History of falls in Parkinson disease is associated with reduced cholinergic activity

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ABSTRACT

Objective: To investigate the relationships between history of falls and cholinergic vs dopaminergic denervation in patients with Parkinson disease (PD).

Background: There is a need to explore nondopaminergic mechanisms of gait control as the majority of motor impairments associated with falls in PD are resistant to dopaminergic treatment. Alterations in cholinergic neurotransmission in PD may be implicated because of evidence that gait control depends on cholinergic system–mediated higher-level cortical and subcortical processing, including pedunculopontine nucleus (PPN) function.

Methods: In this cross-sectional study, 44 patients with PD (Hoehn & Yahr stages I–III) without dementia and 15 control subjects underwent a clinical assessment and [^{11}C]methyl-4-piperidinyl propionate (PMP) acetylcholinesterase (AChE) and [^{11}C]dihydrotetrabenazine (DTBZ) vesicular monoamine transporter type 2 (VMAT2) brain PET imaging.

Results: Seventeen patients (38.6%) reported a history of falls and 27 patients had no falls. Analysis of covariance of the cortical AChE hydrolysis rates demonstrated reduced cortical AChE in the PD fallers group (−12.3%) followed by the PD nonfallers (−6.6%) compared to control subjects ($F = 7.22$, $p = 0.0004$). Thalamic AChE activity was lower only in the PD fallers group (−11.8%; $F = 4.36$, $p = 0.008$). There was no significant difference in nigrostriatal dopaminergic activity between PD fallers and nonfallers.

Conclusions: Unlike nigrostriatal dopaminergic denervation, cholinergic hypofunction is associated with fall status in Parkinson disease (PD). Thalamic AChE activity in part represents cholinergic output of the pedunculopontine nucleus (PPN), a key node for gait control. Our results are consistent with other data indicating that PPN degeneration is a major factor leading to impaired postural control and gait dysfunction in PD. *Neurology*® 2009;73:1670–1676

GLOSSARY

AChE = acetylcholinesterase; **ANCOVA** = analysis of covariance; **MMSE** = Mini-Mental State Examination; **PD** = Parkinson disease; **PPN** = pedunculopontine nucleus; **PSP** = progressive supranuclear palsy; **UPDRS** = Unified Parkinson's Disease Rating Scale; **VOI** = volume of interest.

Falls are common and disabling in Parkinson disease (PD).[1] Because of nigrostriatal pathology in PD, it is asserted often that postural instability is attributable mainly to striatal dopaminergic denervation. However, balance-related deficits are least responsive to levodopa treatment.[1,2] Therefore, there is a need to explore nondopaminergic mechanisms of gait control in PD. Until recently, gait was generally viewed as a largely automated motor task, requiring minimal cognitive input. Increasing evidence, however, links alterations in cognitive function to gait disturbances.[3] Cortical cholinergic denervation in PD is associated with cognitive impairment[4] but effects of alterations in cholinergic neurotransmission on mobility control in PD are poorly understood. There are 2 major sources of cholinergic projections in the brain. The nucleus basalis of Meynert (NBM) provides the principal cholinergic input of the entire cortical mantle and degenerates in PD.[5] The pedunculopontine nucleus (PPN), a brainstem locomotor center, provides cholinergic

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inputs to the basal ganglia, thalamus, cerebellum, several brainstem nuclei, and the spinal cord,[6] and also degenerates in PD.[7]

[^{11}C]PMP PET imaging assesses cholinergic terminal integrity with cortical activity reflecting NBM integrity and thalamic uptake reflecting PPN integrity. It was the goal of the present study to investigate associations of fall status in PD with cortical-NBM and thalamic-PPN cholinergic function and to compare this to the degree of nigrostriatal dopaminergic denervation. We hypothesized that pathology within the NBM and/or PPN may be associated with fall status in PD.

METHODS

Subjects and clinical test battery. This cross-sectional study involved 44 subjects with PD (34 male and 10 female) and 15 control subjects without PD (7 male and 8 female). Patients met the UK PD Society Brain Bank Research Center clinical diagnostic criteria for PD.[8] In keeping with these criteria, none of the patients had clinical evidence of supranuclear gaze palsy, cervical dystonia, spastic bulbar symptoms, ataxia, prominent dysautonomia, or prominent postural instability within the first year of disease onset.

