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ORIGINAL ARTICLE

Distinct FP-CIT PET patterns of Alzheimer's disease with parkinsonism and dementia with Lewy bodies

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Abstract

Purpose Little is known regarding the clinical relevance or neurobiology of subtle motor disturbance in Alzheimer's disease (AD). This study aims to investigate the patterns of striatal ^{18}F-FP-CIT uptake in patients with AD-related cognitive impairment (ADCI) with mild parkinsonism.

Methods We recruited 29 consecutive patients with ADCI with mild parkinsonism. All patients underwent ^{18}F-FP-CIT PET scans and dopamine transporter (DAT) availability in striatal subregions (anterior/posterior caudate, anterior/posterior putamen, ventral putamen, ventral striatum) was quantified. Additionally, 32 patients with dementia with Lewy bodies (DLB) and 21 healthy controls were included to perform inter-group comparative analyses of the striatal DAT availability. The discriminatory power of striatal DAT availability to differentiate ADCI from DLB was assessed using receiver operating characteristics (ROC) analyses. The Spearman's correlation coefficient was calculated to assess the relationship between motor severity and DAT availability in striatal subregions.

Results Patients with ADCI with mild parkinsonism exhibited decreased DAT availability in the caudate that was intermediate between healthy controls and patients with DLB. The DAT availability in other striatal subregions, including the posterior putamen, did not differ between the ADCI with parkinsonism and healthy control groups. The ROC analysis showed that DAT availability of all striatal subregions, especially the whole striatum, had a fair discriminatory power. Parkinsonian motor severity did not correlate with the striatal DAT availability in ADCI with parkinsonism.

Conclusions The present study demonstrated that patients with ADCI with mild parkinsonism had distinct DAT scan patterns and suggests that parkinsonism is associated with the extranigral source of pathology.

Keywords Alzheimer's disease · Dementia with Lewy bodies · Dopamine transporter · Parkinsonism

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Introduction

The significance of parkinsonism in Alzheimer's disease (AD) has been overlooked because these motor signs are often considered as part of the normal aging process or frequently manifested in the late stage of AD [1–3]. Despite the large degree of variation in prevalence, parkinsonian motor symptoms are observed in the early stage of AD in up to 13% of patients [3, 4]. Ample evidence has suggested that the presence of parkinsonism in AD is associated with more rapid cognitive and functional decline [5]. Moreover, given that differentiation between AD with parkinsonism and dementia with Lewy bodies (DLB) is a major diagnostic challenge, it is important to understand the neuropathological basis of parkinsonism in AD.

Several studies have shown that Lewy bodies (LB) in the substantia nigra (SN) were associated with parkinsonism in

AD [6–8], whereas some evidence has suggested that AD pathology in extranigral areas could contribute to the development of parkinsonism in AD [8–12]. Since neuropathological studies can only be performed on patients at an advanced stage of AD, neuroimaging studies provide opportunities to reveal the underlying neural basis of mild parkinsonism in the early stages of AD. In terms of the nigrostriatal dopamine pathway, a few studies using dopamine transporter (DAT) scans have reported inconsistent results of either normal or abnormal striatal uptake [13–15]. However, these studies were limited by their small sample size and uncertainty over the clinical diagnosis of AD. In this study, we measured the extent of presynaptic dopaminergic density by quantitatively analyzing ^{18}F-N-(3-fluoropropyl)-2β-carbon ethoxy-3β-(4-iodophenyl) nortropane (^{18}F-FP-CIT) positron emission tomography (PET) to evaluate whether parkinsonism is associated with nigrostriatal dopamine depletion in a relatively large sample of patients with AD with mild parkinsonism who exhibited β-amyloid accumulation on ^{18}F-florbetaben (^{18}F-FBB) PET scans. In addition, by comparing the pattern of DAT availability, we examined whether this pattern could differentiate between AD and DLB.

