

Serial Nigrostriatal Dopaminergic Imaging in Mild Cognitive Impairment With Lewy Bodies, Alzheimer Disease, and Age-Matched Controls

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Abstract

Background and Objectives

Progressive nigrostriatal pathway degeneration occurs in individuals with dementia with Lewy bodies (LB). Our objective was to investigate whether repeat 123[I]-N-(3-fluoropropyl)-2 β -carboxymethoxy-3 β -(4-iodophenyl) nortropine (FP-CIT) single photon emission computed tomography (SPECT) can identify progressive dopaminergic loss in mild cognitive impairment (MCI) with Lewy bodies (MCI-LB).

Methods

Individuals with MCI-LB and MCI due to Alzheimer disease (MCI-AD) underwent comprehensive clinical assessment, 123[I]-FP-CIT SPECT at baseline and annual reviews, and baseline cardiac ¹²³Iodine metaiodobenzylguanidine (I-MIBG). Mixed-effects models were used to investigate changes in 123[I]-FP-CIT specific binding ratio (SBR) in the striatum for each diagnostic group compared with controls. The time interval to the development of a quantitatively abnormal 123[I]-FP-CIT SPECT in the possible and probable MCI-LB groups was determined as the time it took for these groups to reach a striatal uptake 2 SDs below age-matched controls. Test-retest variation was assessed using baseline and repeat scans in controls.

Results

We recruited 20 individuals with MCI-AD, 11 with possible MCI-LB, 25 with probable MCI-LB, and 29 age-matched controls. The mean time between baseline and the final image was 1.6 years (SD = 0.9, range 1.0–4.3). The annual estimated change in SBR was 0.23 for controls (95% CI –0.07 to 0.53), –0.09 (–0.55 to 0.36) for MCI-AD, –0.50 (–1.03 to 0.04) for possible MCI-LB, and –0.48 (–0.89 to –0.06) for probable MCI-LB. The median annual percentage change in SBR in MCI-LB was –5.6% (95% CI –8.2% to –2.9%) and 2.1% (–3.5% to 8.0%) for MCI-AD. The extrapolated time for a normal scan to become abnormal was 6 years. Controls and MCI-AD showed no significant change in dopaminergic binding over time. The mean test-retest variation in controls was 12% (SD 5.5%), which cautions against overinterpretation of small changes on repeat scanning.


Discussion

Progressive dopaminergic loss in the striatum is detectable using 123[I]-FP-CIT SPECT in MCI-LB at a group level. In clinical practice, individual change in striatal 123[I]-FP-CIT uptake seems to be of limited diagnostic value because of high test-retest variation.


Classification of Evidence

This study provides Class II evidence that longitudinal declines in striatal uptake measured using 123[I]-FP-CIT SPECT are associated with MCI due to Lewy body disease but not MCI due to Alzheimer disease.

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Glossary

ACE-R = Addenbrooke's Cognitive Examination-Revised; **AD** = Alzheimer disease; **DLB** = dementia with Lewy bodies; **FP-CIT** = N-(3-fluoropropyl)-2 β -carboxymethoxy-3 β -(4-iodophenyl) nortropine; **I** = iodine; **IRBD** = idiopathic REM behavioral disorder; **MCI-LB** = mild cognitive impairment with Lewy bodies; **MIGB** = metaiodobenzylguanidine; **MMSE** = Mini Mental State Examination; **PD** = Parkinson disease; **SBR** = specific binding ratio; **SPECT** = single photon emission computed tomography.

Introduction

Dementia with Lewy bodies (DLB) is associated with progressive degeneration of the dopaminergic nigrostriatal pathway¹ and is present in approximately 90% cases of DLB at postmortem.² Striatal dopaminergic deficits can be detected several years ahead of clinical parkinsonism in other prodromal α -synucleinopathies such as idiopathic REM sleep behavior disorder.^{3,4} It is known that dopaminergic deficits are present in some individuals with mild cognitive impairment with Lewy bodies (MCI-LB),⁵ but not whether degeneration over time can be detected at this stage.

The functional integrity of the dopaminergic nigrostriatal pathway can be studied in vivo using 123[I]-N-(3-fluoropropyl)-2 β -carboxymethoxy-3 β -(4-iodophenyl) nortropine (FP-CIT) single photon emission computed tomography (SPECT), a radiopharmaceutical that binds to the dopamine transporter. Degeneration of dopaminergic nigrostriatal neurons leads to reduced binding of striatal 123[I]-FP-CIT, and the decreased uptake of 123[I]-FP-CIT correlates with dopamine transporter density.⁶ 123[I]-FP-CIT SPECT is a well-established imaging modality first used in the diagnosis of Parkinson disease (PD) and aids in differentiating between dementia subtypes.⁷

Serial 123[I]-FP-CIT SPECT imaging is an understudied topic in Lewy body disorders, but has previously demonstrated merit in early DLB to identify disease evolution in vivo. For instance, a 2016 study⁸ found that 10% of patients with probable DLB had an initial normal 123[I]-FP-CIT SPECT, which all became abnormal on repeat imaging an average of 1.5 years later.