The diagnosis of PD was also confirmed by the presence of nigrostriatal dopaminergic denervation on DTBZ PET imaging. Patients had mild to moderate severity of disease: 2 patients in stage 1, 1 patient in stages 1.5, 11 patients in stage 2, 17 patients in stage 2.5, and 13 patients in stage 3 of the modified Hoehn & Yahr classification.[9] The mean duration of disease was 7.1 ± 4.2 (SD) years (range 1–17). Subjects with a Mini-Mental State Examination (MMSE) score of 24 or less were not eligible for the study.[10] The mean MMSE score was 29.0 ± 1.4 (range 25–30).

The Unified Parkinson's Disease Rating Scale (UPDRS) was performed.[11] Axial motor score was calculated as the summed score of the UPDRS items 27–30 (arising from chair, posture, gait, postural stability). Subjects on dopaminergic drugs were examined and imaged in the morning after withholding dopaminergic drugs overnight. The mean UPDRS motor score was 25.6 ± 8.2 (range 5–40). Patients also completed a 2-day motor "on-off" diary at home to estimate average daily time spent in "off" state.[12] The UPDRS part II, item 13 on falling (unrelated to freezing) was used to determine fall status, with nonfallers having a score of 0 and fallers a score of 1 or higher.

Twenty-five patients were taking a combination of dopamine agonist and carbidopa-levodopa medications, 13 on carbidopa-levodopa alone, 4 on dopamine agonists alone, and 2 were not on dopaminergic drugs. No patients were on (anti-) cholinergic drugs. Patients with PD were recruited from the movement disorders clinic at the University of Michigan and Ann Arbor VA during the period 2006–2008.

Standard protocol approvals, registrations, and patient consents. The study was approved by the Institutional Review Boards of the University of Michigan and Ann Arbor VA for studies involving human subjects. Written informed consent was obtained from all subjects. ClinicalTrials.gov identifiers: NCT00737217 and NCT00736671.

Imaging techniques. DTBZ and PMP PET imaging was performed in 3-dimensional imaging mode using an ECAT HR+ tomograph (Siemens Molecular Imaging, Inc., Knoxville, TN), which acquires 63 transaxial slices (slice thickness: 2.4 mm; intrinsic in-plane resolution: 4.1 mm full-width at half maximum over a 15.2 cm axial field of view). A NeuroShield (Scanwell Systems, Montreal, Canada) head-holder/shielding unit was attached to the patient bed to reduce the contribution of detected photon events originating from the body outside the scanner field of view.[13] Prior to the DTBZ and PMP injections, a 5-minute transmission scan was acquired using rotating ^{68}Ge rods for attenuation correction of emission data using the standard vendor-supplied segmentation and reprojection routines.

DTBZ PET imaging. No-carrier-added (+)-[^{11}C]DTBZ (250 to 1000 Ci/mmol at the time of injection) was prepared as reported previously.[14] Dynamic PET scanning was performed for 60 minutes immediately following a bolus injection of 55% of 666 MBq (18 mCi) of (+)-[^{11}C]DTBZ dose (containing less than 50 μg of cold DTBZ mass) over the first 15 to 30 seconds of the study, while the remaining 45% of the dose was continuously infused over the next 60 minutes, resulting in stable arterial tracer levels and equilibrium with brain tracer levels after 30 minutes.[15] A series of 15 frame sequence of scans over 60 minutes were obtained as following: 4 × 30 seconds; 3 × 1 minute; 2 × 2.5 minutes; 2 × 5 minutes; and 4 × 10 minutes.

[^{11}C]PMP was prepared in high radiochemical purity (>95%) by N-[^{11}C]methylation of piperidin-4-yl propionate using a previously described method.[16] Dynamic PET scanning was performed for 70 minutes immediately following a bolus IV injection of 666 MBq (18 mCi) of [^{11}C]PMP. The dose contained less than 200 μg cold PMP mass. Emission data were collected in 16 sequential emission scans (the DTBZ protocol plus an additional 10-minute frame). All subjects were studied supine, with eyes and ears unoccluded, resting quietly in a dimly lit room.