Materials and methods

Subjects

The present study included a total of 29 patients with AD-related cognitive impairment (ADCI) with mild parkinsonism who were consecutively recruited from the dementia outpatient clinic at Severance Hospital from March 2015 to February 2018. ADCI (either dementia or mild cognitive impairment) was diagnosed based on clinical diagnostic criteria as described in our previous work [16] (see Supplementary Methods) and findings on ^{18}F-FBB PET (deposition of β-amyloid; $n = 22$) and ^{18}F-fludeoxyglucose (^{18}F-FDG) PET (hypometabolism in AD signature region of interest [17, 18]; $n = 29$). Parkinsonian motor symptoms were assessed using a modified version of the motor portion of the Unified Parkinson's Disease Rating Scale (mUPDRS; see Supplementary Methods) [19–21], which was intended to make the scale more applicable to persons without a clinical diagnosis of PD. Twenty-six items concerning four parkinsonian signs (parkinsonian gait, rigidity, bradykinesia, and tremor) were scored from 0 to 5, by adding an additional level between the original UPDRS score of 0 and 1. The presence of mild parkinsonism was defined as having two or more parkinsonian signs with a score of 1 [21]. All subjects underwent a detailed neuropsychological test, brain magnetic resonance imaging (MRI), and ^{18}F-FP-CIT PET scans. Patients with previous neuroleptic exposure ($n = 9$) or multiple lacunes in basal ganglia on MRI ($n = 5$) were excluded. Two patients who were clinically closer to ADCI than DLB, but who showed visually decreased striatal ^{18}F-FP-CIT uptake (particularly, in the posterior putamen) were also excluded.

Thirty-two patients with DLB and 35 patients with Parkinson's disease (PD) from the Yonsei Parkinson Center database were also included as the reference groups with parkinsonism. The diagnosis of probable DLB was based on the fourth consortium criteria [22], and prodromal DLB was defined as having MCI meeting probable DLB criteria except for the presence of dementia (see Supplementary Methods) [23]. PD was diagnosed according to the clinical diagnostic criteria of the UK PD Society Brain Bank [24]. To ensure clinical diagnostic accuracy, ^{18}F-FP-CIT PET scans were performed on these patients and all except for four patients with DLB showed decreased DAT availability in the posterior putamen. The four patients with DLB with visually normal DAT scans had two or more core clinical features of DLB with biomarker evidence (one showed low uptake on ^{123}I-metaiodobenzylguanidine [^{123}I-MIBG] myocardial scintigraphy and three patients demonstrated reduced occipital activity on ^{18}F-FDG PET imaging) [22]. Fourteen patients with DLB additionally underwent ^{18}F-FBB PET scans, and 11 (78.6%) patients showed the evidence of deposition of β-amyloid. All subjects underwent a detailed neuropsychological test and brain MRI scans, and patients with multiple lacunes in basal ganglia on MRI were excluded in this study.

Additionally, 21 healthy subjects with no neurological disease history and parkinsonism (mean age, 72.7 ± 4.3; female, 52.4%; mUPDRS scores <2) underwent voluntary brain MRI and ^{18}F-FP-CIT PET scans and were included as a control group. This study was approved by the Yonsei University Severance Hospital institutional review board, and the need for informed consent was waived because of the retrospective nature of the study.

Quantitative analyses of the ^{18}F-FP-CIT PET images

We used the same methodology to obtain the ^{18}F-FP-CIT PET images as previously described [25]. Quantitative analyses of the ^{18}F-FP-CIT PET data were based on volumes of interests, which were defined based on a template in standard space. The striatum was divided into the anterior/posterior caudate, anterior/posterior putamen, ventral putamen, and ventral striatum. The DAT availability of each striatal subregion was then calculated (Supplementary Methods). In addition, the rostrocaudal (i.e., caudate-putamen) gradient was calculated by dividing the DAT availability of the caudate by the DAT availability of the putamen.

Visual rating of white matter hyperintensities

White matter hyperintensities (WMHs) were assessed based on the Clinical Research Center for Dementia of South Korea (CREDOS) WMH visual rating scale (Supplementary Methods) [26].