The objective of this study was to determine whether repeated dopamine transporter imaging can detect longitudinal change in striatal tracer uptake in MCI-LB as compared with MCI-Alzheimer disease (AD) or age-matched controls. Our primary research question was “does longitudinal decline in striatal uptake measured using 123[I]-FP-CIT SPECT occur in patients with MCI-LB?” We hypothesized that the MCI-LB group would show significant decline over time, whereas the MCI-AD group and controls would show no significant change. As a secondary analysis, we estimated the time from baseline for the MCI-LB subset with normal baseline imaging to develop a quantitatively abnormal 123[I]-FP-CIT SPECT.

Methods

Participant Recruitment

Participants with MCI were recruited prospectively from memory clinics in the North-East of England between 2013 and 2015 (study 1) and 2016 and 2019 (study 2). Detailed inclusion and exclusion criteria are given in our previous publications.^{5,9} Healthy controls were 60 years or older with no MCI,¹⁰ dementia, or other suspected brain pathology. They had a normal brain MRI and Mini Mental State Examination [MMSE] score ≥ 26 .

Clinical assessment included the following: the Movement Disorders Society-Unified Parkinson's Disease Rating Scale motor examination,¹¹ Epworth Sleepiness Scale,¹² Cumulative Illness Rating Scale for Geriatrics,¹³ and Geriatric Depression Scale.¹⁴

Standard Protocol Approvals, Registrations, and Patient Consents

The study received ethical approval (Research Ethics Committee Identification Number 15/NE/0420), and all participants gave written informed consent.

123[I]-FP-CIT SPECT Imaging

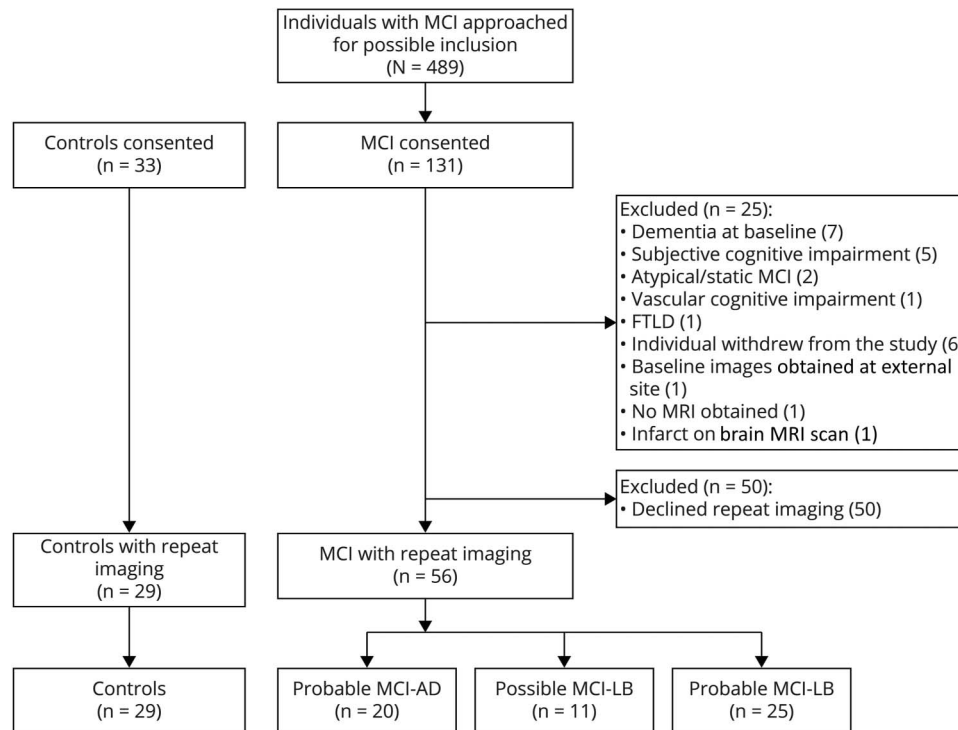
Participants were scanned 3–6 hours after a bolus intravenous injection of 185 MBq of 123[I]-FP-CIT (DaTSCAN; GE Healthcare, UK) was administered using a dual-headed gamma camera (Siemens Symbia S or Siemens Intevo) fitted with low-energy high-resolution parallel hole collimators. One hundred twenty 25-second views over a 360° orbit (60 views per detector) were acquired on a 128 \times 128 matrix with a zoom of 1.23 \times giving a pixel size of 3.9 \times 3.9 mm. Overall image acquisition time was 25 minutes. Participants also had a cardiac ¹²³I-MIBG scan as detailed in our previous publication.¹⁵

All participants in our first study (2013–2015) were invited to join our second study (2016–2021), where they had a repeat 123[I]-FP-CIT SPECT scan 1–3 years after baseline imaging and were invited to undergo a further repeat scan at least 1 year after that. We also recruited new participants to have baseline and repeat scans within the second study. Therefore, all participants included in this analysis had either 2 or 3 123[I]-FP-CIT SPECT scans, all using the same scanner.