MRI. All subjects underwent brain MRI on a 3 Tesla Philips Achieva system (Philips, Best, the Netherlands) utilizing an 8-channel head coil and the ISOVOX examination card protocol primarily designed to yield isotropic spatial resolution. A standard T1-weighted series of a 3-dimensional inversion recovery–prepared turbo-field echo was performed in the sagittal plane using repetition time/echo time/inversion time = 9.8/4.6/1041 msec; turbo factor = 200; single average; field of view = 240 × 200 × 160 mm; acquired matrix = 240 × 200. A total of 160 slices were reconstructed to 1 mm isotropic resolution. This sequence maximizes contrast among gray matter, white matter, and CSF and provides high-resolution delineation of cortical and subcortical structures. The brain MRI scans of the patients were also reviewed with specific attention to signs of atypical parkinsonism, such as midbrain atrophy (including the "hummingbird" sign), pontine atrophy (including the "hot cross bun" sign), cerebellar atrophy, or hyperintense signal at the posterolateral portion of the putamen. None of the scans demonstrated imaging evidence of either multiple system atrophy or progressive supranuclear palsy in the patients.[17] Subjects with evidence of focal intracranial pathology or large vessel stroke were not eligible for the study.

Data analysis. All image frames were spatially coregistered within subjects with a rigid-body transformation to reduce the effects of subject motion during the imaging session.[18] IDL im-

Table 1 Mean ± SD thalamic and cortical AChE hydrolysis rates (k_3; min^{-1}) and striatal VMAT2 (BP_{ND}) activity in the patients with PD and control subjects

	PD (n = 44)	Control subjects (n = 15)	Statistical significance
Cortical AChE k_3	0.0273 ± 0.0031	0.0304 ± 0.0032	$t = 3.24; p = 0.002$
Thalamic AChE k_3	0.0599 ± 0.0071	0.0640 ± 0.0040	$t = 3.37; p = 0.002$
Putamen DTBZ BP_{ND}	0.71 ± 0.18	1.85 ± 0.29	$t = 14.41; p < 0.0001$
Caudate nucleus DTBZ BP_{ND}	0.89 ± 0.33	1.53 ± 0.32	$t = 6.51; p < 0.0001$

AChE = acetylcholinesterase; PD = Parkinson disease.

age analysis software (Research Systems, Inc., Boulder, CO) was used to manually trace volumes of interest (VOIs) on the MRI to include the thalamus, caudate nucleus, and putamen of each hemisphere. Total cortical VOI were defined using semiautomated thresholding delineation of cortical gray matter signal on the MRI. Left and right hemispheric VOIs were averaged because of absence of significant differences in left-to-right hemispheric AChE activity.

DTBZ images were analyzed using equilibrium modeling to estimate the nondisplaceable binding potential (BP_{ND}), which is equivalent to the ratio of specific (V_S) to nondisplaceable (V_{ND}) binding in each imaged voxel or target VOI.[15] The total volume of distribution (V_T) in any voxel or VOI contains contributions of nondisplaceable ligand (V_{ND}) in addition to that of specifically bound ligand (V_S).[19] We estimated specific DTBZ binding by subtraction of the occipital cortex value (V_{ctx}), a reference region very low in VMAT2 binding sites, with the assumption that the nondisplaceable distribution is uniform across the brain ($V_{ND} = V_{ctx}$) at equilibrium:

$$V_S = V_T - V_{ND} \quad (1)$$

Reporting specific binding relative to the nondisplaceable as measured in the occipital cortex yields the nondisplaceable binding potential measure BP_{ND}:

$$BP_{ND} = V_S/V_{ND} = (V_T - V_{ND})/V_{ND} = (V_S/V_{ND}) - 1 \quad (2)$$

AChE hydrolysis rates (k_3) were estimated using a method using the striatal VOI (defined by manual tracing on MRI) as the reference input tissue.[20] The operational equation is:

$$A(T) = p_1 \cdot R(T) + p_2 \cdot \int R(t)dt - p_3 \cdot \int A(t)dt \quad (3)$$

where A(T) and R(T) are radioactivity concentrations in VOIs and the reference tissue, striatum, which is assumed to have complete trapping of PMP.

Standard pooled-variance t or Satterthwaite's method of approximate t tests were used for group comparisons (SAS version 9.1, SAS institute, Cary, NC). Pearson correlation coefficients were calculated for correlation between clinical or PET variables. Analysis of covariance (ANCOVA) was performed to compare differences between groups while controlling for age and/or the degree of nigrostriatal denervation. Duncan multiple range post hoc test was used to determine differences between subgroups.

RESULTS The mean age of the patients was 68.9 ± 9.5 years (range 51–83) and did not differ from the non-PD control subjects (64.4 ± 9.6 years; range 50–81; $t = -1.57$, $p = 0.12$). Cortical and thalamic AChE hydrolysis rates and striatal DTBZ BP_{ND} were significantly lower in the patients compared to the control subjects (table 1).

