}C\)DTBZ show a high correlation between clinical and \(^{18}F\)AV-133 asymmetry indices as well as the associations observed between the clinical subscores and striatal VMAT2 densities in PD are suggestive of disease severity.\(^18\) While more accurate than \(^{18}F\)-DOPA,\(^18\) \(^{18}F\)AV-133 RT might not be reflecting the true extent of nigrostriatal neurodegeneration, where compensatory mechanisms such as overproduction of dopamine and aberrant sprouting of ter-

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**COMMENT**

The results presented here demonstrate the usefulness of assessing the integrity of the nigrostriatal pathways, either by visual inspection of images or semi-quantitatively with \(^{18}F\)AV-133, which displayed a more than 95% accuracy in distinguishing DBL from AD. There were significant lower VMAT2 densities as measured by \(^{18}F\)AV-133 in the striatum and midbrain of patients with PD and DBL, while no reductions were observed in patients with AD. The greatest VMAT2 reductions were observed in the posterior putamen followed by the anterior putamen and caudate nucleus. These results are consistent with previous \(^{11}C\)DTBZ PET results showing the largest reduction in the posterior putamen of patients with PD and DBL\(^16,20\) and in agreement with postmortem reports showing VMAT2 reductions in the striatum of patients with DBL\(^20\) and PD.\(^42\)

Partial volume correction of the data will be required to avoid misinterpretation of the results if longitudinal \(^{18}F\)AV-133 studies are undertaken in the context of neurodegenerative processes associated with progressive brain atrophy.\(^43\)

Similar to our previous report on patients with PD,\(^25\) there was no intergroup overlap between the putaminal \(^{18}F\)AV-133 RT of patients with DBL with controls or patients with AD. \(^{18}F\)AV-133 RT values in the posterior putamen of all patients with DBL were more than 3 SDs below healthy controls. These results suggest \(^{18}F\)AV-133 is a robust tool to detect dopaminergic dysfunction in patients with Lewy body disease.

Significant reductions in \(^{18}F\)AV-133 RT values were also observed in the anterior midbrain. VMAT2 are highly concentrated in the striatum but they are also localized in extrastriatal cortical regions. Human PET studies using stereoisomers of \(^{11}C\)DTBZ demonstrated specific in vivo binding of \(^{11}C\)DTBZ in the midbrain\(^16,20\) and in vivo studies in mice confirmed \(^{18}F\)AV-133 binding to VMAT2 in the substantia nigra.\(^16,44\) Previous \(^{11}C\)DTBZ PET studies demonstrated a 50% VMAT2 reduction in the substantia nigra of patients with PD.\(^45\) In a similar fashion, the present study demonstrated a 37% reduction of \(^{18}F\)AV-133 binding in the anterior midbrain of patients with PD and DBL, consistent with previous reports of nigral VMAT2 reductions.\(^10\)

As pointed out in our report on patients with PD, the high correlation between clinical and \(^{18}F\)AV-133 asymmetry indices as well as the associations observed between the clinical subscores and striatal VMAT2 densities in PD are suggestive of disease severity.\(^18\) While more accurate than \(^{18}F\)-DOPA,\(^18\) \(^{18}F\)AV-133 RT might not be reflecting the true extent of nigrostriatal neurodegeneration, where compensatory mechanisms such as overproduction of dopamine and aberrant sprouting of ter-

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minals compensate for the reduction in axons, precluding a true evaluation of the pathological process. Furthermore, the associations or lack thereof observed between the clinical scores and subscores in patients with DBL should be interpreted cautiously. The neurologial assessments in this group were performed while “on” medication, and moreover, not all patients were receiving dopaminergic medication. Seven of the 9 patients with DBL also had a previous amyloid imaging scan. Interestingly, while there were no differences in either $[^{18}F]AV-133$ $R_t$ values or motor or fluctuation scale scores, patients with DBL with high $A_{\beta}$ burden in the brain had a much shorter time from onset of symptoms to clinical diagnosis. While the very small number of subjects precludes drawing definitive conclusions, these results suggest that in addition to the reductions of dopaminergic nigrostriatal afferents, those patients with DBL with significant $A_{\beta}$ deposits in the brain have a shorter prodromal phase, in agreement with our previous reports and with the proposed role of $A_{\beta}$ in DBL, where $A_{\beta}$ deposits result in greater aggregation and exacerbation $\alpha$-synuclein–dependent neuronal injury.

There are some limitations in the present study. A severe limitation in the present study is that group classification was based on clinical evaluation, and although they fulfilled diagnostic criteria, postmortem confirmation was not available. Given the complexity and sometimes overlapping clinical features of AD and DBL, especially early in the disease course, neuropathological examination will be required not only to characterize the relationship between the integrity of monoaminergic innervation and the $[^{18}F]AV-133$ PET signal, but also to ascertain if VMAT2 imaging with $[^{18}F]AV-133$ is able to provide the diagnostic certainty required for the detection of nigrostriatal degeneration. Another weakness in the present study is that there were a limited number of patients examined. This study by its design cannot show that VMAT2 imaging has any advantage over clinical diagnosis. Prospective studies in at-risk persons, such as subjects with rapid eye movement sleep behavioral disorder, or patients with atypical presentations that compare initial clinical diagnosis and management with and without $[^{18}F]AV-133$ PET findings with long-term clinical or postmortem outcome are needed. Such studies have demonstrated the value of DAT imaging with SPECT for more accurate diagnosis than can be achieved from clinical assessment. It is likely that VMAT2 imaging will have similar clinical benefits.

In conclusion, similar to what has been observed in PD, significant VMAT2 reductions were detected in the striatum and midbrain of patients with DBL with $[^{18}F]AV-133$, while there were no VMAT2 alterations in patients with AD. These observations indicate that a 20-minute $[^{18}F]AV-133$ PET scan is a suitable technique for the noninvasive assessment of striatal VMAT2 in the human brain and can robustly distinguish AD from DBL by either visual inspection of images or a simple semiquantitative measure.

CONCLUSIONS

In conclusion, similar to what has been observed in PD, significant VMAT2 reductions were detected in the striatum and midbrain of patients with DBL with $[^{18}F]AV-133$, while there were no VMAT2 alterations in patients with AD. These observations indicate that a 20-minute $[^{18}F]AV-133$ PET scan is a suitable technique for the noninvasive assessment of striatal VMAT2 in the human brain and can robustly distinguish AD from DBL by either visual inspection of images or a simple semiquantitative measure.

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Online-Only Material: The eFigure is available at http://www.archneurol.com.

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