123[I]-FP-CIT Specific Binding Ratio Analysis

123[I]-FP-CIT uptake was measured using specific binding ratios (SBRs) obtained from DaTQUANT v2.0 software (GE

Figure 1 Participant Flowchart Showing Study Recruitment and Inclusion in This Repeat 123[I]-FP-CIT SPECT Analysis



Healthcare, Chalfont St. Giles, UK).¹⁶ The software registers the scan to a normal database and overlays volumes of interest over the whole striatum, caudate, and putamen as well as a reference region in the occipital lobe representing nonspecific, displaceable activity. The SBR is defined as the ratio between the background subtracted count density in the striatal volume and the count density in the background volume. We did not move any striatal volumes, but did move the background volume anteriorly if the signal was reduced because of atrophy, because this would otherwise make the SBRs artificially high. Left and right-sided SBRs were recorded for the striatum, caudate, and putamen.

Diagnosis

An expert 3-person consensus panel of experienced old-aged psychiatrists (A.J.T., P.C.D., J.-P.T.) allocated participants with MCI to one of 3 clinical diagnoses, following National Institute on Aging and the Alzheimer's Association criteria¹⁰ and core features for DLB¹ (later incorporated into research criteria for MCI-LB¹⁷). The 4 core features are parkinsonism, visual hallucinations, cognitive fluctuations, and REM sleep behavior disorder. The 3 categories are possible MCI-LB (MCI plus one core symptom of DLB or MCI with none of the 4 core symptoms of DLB but having an abnormal cardiac MIBG), probable MCI-LB (MCI plus 2 or more of the 4 core symptoms of DLB or MCI plus one core symptom of DLB and an abnormal cardiac MIBG), and MCI-AD (fulfilling criteria for MCI-AD¹⁰ with none of the 4 core symptoms of DLB and a normal cardiac MIBG).

The presence of parkinsonism was based on clinical judgment as to whether the participant exhibited “one or more spontaneous cardinal features of parkinsonism” defined in the MCI-LB research criteria¹⁷ as “bradykinesia (defined as slowness of movement and decrement in amplitude or speed), rest tremor, or rigidity.” MCI due to PD (PD-MCI) was excluded using the “1-year rule”—if parkinsonism was present more than 1 year before the onset of cognitive impairment, participants were classified as having preexisting PD and excluded.

Statistical Analysis

Mixed models were used to investigate differential changes in total striatal 123[I]-FP-CIT uptake primarily, and secondarily for the caudate and putamen separately, for each diagnostic group compared with controls. SBRs for both sides were input into the model, with side a random effect (as opposed to taking the mean value between left and right for each scan). All analyses were conducted using R statistical software (Version 3.5.2; R Foundation for Statistical Computing, Vienna, Austria). Fixed effects included were age (centered at 60 years), time in years from baseline imaging, sex, and diagnostic group (MCI-AD, possible MCI-LB, and probable MCI-LB, reference: controls). Random intercept and slopes were included for each hemisphere nested within each subject. We also ran an analysis with “most affected hemisphere” as a fixed effect, where the most affected hemisphere (right or left) was defined as the side with the largest decrease in whole striatal SBR between baseline and the most recent scan. This

Table 1 Demographic and Clinical Characteristics of the 4 Diagnostic Groups

	Control, N = 29 ^a	MCI-AD, N = 20 ^a	Possible MCI-LB, N = 11 ^a	Probable MCI-LB, N = 25 ^a	p Value ^b
Baseline age	74 (7)	75 (8)	73 (7)	73 (7)	>0.9
Female sex	8 (28%)	9 (45%)	4 (36%)	3 (12%)	0.094
Instrumental activities of daily living	—	7 (1)	6 (1)	6 (2)	0.6
Geriatric Depression Scale	1.1 (1.8)	4.0 (2.8)	3.2 (2.8)	5.2 (4.1)	<0.001
Cumulative Illness Rating Scale for Geriatrics	5 (3)	7 (3)	10 (4)	8 (4)	<0.001
Clinical Dementia Rating	0 (0)	0.5 (0)	0.5 (0)	0.44 (0.17)	<0.001
Mini Mental State Examination	28.4 (1.2)	26.6 (2.2)	26.2 (2.8)	27.0 (2.1)	0.002
ACE-R total score	92.6 (4.3)	82.4 (10.1)	81.5 (7.6)	84.2 (8.9)	<0.001
Epworth Sleepiness Scale	5 (3)	5 (5)	6 (5)	8 (4)	0.018
MDS-UPDRS III score	5 (4)	17 (10)	22 (13)	21 (15)	<0.001
Neuropsychiatric inventory total score	—	13 (11)	13 (14)	16 (11)	0.8
Receiving cholinesterase inhibitors	0 (0%)	3 (16%)	4 (36%)	10 (40%)	0.002
Receiving antiparkinsonian medication	0 (0%)	0 (0%)	0 (0%)	4 (16%)	0.021
Receiving antidepressants	3 (11%)	6 (32%)	9 (82%)	9 (36%)	<0.001
Cognitive fluctuations present	0 (0%)	0 (0%)	1 (9.1%)	16 (64%)	n/a
Visual hallucinations present	0 (0%)	0 (0%)	1 (9.1%)	5 (20%)	n/a
REM sleep behavior disorder present	0 (0%)	0 (0%)	4 (36%)	22 (88%)	n/a
Parkinsonism present	0 (0%)	0 (0%)	1 (9.1%)	10 (40%)	n/a
Abnormal MIBG present	1 (3.4%)	0 (0%)	4 (40%)	19 (76%)	n/a
Baseline SBR (whole striatum; L-R averaged)	1.64 (0.22)	1.68 (0.36)	1.53 (0.25)	1.26 (0.41)	<0.001
Baseline Z-score	-0.40 (1.03)	-0.20 (1.70)	-0.91 (1.18)	-2.24 (1.94)	<0.001