Longer duration of disease correlated with lower striatal DTBZ binding ($R = -0.42$, $p = 0.005$) and lower thalamic AChE hydrolysis rates ($R = -0.33$, $p = 0.02$). There was a borderline relationship between longer duration of disease and lower cortical AChE hydrolysis rates ($R = -0.29$, $= 0.055$). UPDRS motor scores correlated with striatal DTBZ binding ($R = -0.35$, $p = 0.024$) and cortical AChE hydrolysis rates ($R = -0.43$, $p = 0.004$). There was a borderline relationship between higher UPDRS motor scores and lower thalamic AChE hydrolysis rates ($R = -0.25$, $p = 0.09$). Higher UPDRS axial motor scores correlated with lower striatal DTBZ binding ($R = -0.32$, $p = 0.04$), lower cortical ($R = -0.34$, $p = 0.03$) but not with thalamic AChE hydrolysis rates (-0.10, $p = 0.48$).

Higher MMSE scores correlated with higher cortical AChE hydrolysis rates ($R = 0.36$, $p = 0.02$) but not with thalamic AChE activity ($R = 0.13$, $p = 0.41$) or striatal DTBZ binding ($R = -0.03$, $p = 0.86$). Higher scores on the UPDRS activities of daily living scale correlated with lower cortical AChE hydrolysis rates ($R = -0.35$, $p = 0.02$) but not with striatal DTBZ binding ($R = -0.22$, $p = 0.14$) and borderline with thalamic AChE activity ($R = -0.27$, $p = 0.08$).

Seventeen patients (38.6%) reported a history of falls and 27 patients had no falls. PD fallers were slightly older, had longer duration of disease, and had higher motor UPDRS scores compared to the PD nonfallers (table 2). There were no significant differences in mean MMSE scores or average daily time spent in "off" states (table 2).

ANCOVA was used to compare striatal DTBZ and thalamic and cortical AChE activity in the PD fallers, PD nonfallers, and control subjects while adjusting for the effects of age. As expected, striatal DTBZ binding was significantly lower in the pa-

Table 2 Mean ± SD age, duration of disease, MMSE scores, UPDRS motor scores, and average daily "off" time (in hours) in the PD fallers and nonfallers groups

	PD fallers (n = 17)	PD nonfallers (n = 27)	Statistical significance
Age, y	72.5 ± 9.3	66.6 ± 9.1	$t = 2.07; p = 0.047$
Duration of disease, y	8.8 ± 4.3	6.0 ± 3.9	$t = 2.19; p = 0.034$
MMSE	28.8 ± 1.5	29.2 ± 1.4	$t = 0.86; p = 0.40$
UPDRS motor	30.4 ± 6.5	22.6 ± 7.8	$t = 3.44; p = 0.001$
UPDRS axial motor	6.6 ± 2.3	4.2 ± 1.9	$t = 3.93; p = 0.0003$
Daily "off" time	3.9 ± 4.3	3.3 ± 3.9	$t = 0.47; p = 0.63$

MMSE = Mini-Mental State Examination; UPDRS = Unified Parkinson's Disease Rating Scale; PD = Parkinson disease.

Table 3 Mean ± SD cortical and thalamic AChE hydrolysis rates (k_3; min^{-1}) and striatal VMAT2 BP_{ND} activity in the PD fallers, PD nonfallers, and control subjects

	PD fallers (n = 17)*	PD nonfallers* (n = 27)	Control subjects* (n = 15)	Age effect	Group effect	Overall model
Cortical AChE k	0.0264 ± 0.0029 A	0.0281 ± 0.0030 B	0.0301 ± 0.0032 C	$F = 3.84, p = 0.055$	$F = 5.77, p = 0.005$	$F = 7.22, p = 0.0004$
Thalamic AChE k_3	0.0572 ± 0.0057 A	0.0617 ± 0.0074 B	0.0648 ± 0.0040 B	$F = 0.18, p = 0.68$	$F = 5.31, p = 0.008$	$F = 4.36, p = 0.008$
Putamen DTBZ BP_{ND}	0.69 ± 0.12 A	0.72 ± 0.21 A	1.84 ± 0.29 B	$F = 0.4, p = 0.52$	$F = 150.87, p < 0.0001$	$F = 106.55, p < 0.0001$
Caudate nucleus DTBZ BP_{ND}	0.91 ± 0.18 A	0.91 ± 0.27 A	1.29 ± 0.19 B	$F = 4.73, p = 0.034$	$F = 15.53, p < 0.0001$	$F = 14.26, p < 0.0001$