Neuropsychological assessment

All patients with AD with mild parkinsonism, DLB, and PD underwent a detailed neuropsychological test, i.e., the Seoul Neuropsychological Screening Battery (SNSB) [27]. The SNSB covers five cognitive domains (attention and working memory, language and related functions, visuospatial function, verbal and visual memory, and frontal/executive function; a detailed description is provided in the Supplementary Methods). The composite score of each cognitive domain was calculated by dividing the sum of the z-scores by the number of tests. In addition, the Korean version of the Mini-Mental State Examination (K-MMSE) was used to assess general cognition.

Statistical analyses

The baseline demographic characteristics were compared with a one-way analysis of variance (ANOVA) and Pearson's χ^2 tests for continuous and categorical variables, respectively. To compare the DAT availability of each striatal subregion, an analysis of covariance (ANCOVA) was used while adjusting for age and sex as covariates. The caudate-to-putamen gradient was compared using an ANOVA. A Bonferroni correction was used for multiple comparisons correction after one-way ANOVA and ANCOVA. The discriminatory power of DAT availability in each striatal subregion to differentiate ADCI with parkinsonism from DLB was investigated using receiver operating characteristics (ROC) analyses. Sensitivity and specificity are presented for cut-off values that maximize the Youden-Index (Sensitivity + Specificity - 1). A Bootstrap method was used to compare the area under curve (AUC) between each variable. The Spearman's correlation coefficient was calculated to assess the relationship between motor severity (mUPDRS scores in patients with ADCI with mild parkinsonism and UPDRS part III scores in patients with DLB and PD) and DAT availability in the striatal subregions. The association between the composite score of each cognitive domain and striatal DAT availability was also assessed by Spearman's correlation coefficient with false discovery rate (FDR) adjustment. The statistical analyses were performed using the R software package, version 3.4.0 (http://www.r-project.org), and results with a two-tailed p value <0.05 were considered statistically significant.

Results

Clinical characteristics of patients with ADCI with mild parkinsonism

Bradykinesia was the most frequent sign in 75.9% (22 out of 29) of patients with ADCI with mild parkinsonism, followed by rigidity (65.5%), parkinsonian gait (55.2%), and postural tremor (34.5%). No patients exhibited signs of a resting tremor.

There were no significant differences in age, sex, years of education, or the presence of moderate to severe WMHs between patients with ADCI with parkinsonism and other groups (DLB, PD, and healthy controls; Table 1 and Supplementary Table 1). Patients with ADCI with parkinsonism showed comparable levels of cognitive performance to those with DLB. All patients with PD were not demented and had better cognitive function than those with ADCI with parkinsonism and DLB (Supplementary Table 1).

Pattern of striatal DAT availability in patients with ADCI with mild parkinsonism

The patterns of striatal DAT availability in each group are illustrated in Fig. 1. Compared to the healthy controls, patients with ADCI with mild parkinsonism exhibited more severely decreased DAT availability in the anterior caudate (estimated mean, 2.72 in the ADCI group and 3.12 in the control group; $p = 0.019$) and posterior caudate (1.67 in the ADCI group and 1.95 in the control group; $p = 0.022$). However, the DAT availability in the anterior putamen (ADCI group, 4.12; control group, 4.25; $p = 0.550$), posterior putamen (ADCI group, 3.92; control group, 4.16; $p = 0.266$), ventral putamen (ADCI group, 3.32; control group, 3.39; $p = 0.722$) and ventral striatum (ADCI group, 3.00; control group, 3.07; $p = 0.678$) did not differ between the two groups (Table 1).

Compared to patients with DLB, patients with ADCI with mild parkinsonism exhibited relatively preserved DAT availability in all striatal subregions, including the anterior caudate (DLB group, 1.74; $p < 0.001$), posterior caudate (DLB group, 1.09; $p < 0.001$), anterior putamen (DLB group, 2.53; $p < 0.001$), posterior putamen (DLB group, 2.20; $p < 0.001$), ventral putamen (DLB group, 1.99; $p < 0.001$), and ventral striatum (DLB group, 2.03; $p < 0.001$; Table 1).