Abbreviations: ACE-R = Addenbrooke's Cognitive Examination-Revised; MCI-LB = mild cognitive impairment due to Alzheimer disease; MCI-LB = mild cognitive impairment with Lewy bodies; MIBG = metaiodobenzylguanidine; SBR = specific binding ratio; UPDRS = Unified Parkinson's Disease Rating Scale.

^a Mean (SD); n (%).

^b One-way analysis of variance; Pearson χ^2 test.

analysis enabled us to determine whether including only the most affected side in the model would yield a significantly greater rate of change than that obtained with the default of both sides included. The correlation between striatal SBR and markers of cognition (Addenbrooke's Cognitive Examination-Revised [ACE-R]) and parkinsonism (Unified Parkinson's Disease Rating Scale [UPDRS]) was examined at baseline and over time.

As a secondary analysis, we assessed how long it would take on average for participants with MCI-LB with a normal scan z-score at baseline (defined as striatal SBR within 2 SDs of control mean) to reach an abnormal z-score of -2 or lower.

A subgroup of participants with MCI-LB was identified with quantitatively normal striatal SBR z-scores at baseline (above -2). Their average rate of SBR change was assessed with mixed models as above. Estimated marginal means for SBR uptake for the subgroup were calculated at 1-month intervals

from baseline to 5 years initially to calculate the expected time until the average ^{123}I -FP-CIT uptake fell below 2 z-scores in the striatum or putamen, as an indicative marker of the development of abnormal ^{123}I -FP-CIT uptake.

The annual percentage change in SBR was calculated for each participant in the possible and probable MCI-LB groups. The median annual rate of change in SBR for the striatum, caudate, and putamen and the interquartile range were derived from linear interpolation for each diagnostic group.

Test-retest variation in ^{123}I -FP-CIT SPECT uptake (SBR) was assessed using the baseline and repeat scans for the healthy controls. The expected decline in uptake due to aging over 1 year is less than 1%,¹⁸ so differences above this level can be attributed to variation from scan to scan. The change in SBR between baseline and the repeat scan as a percentage of baseline value was calculated for each control for the striatal, caudate, and putamen regions. The mean and maximum

Table 2 Yearly Change in Standardized SBR in Controls and Difference vs Controls in MCI

	Striatum		Caudate		Putamen	
	Estimate (95% CI)	p Value	Estimate (95% CI)	p Value	Estimate (95% CI)	p Value
Control	0.23 (-0.07 to 0.53)	0.126	0.14 (-0.15 to 0.44)	0.336	0.26 (-0.04 to 0.55)	0.087
MCI-AD vs control	-0.09 (-0.55 to 0.36)	0.684	0.10 (-0.34 to 0.54)	0.664	-0.22 (-0.66 to 0.23)	0.336
Poss. MCI-LB vs control	-0.50 (-1.03 to 0.04)	0.067	-0.17 (-0.68 to 0.35)	0.524	-0.62 (-1.14 to -0.11)	0.018
Prob. MCI-LB vs control	-0.48 (-0.89 to -0.06)	0.025	-0.26 (-0.66 to 0.15)	0.210	-0.55 (-0.96 to -0.14)	0.008

Abbreviations: AD = Alzheimer disease; MCI-LB = mild cognitive impairment with Lewy bodies; SBR = specific binding ratio.

percentage change in SBR was calculated for all regions for each side. Change in SBR was expressed as the absolute difference, that is, the modulus of the difference was used, so that all percentage difference results were positive.

Data Availability

Anonymized data not published within this article will be made available on request to any qualified investigator.