Analysis of covariance F values (with levels of significance) are listed for the age covariate and overall group effect with Duncan' Multiple Range post hoc testing between subgroups: subgroup means with the same letter are not significantly different. The group means are adjusted for the age covariate.
*The group means are age-adjusted.
AChE = acetylcholinesterase; PD = Parkinson disease.

tients with PD compared to the control subjects. However, Duncan post hoc analysis did not demonstrate significant differences between PD fallers and PD nonfallers in either putamen or caudate nucleus DTBZ binding (table 3).

Age-adjusted ANCOVA of the cortical AChE hydrolysis rates demonstrated significant differences between all groups, with lowest rates seen in the PD fallers group (−12.3%) followed by the PD nonfallers (−6.6%), both significantly different from control subjects. Group differences between the PD fallers and PD nonfallers were also significant. ANCOVA of the thalamic AChE hydrolysis rates did demonstrate significantly lower rates in PD fallers (−11.8%) compared to both PD nonfallers and control subjects. However, there was no significant difference between the PD nonfallers and control subjects (table 3).

A post hoc ANCOVA was performed to evaluate group differences in AChE rates while controlling for the effects of age and the degree of nigrostriatal dopaminergic denervation (table 4). The addition of striatal DTBZ binding as a covariate into the model did not change the significantly decreased thalamic AChE hydrolysis rates in the PD fallers compared to the PD nonfallers and control subjects. However, the differences in cortical AChE activity between the PD fallers and control subjects trended but failed to achieve statistical significance (table 4).

DISCUSSION Our findings indicate that unlike nigrostriatal dopaminergic denervation, thalamic cholinergic denervation is associated with falls in PD. Although PD fallers had significantly lower cortical and thalamic AChE activity compared to nonfallers and control subjects, thalamic AChE enzyme hydrolysis rates remained significantly decreased even after adjusting for the degree of nigrostriatal dopaminergic denervation. Thalamic AChE activity derives mainly from terminals of brainstem PPN neurons that play a central role in the generation of movement.[7] The PPN is located in the dorsolateral part of the pontomesencephalic tegmentum,[21] and is composed of 2 groups of neurons: a pars compacta predominantly containing cholinergic projection neurons and a pars dissipata containing glutamatergic projections. The PPN sends profuse ascending cholinergic efferent fibers to several thalamic nuclei, particularly the intralaminar complex that is also reciprocally connected with the basal ganglia.[7] PPN efferents appear to be highly collateralized and loss of thalamic AChE is likely to reflect PPN neuron dysfunction or degeneration. Our results are consistent with a key role for the PPN in the maintenance of balance in humans and with PPN dysfunction/degeneration as a cause of impaired postural control and gait in PD.

A previous cholinergic neuroimaging study found a nonsignificant reduction of thalamic AChE activity of about 13% in patients with PD compared to control subjects.[22] The same authors reported a greater loss of thalamic AChE activity (−38%) in patients with progressive supranuclear palsy (PSP). The much higher incidence of falls in PSP compared to PD may reflect the more prominent degree of thalamic cholinergic denervation and PPN pathology in PSP. The importance of thalamic cholinergic denervation in PSP is further emphasized by the relatively preserved cortical cholinergic innervation in this disorder compared to PD.[22] In PSP patients, experimental administration of the antimuscarinic drug scopolamine has been reported to worsen gait in a dose-dependent manner.[23] Although scopolamine worsened gait functions, it did not negatively affect UPDRS motor ratings of bradykinesia or rigidity. Although anticholinergic drugs have been used to treat tremor or rigidity in PD we are unaware of formal studies on the effects of these drugs on falls in PD. However, a recent study on antimuscarinic anticholinergic drug effects in non-PD elderly found evidence of significant slowing in both gait speed and simple response time that may contribute to an increased risk of falls.[24]

Table 4 Mean ± SD cortical and thalamic AChE hydrolysis rates (k_3; min^{-1}) activity in the PD fallers, PD nonfallers, and control subjects