Additionally, the degree of decreased DAT availability in the DLB group was similar to that in the PD group. However, the DLB group exhibited a rostro-caudal gradient similar to that seen in the ADCI with mild parkinsonism group (DLB group, 0.71 ± 0.20; ADCI group, 0.63 ± 0.09; $p = 0.256$), contrasting with the sharp gradient pattern in the PD group (0.91 ± 0.16; $p < 0.001$; Fig. 1, Supplementary Fig. 1, and Supplementary Table 1).

ROC analyses of differentiating ADCI with mild parkinsonism from DLB

All striatal subregions had a fair discriminatory power when differentiating ADCI with mild parkinsonism from DLB with AUC > 0.8 (anterior caudate, 0.874; posterior caudate, 0.830; anterior putamen, 0.898; posterior putamen, 0.900; ventral putamen, 0.896; ventral striatum, 0.883; whole striatum,

Table 1 Striatal dopamine transporter availability in patients with Alzheimer's disease with mild parkinsonism and dementia with Lewy bodies

Measure	AD-p ($n = 29$)	DLB ($n = 32$)	Control ($n = 21$)	p value[a]	AD-p vs. DLB[b]	AD-p vs. Control[b]	DLB vs. Control[b]
Demographic characteristics							
Age (years)	74.66 ± 6.60	74.84 ± 6.85	72.71 ± 4.33	0.432	> 0.999	0.837	0.678
Female, No. (%)	15 (51.7%)	10 (31.3%)	11 (52.4%)	0.181			
Education (years)	11.45 ± 3.87	9.64 ± 5.77	9.95 ± 5.12	0.342	0.488	0.900	> 0.999
Dementia, No. (%)	23 (79.3%)	31 (96.9%)	–	0.046			
Moderate to severe WMHs	14 (48.3%)	14 (43.8%)	8 (38.1%)	0.774			
DAT availability							
Whole striatum	3.374 (0.115)	2.087 (0.111)	3.532 (0.136)	< 0.001	< 0.001	0.376	< 0.001
Anterior caudate	2.720 (0.107)	1.740 (0.103)	3.115 (0.126)	< 0.001	< 0.001	0.019	< 0.001
Posterior caudate	1.669 (0.077)	1.090 (0.074)	1.948 (0.091)	< 0.001	< 0.001	0.022	< 0.001
Anterior putamen	4.120 (0.141)	2.529 (0.136)	4.251 (0.167)	< 0.001	< 0.001	0.550	< 0.001
Posterior putamen	3.919 (0.141)	2.196 (0.136)	4.164 (0.167)	< 0.001	< 0.001	0.266	< 0.001
Ventral putamen	3.317 (0.122)	1.993 (0.118)	3.385 (0.145)	< 0.001	< 0.001	0.722	< 0.001
Ventral striatum	2.996 (0.109)	2.032 (0.105)	3.067 (0.129)	< 0.001	< 0.001	0.678	< 0.001

The values are expressed as mean ± standard deviation, number (percentage), or estimated mean (standard error)

Abbreviations: *AD-p* Alzheimer's disease with mild parkinsonism, *DLB* dementia with Lewy bodies, *WMHs* white matter hyperintensities, *DAT* dopamine transporter

[a] p value from ANOVA

[b] Bonferroni correction p values of the post-hoc comparison test

0.905; Table 2). The sensitivity and specificity at a cut-off that maximizes the Youden-Index of DAT availability in each striatal subregion are listed in Table 2. In particular, the sensitivity was 100% and the specificity was 78.1% at cut-off values of 3.050 for DAT availability in the posterior putamen and 2.478 for DAT availability in the whole striatum. Meanwhile, the sensitivity was 96.6% and the specificity was 59.4% at a cut-off value of 1.075 for DAT availability in the posterior caudate. When comparing the ROC curves between each striatal subregion, the AUC for DAT availability in the posterior caudate tended to be smaller than that in the anterior putamen ($p = 0.093$), posterior putamen ($p = 0.076$), and the whole striatum ($p = 0.042$; Table 2 and Fig. 2).