Results

Exclusion of Participants

A total of 131 participants with MCI and 33 controls were consented and enrolled in this study, after confirming eligibility at the baseline visit (Figure 1). Twenty-five participants with MCI were excluded from the study for the reasons detailed in Figure 1. Fifty participants with MCI consented to

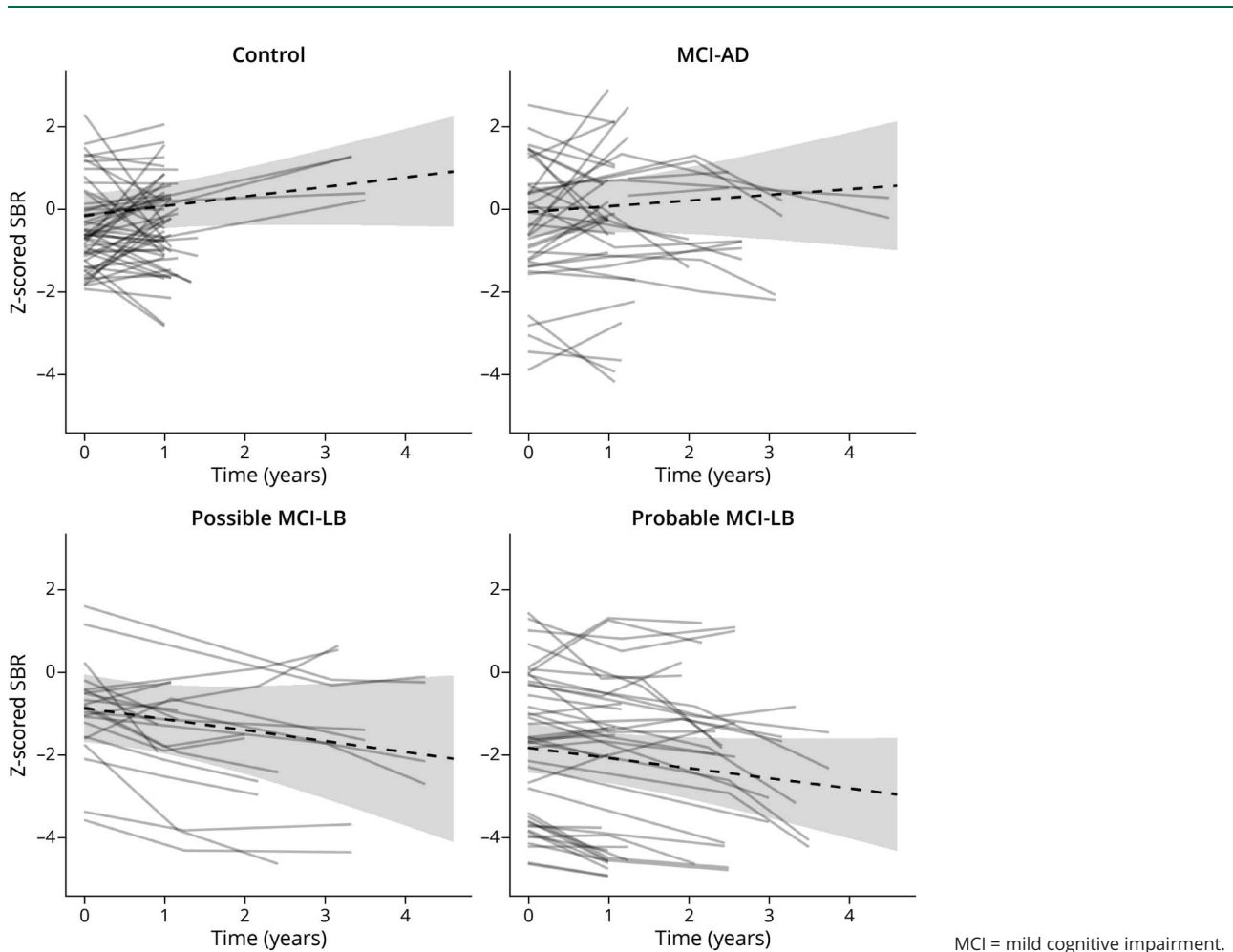
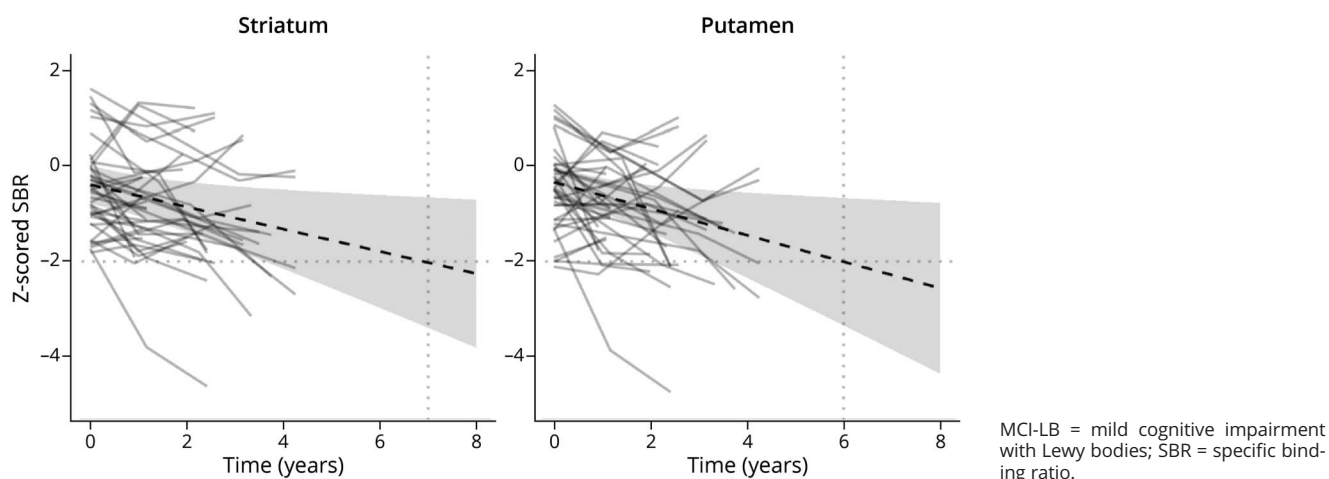
Figure 2 Standardized Trajectories of FPCIT Uptake to the Striatum in Control and MCI Groups (Dashed) and Individual Trajectories for the Left and Right Hemispheres (Solid; One Line for Left and One Line for Right)