	PD fallers (n = 17)*	PD nonfallers* (n = 27)	Control subjects* (n = 15)	Age effect	Striatal DTBZ effect	Group effect	Overall model
Cortical AChE k_3	0.0265 ± 0.0034 n/a	0.0279 ± 0.0035 n/a	0.0299 ± 0.0050 n/a	$F = 5.29, p = 0.025$	$F = 0.04, p = 0.85$	$F = 2.11, p = 0.13$	$F = 6.16, p = 0.0004$
Thalamic AChE k_3	0.0567 ± 0.0074 A	0.0609 ± 0.0076 B	0.0663 ± 0.0110 B	$F = 0.44, p = 0.51$	$F = 0.49, p = 0.48$	$F = 3.78, p = 0.029$	$F = 3.33, p = 0.017$

Analysis of covariance *F* values (with levels of significance) are listed for the age and striatal DTBZ binding covariates and overall group effect with Duncan Multiple Range post hoc testing between subgroups: subgroup means with the same letter are not significantly different.
*The group means are age-adjusted.
AChE = acetylcholinesterase; PD = Parkinson disease.

Our findings and prior work raise the question as to whether cholinergic therapy may have a place in the management of mobility problems in PD. Currently approved cholinesterase inhibitors have been mainly evaluated for cognitive or behavioral benefits in patients with dementia. It is uncertain whether the current generations of cholinesterase inhibitors have sufficient brain penetrance to produce meaningful clinical benefits. We showed previously that about 60% of patients with AD treated with donepezil (10 mg/day) had limited cerebral enzyme inhibition in vivo.[25] There is preliminary evidence that selective $\alpha4\beta2$ nicotinic cholinergic receptor drugs may have a beneficial effect on gait. A recent case series reported improved gait functions in patients with ataxia taking varenicline.[26] Varenicline is a selective partial agonist at the $\alpha4\beta2$ nicotinic cholinergic receptor that is approved by the Food and Drug Administration for smoking cessation. These preliminary clinical observations suggest that $\alpha4\beta2$ nicotinic cholinergic receptors may play a role in human mobility.

We previously determined in vivo cortical AChE activity with PET imaging in PD subjects with and without dementia. Reductions in cortical AChE levels were greater and more extensive in parkinsonian dementia than in PD without dementia.[27] Studies have also shown an association between the postural instability and gait difficulty motor phenotype in PD and increased risk of dementia.[28,29] These findings raise the question whether postural instability and gait difficulty and PD dementia share a common cholinergic mechanism contributing to these 2 clinical manifestations.

Gait is no longer considered as merely an automated motor activity and the multifaceted neuropsychological influences on walking are increasingly appreciated.[3,30] Unlike cortical AChE activity, we did not find a significant correlation between thalamic AChE levels and MMSE scores. Therefore, our findings cannot be exclusively explained by pure cortical or cognitive mechanisms. A previous study found a correlation between lower cortical AChE activity and higher total UPDRS scores in patients with PD.[22] These authors interpreted these findings that the ascending cholinergic system from the NBM to the cerebral cortex is impaired more severely as PD advances. We also found similar findings for cortical AChE activity. Although PD fallers had higher UPDRS motor scores, our findings of reduced thalamic cholinergic activity remained significant in this group while controlling for the degree of nigrostriatal dopaminergic denervation. Therefore, nigrostriatal dopaminergic denervation is insufficient to explain fall status in PD by itself. The pathophysiology of

falls in PD may reflect multifactorial mechanisms and may relate both to motor functions, such as postural imbalance and gait, and nonmotor functions. Such multifactorial mechanisms are expected to reflect complicated disease processes to be caused by multiple transmitter deficiencies. Although our data provide supportive evidence for a role of cholinergic hypofunction and fall risk in PD, cholinergic denervation does not occur in isolation, but is associated with other neurodegenerative processes in this disorder.

A limitation of our study is that categorization of groups into fallers and nonfallers glosses over the multidimensional nature of falls in PD. Motor fluctuations, for example, have been identified as a significant cause of falls. We did not find significant differences between fallers and nonfallers in average daily time spent in the motor "off" state. There are also other limitations of our study. The [^{11}C]PMP radioligand PET imaging technique cannot reliably assess striatal AChE hydrolysis assessed because high activity striatal AChE activity makes it flow dependent.[31] Effects of striatal cholinergic neurons on mobility control in PD cannot be excluded. Another limitation of the PET technique is that accurate assessment of small brainstem nuclei, such as the PPN, is technically challenging because of partial volume effects.

AUTHOR CONTRIBUTIONS

Statistical analysis was conducted by Dr. Martijn Müller and Dr. Nicolaas I. Bohnen.

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