Correlation analyses between motor severity or cognitive function and striatal DAT availability

In patients with ADCI with mild parkinsonism, mUPDRS scores (mean, 9.97 ± 5.07) were not significantly correlated with the striatal DAT availability, including the posterior putamen ($\gamma = -0.102$, $p = 0.742$; Supplementary Fig. 2). UPDRS-III scores also did not correlate well with the striatal DAT availability, including the posterior putamen ($\gamma = 0.171$, $p = 0.498$) in the DLB group. In addition, the composite scores of all five cognitive domains were not significantly correlated with DAT availability in all striatal subregions in patients with ADCI with mild parkinsonism and DLB. Expectedly, the UPDRS-III scores were negatively correlated with DAT availability in the putamen and the composite scores of frontal/executive function domain were positively correlated with DAT availability in the anterior caudate in the PD group (Supplementary Table 2).

Discussion

The present study investigated the pattern of striatal ^{18}F-FP-CIT uptake in patients with ADCI with mild parkinsonism. The major findings were as follows: (1) patients with ADCI with mild parkinsonism exhibited decreased DAT availability in the caudate that was at a level between that in healthy controls and patients with LB diseases. The DAT availability in other striatal subregions did not differ between the ADCI with mild parkinsonism and healthy control groups. (2) DAT availability in all striatal subregions had a fair discriminatory power to differentiate ADCI with mild parkinsonism from DLB, although the AUC for DAT availability in the posterior caudate tended to be smaller than that in the anterior putamen, posterior putamen, and whole striatum. (3) Parkinsonian motor severity assessed using the mUPDRS and the level of cognitive performance did not correlate with the striatal DAT availability in patients with ADCI with mild parkinsonism. Our study demonstrated that patients with ADCI with mild parkinsonism showed patterns of DAT scans distinct from those in patients with LB diseases as well as healthy controls. These findings suggest that parkinsonism in ADCI might not be secondary to nigral pathology involving nigrostriatal dopaminergic neurons.