Figure 3 Estimated Time Taken for Participants With MCI-LB With Baseline Striatal SBR Z-scores of > -2 to Reach ≤ -2 SDs Below the Control Mean



baseline imaging only. Eighty-five participants (MCI: $n = 56$ and controls: $n = 29$) were included in the repeat ^{123}I -FP-CIT SPECT analysis.

Timing of Repeat ^{123}I -FP-CIT SPECT

Of the 85 individuals with MCI included, 74 underwent the first repeat scan between 12 and 18 months after baseline and 11 underwent the first repeat ^{123}I -FP-CIT SPECT 19–36 months after baseline. Twenty-two had a third ^{123}I -FP-CIT SPECT between 12 and 20 months after the second ^{123}I -FP-CIT SPECT. There was a mean of 1.6 years (SD = 0.9) between the first and last images (range 1.0–4.3 years).

Demographics and Clinical Characteristics

The baseline demographic and clinical characteristics of the different diagnostic groups are summarized in Table 1. All 4 groups (controls, MCI-AD, possible MCI-LB, and probable MCI-LB) were similar in age. There were no significant differences between global cognitive scores (MMSE, ACE-R) of MCI groups, but controls had higher cognitive scores than MCI groups (Table 1).

Assessment of Change in ^{123}I -FP-CIT SPECT Uptake Over Time

Nonlinear terms were not supported for any continuous effect. Therefore, a linear mixed-effects model was used to assess the association between change in ^{123}I -FP-CIT striatal uptake over time and diagnostic group.

Significant predictors of longitudinal decline in striatal uptake are listed in Table 2. Probable MCI-LB was a significant predictor of longitudinal decline over time in ^{123}I -FP-CIT uptake in the striatum ($p = 0.025$), and this was due to significant decline in putamen uptake ($p = 0.008$), but not caudate ($p = 0.21$). Possible MCI-LB was a predictor of decline in ^{123}I -FP-CIT uptake in the putamen only ($p = 0.018$). MCI-AD was

not a significant predictor of longitudinal striatal change ($p = 0.68$). Plots of the SBR results for longitudinal change over time in the whole striatum, caudate, and putamen for all diagnostic groups (controls, MCI-AD, possible MCI-LB and probable MCI-LB) are shown in Figure 2. We repeated the analysis with “most affected hemisphere” as a fixed effect in the mixed-effects model and found no significant interaction (time \times MCI-LB \times most affected hemisphere interaction: $p = 0.93$, whole striatum; $p = 0.55$, caudate; $p = 0.74$, putamen). This demonstrates that although, by definition, the most affected hemisphere declines in MCI-LB more than the least affected hemisphere, the additional decline compared with controls is not statistically significant. The plots of the average decline for all diagnostic groups for the most and least affected hemispheres are shown in eFigure 1, [links.lww.com/WNL/D16](https://www.lww.com/WNL/D16). The baseline SBR is slightly higher for the most affected hemisphere than the least affected hemisphere in MCI-LB (striatum $\beta = +0.30$, $p = 0.047$).

At baseline, there is no significant relationship between striatal SBR and ACE-R ($r = 0.20$, $p = 0.251$) or UPDRS ($r = -0.29$, $p = 0.083$) in the MCI-LB group. There are weak correlations with ACE-R ($r = 0.15$, $p = 0.021$) and UPDRS ($r = -0.14$, $p = 0.020$) over time for the MCI-LB group.