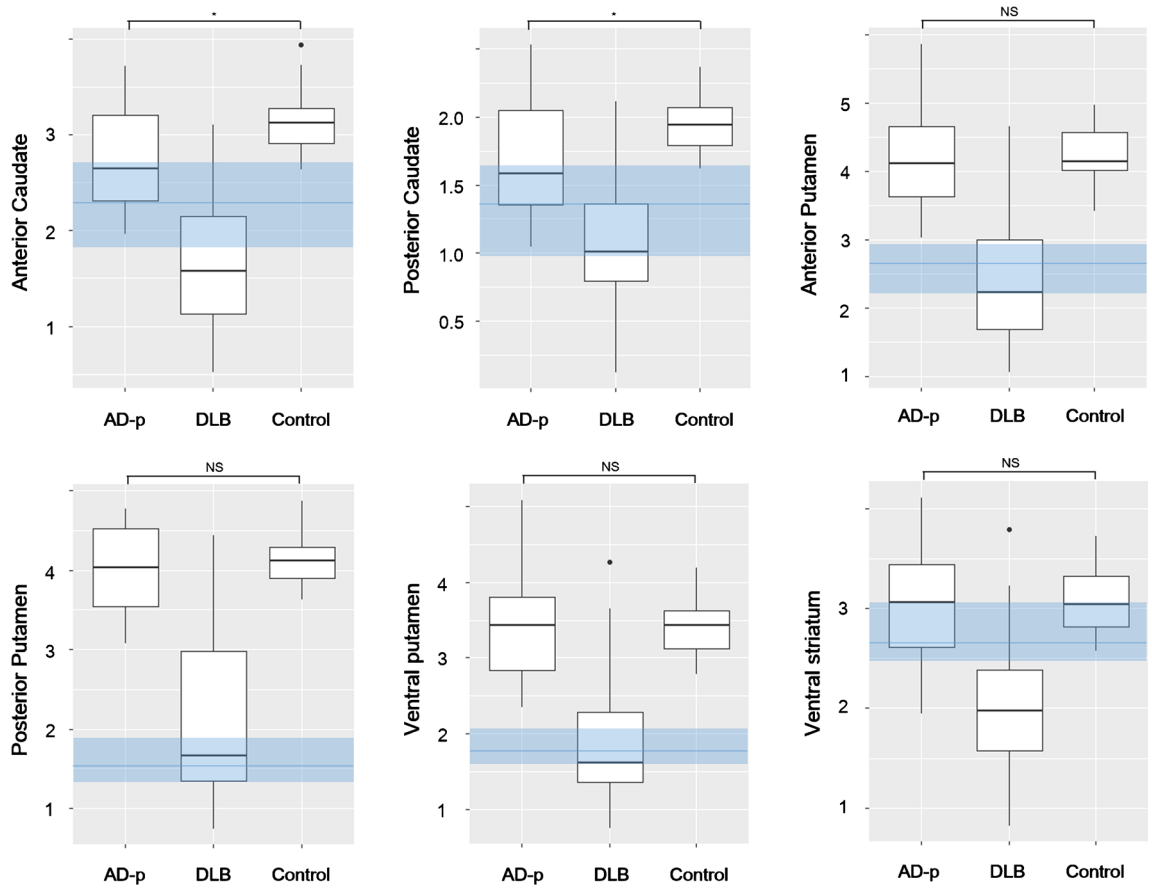

Fig. 1 Comparison of ^{18}F-FP-CIT binding in the striatal subregions between the groups. The *blue line* and *shading* indicate the median and interquartile range of DAT availability in each striatal subregion of the PD group as a reference, respectively. The patients with ADCI with mild parkinsonism exhibited a greater decrease in DAT availability in the anterior caudate and posterior caudate than that in healthy controls. The DLB group exhibited a greater decrease in DAT availability in the anterior and posterior caudate and a lesser decrease in DAT availability in the posterior putamen and ventral striatum compared with the PD group. Abbreviations: AD-p, Alzheimer's disease with mild parkinsonism; DLB, dementia with Lewy bodies. * $p < 0.05$; NS, not significant

To understand the neuropathological correlate of parkinsonism in AD, several postmortem studies have mainly focused on pathology of the SN given that dopaminergic neuronal loss in the ventrolateral SN is the pathological hallmark of PD [28]. However, involvement of the SN was so variable that the neural basis for parkinsonian motor symptoms in AD has still not been confirmed. Some authors demonstrated that there were concomitant PD-related pathologies (i.e., nigral neuronal loss associated with LB) in AD patients with parkinsonism [6–8], while others found that parkinsonian motor symptoms were associated with neurofibrillary tangle pathology in the SN but did not require the presence of LB [29, 30]. Furthermore, some cases had neither histological changes nor reduced neuronal densities in the SN [8, 9, 11], suggesting the contribution of extranigral pathology to parkinsonism associated with AD. Furthermore, studies of DAT scans have reported inconsistent findings. Rinne et al. [13] observed the decreased striatal uptake of DAT ligands in both the putamen and caudate that correlated well with the severity of parkinsonism in AD, while other studies found a lack of striatal DAT changes [14, 15]. In the present study, patients with ADCI with mild parkinsonism showed a reduction of DAT availability in the caudate, rather than the posterior putamen, compared to that in healthy controls. In addition, the severity of parkinsonian motor signs did not correlate with striatal DAT availability in patients with ADCI in contrast to patients with PD. These findings suggest that PD-related pathology, which is greatest in the ventrolateral tier of the SN pars compacta to induce dopaminergic neuronal loss [28], is less likely to be a major determinant for parkinsonism in patients with ADCI [11, 31]. Instead, postsynaptic alterations of the nigrostriatal pathway, as well as dysfunction in the frontostriatal circuit secondary to AD-related pathology, could be a possible explanation for parkinsonism. In fact, neuropathological studies have shown that the striatum, including the caudate nucleus, is a site of β-amyloid and tau deposition in AD [10, 32], and a significant reduction in the volume of the caudate in AD has been reported by neuroimaging studies

Table 2 Discriminatory power of DAT availability in each striatal sub-region to differentiate ADCI with parkinsonism from DLB

Region	AUC (95% CI)	Cut-off	Sensitivity	Specificity	vs. AC[a]	vs. PC[a]	vs. AP[a]	vs. PP[a]	vs. VP[a]	vs. VS[a]	vs. WS[a]
AC	0.874 (0.788–0.960)	1.919	100%	62.5%	–	0.122	0.299	0.300	0.426	0.754	0.105
PC	0.830 (0.729–0.931)	1.075	96.6%	59.4%	0.122	–	0.093	0.076	0.137	0.242	0.042
AP	0.898 (0.815–0.981)	3.005	100%	75.0%	0.299	0.093	–	0.851	0.871	0.537	0.513
PP	0.900 (0.829–0.981)	3.050	100%	78.1%	0.300	0.076	0.851	–	0.831	0.545	0.708
VP	0.896 (0.809–0.982)	2.297	100%	75.0%	0.426	0.137	0.871	0.831	–	0.613	0.604
VS	0.883 (0.796–0.969)	2.446	89.7%	78.1%	0.754	0.242	0.537	0.545	0.613	–	0.361
WS	0.905 (0.826–0.984)	2.478	100%	78.1%	0.105	0.042	0.513	0.708	0.604	0.361	–

The AUC for DAT availability in the posterior caudate (PC) tended to be smaller than that in the anterior putamen (AP), posterior putamen (PP), and whole striatum (WS)

Abbreviations: *DAT* dopamine transporter, *ADCI* Alzheimer's disease-related cognitive impairment, *DLB* dementia with Lewy bodies, *AC* anterior caudate, *PC* posterior caudate, *AP* anterior putamen, *PP* posterior putamen, *VP* ventral putamen, *VS* ventral striatum, *WS* whole striatum, *AUC* area under curve, *CI* confidence interval

[a] *p*-value for the comparison of AUC between each variable

[33]. Such pathological deposition and atrophy in the caudate nucleus might disrupt the fronto-subcortical motor circuit and lead to parkinsonism in AD [34].

The results of our study are in line with the view that DAT scans are a potentially useful diagnostic tool in differentiating ADCI from other LB diseases [35, 36], even if patients with ADCI have parkinsonism. In particular, we quantified DAT availability in the striatal subregions using a detailed segmentation of the striatum and performed ROC analyses to identify which subregions are better in discriminating between AD and DLB. In this study, the DAT availability of all striatal subregions had a fair discriminatory power to differentiate ADCI with mild parkinsonism from DLB, although the DAT availability of the posterior caudate had a relatively small AUC (0.830) and low specificity (59.4%) which might be due to a slight decrease in ^{18}F-FP-CIT binding in the caudate in the ADCI with mild parkinsonism group. On the other hand, the pattern of the rostro-caudal gradient in DAT availability was similar between the AD with mild parkinsonism group and the DLB group, which was quite different from the sharp rostro-caudal gradient observed in the PD group. Like patients with AD, the patients with DLB frequently exhibit the AD-related pathologies and have a high burden of diffuse amyloid plaques in the striatum [37, 38], especially the rostral portion (i.e., the caudate) [39], which may lead to a flatter rostro-caudal gradient of striatal DAT availability compared to those with PD [40–42]. Thus, it is speculated that the caudate-to-putamen gradient can be a useful marker of β-amyloid and/or tau deposition in the striatum, especially the caudate nucleus, in patients with parkinsonism. A further study regarding whether the pattern of DAT availability would differ depending on β-amyloid burden in patients with DLB or PD with dementia is needed to clarify this issue.

In the correlation analysis, our data did not identify any association between the severity of motor symptoms or cognitive dysfunction and striatal DAT availability in