Annual Percentage Change in ^{123}I -FP-CIT Uptake for MCI-LB Groups

Annual percentage change in ^{123}I -FP-CIT uptake was determined using a log-linear model. There was no significant difference between the possible and probable MCI-LB groups in relation to annual percentage change in ^{123}I -FP-CIT uptake in the striatum or striatal subregions. The median annual change in striatal ^{123}I -FP-CIT uptake in the MCI-LB group was -5.6% for the striatum (95% CI -8.2% to -2.9%), -3.3% for the caudate (95% CI -5.8% to -0.6%), and -7.0% for the putamen (-10.3% to -3.6%). The median

annual decline in ^{123}I -FP-CIT uptake was greater in the putamen than in the caudate for the MCI-LB groups. The median change in SBR in MCI-AD was 2.1% (−3.5% to 8.0%) for the striatum, 4.7% (−1.3% to 11.1%) for the caudate, and 0.1% (−5.7% to 6.2%) for the putamen.

Time Until Expected Uptake Is 2 SDs Below Mean

Six individuals with MCI-LB showed a decline from normal to a clearly abnormal quantified uptake during the study of 23 participants with possible MCI-LB with baseline z-scores above −2 (Figure 3). When considered as a group, the marginal estimate did not reach a z-score of −2 within the time-scale of the study. Projecting the estimate forward and assuming a linear progression, the average MCI-LB case with baseline normal uptake would be expected to reach an abnormal uptake to the putamen or striatum 6 years after baseline.

Test-Retest Variation

The average percentage change in SBR between the control baseline and repeat scans was 11.3% (SD 5.3%), 12.4% (SD 5.7%), and 12.3% (SD 6.0%) for the right striatum, putamen, and caudate regions and 10.5% (SD 5.7%), 12.1% (SD 6.2%), and 13.1% (SD 5.2%) for the left striatum, putamen, and caudate regions, respectively. The maximum percentage changes were 33.4% for the left striatum, 35.4% for the left putamen, and 48.0% for the right caudate.

Classification of Evidence

This study provides Class II evidence that longitudinal declines in striatal uptake measured using ^{123}I -FP-CIT SPECT are associated with MCI-LB but not MCI-AD.

Discussion

We aimed to assess whether a decrease in ^{123}I -FP-CIT SPECT uptake over time was detectable in MCI-LB and MCI-AD groups compared with age-matched controls. Our results show a significantly greater decline in the striatal uptake of ^{123}I -FP-CIT over time in the possible and probable MCI-LB groups, but a nonsignificant rate of change in striatal uptake in the MCI-AD group. The dopaminergic loss predominantly affects the putamen in both MCI-LB groups.

The rationale for repeat ^{123}I -FP-CIT SPECT imaging is based on the observations that 10% of patients with DLB have only neocortical Lewy body pathology, sparing the midbrain², and that 20% of people with DLB and 50% of people with MCI-LB have normal ^{123}I -FP-CIT scans.^{5,9,19} Such findings are consistent with a view that as time progresses, Lewy body disease causes greater involvement of the substantia nigra and thus a higher proportion of abnormal scans. A study in patients with probable DLB demonstrated that those with a normal scan eventually developed an abnormal ^{123}I -FP-CIT SPECT over time, with a median time between scans of 18 months.⁸

Our study indicates that progressive nigrostriatal pathway degeneration is already detectable at the prodromal stage of DLB. Using a linear mixed-effects model assessing rates of decline of ^{123}I -FP-CIT uptake, we found a significant striatal decline of dopamine transporter availability in the putamen in both possible MCI-LB ($p = 0.018$) and probable MCI-LB ($p = 0.008$) groups over time. Decline in the whole striatum was significant in the probable MCI-LB group ($p = 0.025$), but not in the possible MCI-LB group ($p = 0.067$). The MCI-AD group did not have any significant decline in the whole striatum or its subregions, consistent with the lack of involvement of the nigrostriatal pathway in AD pathology.

On average, our model showed that an individual with MCI-LB normal baseline uptake would be expected to reach an abnormal uptake to the putamen or striatum around 6 years later, although this will depend on the level at baseline. Because this forecast lies outside the range of data in this study, this should be interpreted with caution. The model suggests that individuals with MCI-LB are unlikely to develop abnormal SBRs within a few years of a normal baseline scan, although this was seen in 6 of 23 participants in our study.

A previous study in idiopathic REM behavioral disorder (IRBD) found that a baseline reduction of ^{123}I -FP-CIT uptake in the putamen greater than 25% from the mean of normal control values predicted those who developed a α -synucleinopathy after 3 years of follow-up.²⁰ Future longitudinal follow-up of our cohort will inform whether the extent of initial dopaminergic deficit on baseline ^{123}I -FP-CIT imaging predicts time to conversion to DLB.