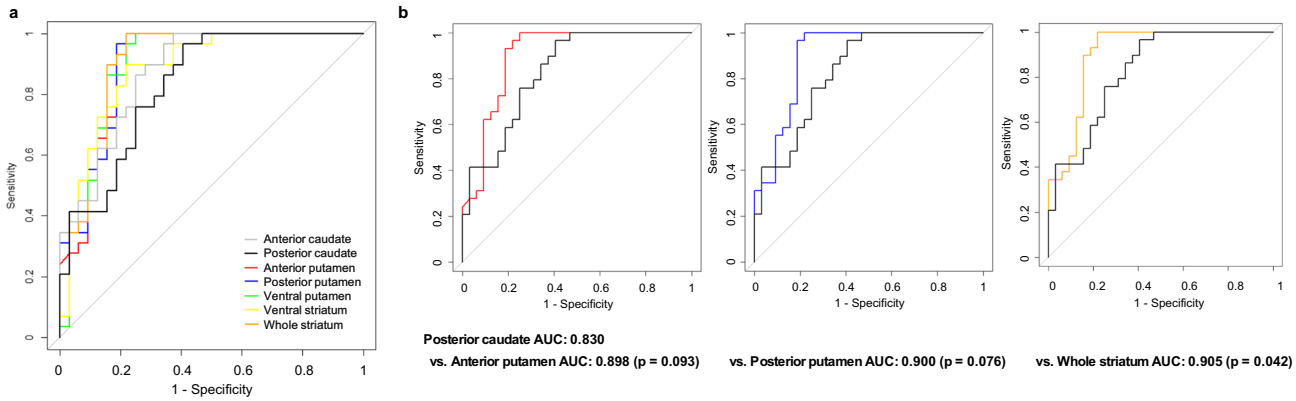

Fig. 2 **a** ROC curves for DAT availability of the striatal subregions to discriminate between ADCI with mild parkinsonism and DLB. **b** Comparison of the ROC curves for the DAT availability of the posterior caudate and that of other striatal subregions. Abbreviations: ROC, receiver operating characteristics; DAT, dopamine transporter; ADCI, Alzheimer's disease-related cognitive impairment; DLB, dementia with Lewy bodies; AUC, area under curve

DLB, in contrast to findings in PD [43]. The relationship between the clinical symptoms and striatal DAT binding has rarely been explored and has not yet been confirmed in DLB [41, 44–46]. Siepel et al. [46] showed that motor UPDRS and executive impairment were associated with striatal DAT binding in DLB, while Walker et al. [41] and Ziebell et al. [45] found no association. These inconsistent results could be due to the different study designs, inter-center variability in the acquisition and analysis of DAT scan data, and heterogeneous study populations [46]. Our results once again support the concept that multifactorial pathology, such as mixed AD-related pathology, may affect the nigrostriatal dysfunction in DLB, which in turn results in abnormal DAT scan findings in a manner different from that seen in PD [47]. Taken together, our data could explain why parkinsonian motor signs and their responsiveness to dopaminergic medications in patients with DLB would differ from patients with PD.

Our study has some limitations. First, none was pathologically diagnosed in this study and an alternative diagnosis of DLB might be possible in some patients with ADCI. However, the diagnosis of ADCI was confirmed based on ^{18}F-FDG and ^{18}F-FBB PET, and in particular, subjects showing reduced occipital activity and/or the cingulate island sign [22] on ^{18}F-FDG PET were rather assigned to the DLB group in this study. Second, caution should be exercised when interpreting the DAT scan findings, since evidence is lacking that FP-CIT PET tracers are reliable surrogate markers for nigrostriatal dopaminergic degeneration [48]. Furthermore, it is possible that the slight decrease in FP-CIT uptake of the caudate might be due to the caudate atrophy in the ADCI group [33]. However, there was no significant difference in the caudate volume between the ADCI and control groups in this study (see Supplementary Methods and Supplementary Table 3). Third, the possibility of some ADCI patients having normal aging-related slowness cannot be completely ruled out, although the presence of minimal to mild bradykinesia was counted when the patients suspiciously showed the amplitude decrements near the end of the tasks. In addition, a direct comparison of DAT scans between ADCI with and without parkinsonism would be needed to draw a solid conclusion about the neurobiology of subtle motor disturbance in AD.

In conclusion, the present study demonstrated that patients with ADCI with mild parkinsonism had distinct patterns of DAT scans which may aid in differentiating between AD and DLB. Our findings would be of clinical value given that accurate diagnosis of AD and DLB is important for establishing a clinical prognosis, patients counselling, and selection of homogeneous disease entity for future clinical trials. The results of this study also suggest that parkinsonism is associated with the extranigral source of pathology in AD.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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