Our study found a median annual decline in the striatum of −6% in both the probable MCI-LB and possible MCI-LB groups. In both MCI-LB groups, the median loss in the striatum was predominately due to loss in the putamen (−7%) rather than the caudate (−3%). Therefore, our results suggest that dopaminergic loss in prodromal DLB occurs predominantly in the putamen, in contrast to early DLB.²¹⁻²⁴ Only one study in DLB examined annual percentage loss in striatal ^{123}I -FP-CIT uptake, and this showed a more uniform loss throughout the striatum and a loss far in excess of values in our study, with an annual decline in caudate uptake of −12.7% and −13.0% in the putamen.²⁵ Our findings are more akin to IRBD and PD studies, which found greater loss in the putamen than the caudate. In IRBD, the annual rate of decline in the putamen was −5.8% and −3.0% in the caudate.²⁶ Studies in PD have shown similar declines in the caudate (−4.6% to −11.0%) and in the putamen (−6.0% to −10.0%).²⁷⁻²⁹ In the IRBD study, those who converted to PD had a more rapid decline in the putamen of approximately 10% per year.²⁶

Our repeat scans in controls showed that variation in SBR between scans is around 11% on average. This suggests that when evaluating a follow-up scan in a patient with MCI-LB, the SBR would need to drop substantially to be confident that

the decline was not due to chance. The first repeat study in 6 healthy controls scanned 3–6 weeks apart reported a similar mean test-retest variation of 7.4% (range 2.1%–23.0%).³⁰ The median annual change in our MCI-LB groups was –6%, so a follow-up scan performed a year or two after normal or equivocal baseline is unlikely to detect progressive dopaminergic loss—although this was seen in 6 individuals in our study.

This study has several strengths: (1) a prospective longitudinal design in a cohort of individuals with MCI-LB, using serial functional imaging at various time points; (2) the inclusion of matched controls to establish whether the process of aging alone could account for the decline in striatal 123[I]-FP-CIT uptake and estimate the test-retest variation; (3) the confirmation of clinical core features of LB disease by a consensus panel blinded to the imaging results; and (4) the use of mixed-effects models that make the best use of data by incorporating both left and right-sided SBR measures.

Limitations of the study include possible diagnostic misattribution, especially as many individuals are early in their disease trajectory. Future pathologic examination may lead to diagnostic reassignment. However, much effort was made to minimize this problem with the incorporation of cardiac MIBG into the diagnostic process. Another limitation is relatively short follow-up with a variable time between baseline and repeat 123[I]-FP-CIT imaging. We have shown that in people with MCI, 12–18 months is typically too short a timescale to detect a decrease in striatal 123[I]-FP-CIT uptake with confidence. Future studies would benefit from a longer period of follow-up. Most of the participants (75/85) were on the same medication throughout the study, so the effect of medication on uptake results is likely to be minimal. However, 4 participants with probable MCI-LB, 4 with possible MCI-LB, one with MCI-AD, and one control reported a change in medication or dose between baseline and follow-up scans.

In conclusion, progressive decline in 123[I]-FP-CIT SPECT uptake over time is present in both possible and probable MCI-LB at a group level. Follow-up 123[I]-FP-CIT SPECT may be of value in patients with MCI-LB who have initial normal imaging. However, the variation in our control subjects on repeat scanning suggests an interval of several years from baseline may be required for a quantitative change in dopaminergic function to be both detectable and clinically meaningful.

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Disclosure

R. Durcan reports no conflicts in relation to this work. J.T. O'Brien has acted as a consultant, has been a recipient of grant support, and received honoraria for talks for GE Healthcare. J.T. O'Brien is supported by the NIHR Cambridge Biomedical Research Centre. Outside of this work, J.T. O'Brien has acted as a consultant for TauRx, Axon, Eisai, Roche, and GE Healthcare and received grant funding from Alliance Medical and Merck. G. Roberts and G.S. Petrides have received honoraria from GE Healthcare for delivering educational workshops on FP-CIT imaging. J.-P. Taylor has received honoraria from GE Healthcare for delivering educational presentations on Lewy body disease. Outside of this work, J.-P. Taylor has acted as a consultant for Kyowa Kirin and Heptares Sosei and received grant funding from Heptares Sosei. P.C. Donaghy has received grant funding from Alzheimer's Research UK, Alzheimer's Society, Lewy Body Society, Weston Brain Institute, and the Medical Research Council. A.J. Thomas has received support for investigator-led studies and honoraria from GE Healthcare. C.A. Hamilton has received remuneration from Roche for public educational materials unrelated to this work. L.M. Allan is supported by the National Institute for Health Research Applied Research Collaboration South West Peninsula. S.J. Colloby, M. Firbank, and S. Lawley declare that they have no conflicts of interest to disclose. Go to [Neurology.org/N](https://www.neurology.org/N) for full disclosures.

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Continued

Appendix (continued)

Name	Location	Contribution
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Appendix (continued)

Name	Location	Contribution
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