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Research Article

Influence of Striatal Dopamine, Cerebral Small Vessel Disease, and Other Risk Factors on Age-Related Parkinsonian Motor Signs

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Abstract

Objective: Parkinsonian motor signs are common and disabling in older adults without Parkinson's disease (PD), but its risk factors are not completely understood. We assessed the influence of striatal dopamine levels, cerebral small vessel disease, and other factors on age-related parkinsonian motor signs in non-PD adults.

Methods: Striatal dopamine transporter (DAT) binding was quantified via [^{11}C]-CFT positron emission tomography in 87 neurologically intact adults (20–85 years, 57.47% female) with concurrent data on: Unified Parkinson's Disease Rating Scale motor (UPDRSm), white matter hyperintensities (WMH), and other risk factors (grip strength, vibratory sensitivity, cardio- and cerebro-vascular comorbidities). Sex-adjusted nonparametric models first estimated the associations of age, DAT, WMH, and other factors with UPDRSm; next, interactions of age by DAT, WMH, or other factors were tested. To quantify the influence of DAT, WMH, and other risk factors on the main association of age with UPDRSm, multivariable mediation models with bootstrapped confidence intervals (CI) were used.

Results: Older age, lower DAT, higher WMH, and worse risk factors significantly predicted worse UPDRSm (sex-adjusted $p < .04$ for all). DAT, but not WMH or other factors, positively and significantly interacted with age ($p = .02$). DAT significantly reduced the age-UPDRSm association by 30% (results of fully adjusted mediation model: indirect effect: 0.027; bootstrapped 95% CI: 0.0007, 0.074).

Conclusions: Striatal dopamine appears to influence to some extent the relationship between age and parkinsonian signs. However, much of the variance of parkinsonian signs appears unexplained. Longitudinal studies to elucidate the multifactorial causes of this common condition of older age are warranted.

Keywords: Parkinsonian, Dopamine, Motor control

Parkinsonian motor signs are common among older persons without Parkinson disease (PD) or other neurological diseases. These motor signs have high clinical relevance, compromising capacity for independent living and increasing risk of falls and disability (1). However, the causes of age-related parkinsonian signs are not completely understood, and there are currently no effective treatments available.

The role of lower nigrostriatal dopaminergic (DA) neurotransmission in the development of age-related parkinsonian signs is potentially very important, but it has only been sparsely examined in human studies of aging. Nigrostriatal DA neurotransmission is mechanistically linked to movement control through the regulation of sensorimotor, attentional, and motivation networks (2). Postmortem studies of non-PD older adults show nigrostriatal DA neuronal loss predicts parkinsonian signs (1,3). In vivo studies of nigrostriatal DA, as measured via Positron Emission Tomography (PET), show significant positive associations with walking speed and upper extremity motor coordination, but did not examine parkinsonian signs (see Seidler et al. for a review (4)). A genetic predisposition to higher DA

neurotransmission was also related to faster walking (5–8); however, these studies did not have direct measures of nigrostriatal DA.

For the most part, prior studies examined measures of striatal DA in very old adults with a very narrow age range and did not account for other potential risk factors. For example, cerebral small vessel disease is a well-known predictor of developing parkinsonian signs among older adults without PD (9–11). However, these studies did not examine in vivo DA neurotransmission; two studies had indirect measures of DA network function: nigral neural loss postmortem (9) and genetic polymorphism markers (12).

Locomotor factors outside the central nervous system, such as poor muscle strength and sensorimotor function, can also potentially influence onset and severity of parkinsonian signs. Other risk factors for parkinsonian signs include chronic cardio-metabolic conditions, especially hypertension and diabetes (1,12). However, these factors have been sparsely examined in conjunction with DA neurotransmission.

We propose to examine striatal DA levels, cerebral small vessel disease, and other factors as potential explanatory factors of the effects of chronological age on worse parkinsonian signs. If these factors explained the effects of chronological age on parkinsonian signs, they could become potential intervention targets to reduce these very common and disabling motor disturbances.

We report on these relations in a well-characterized cohort of non-PD adults with a wide age range, to assess the main association of chronological age with parkinsonian signs. We hypothesize the association of older age with worse parkinsonian signs varies depending on the levels of striatal DA transporters binding levels (a measure of in vivo DA signaling via PET imaging), white matter hyperintensities (a marker of cerebral small vessel disease), and levels of other risk factors (muscle strength vibratory sensitivity, vascular comorbidities). Additionally, we quantify the contribution of each of these candidate explanatory variables to explain the main effect of older chronological age on worse parkinsonian signs.

Methods

A total of 113 participants aged 20–85 years were recruited via advertisement to conduct a clinical fall assessment and PET imaging. Study details have been previously reported for a subsample of 50 of these participants, in relation to computerized measures of gait and balance (13,14). All participants underwent a medical and neurological examination consisting of visual acuity, UPDRS parkinsonian motor examination (15), measurement of orthostatic vital signs, weight, height, and lower-limb large-fiber sensory function.

Participants were excluded from the study for any of the following criteria: clinical evidence of impairments affecting balance or gait (ie, orthostatic hypotension, impaired vision, vertiginous disorder, myelopathy, myopathy, radicular, or cerebellar syndromes); abnormal neurological examination and DAT PET evidence of PD: (asymmetric) gradient of putaminal more than caudate nucleus dopaminergic denervation (16); history of joint prosthetic surgery; taking central nervous system suppressant medications (ie, benzodiazepines, barbiturates, or skeletal muscle relaxants); presence of dementia (Mini-Mental State Examination [MMSE] <24) (17); evidence of tumor, focal intracranial lesion, or significant leukoaraiosis (ie, stage >3 on the Brandt-Zawadzki scale (18)) as detected on brain magnetic resonance imaging (MRI); or evidence of large-vessel stroke as detected on medical history and neuroimaging. None of the subjects included in this study reported intake of neuroleptic drugs, dopamine agonists, or potent anticholinergic.

Standard Protocol Approvals, Registrations, and Patient Consents

All participants provided informed, written consent. This study was approved by the Institutional Review Boards of the VA Pittsburgh Healthcare System, and the University of Pittsburgh.

Analytic Sample

Of the 113 participants enrolled in the study, 111 had complete UPDRS data. Of those, 103 also had data on WMH and 88 had brain PET assessment for DAT binding; one participant had a DAT level greater than three standard deviations below the mean and was excluded as an extreme outlier. The remaining 87 participants comprised our analytic sample.

Dependent Variable

The modified UPDRSm was used to rate the presence of nonspecific parkinsonian motor impairments in older adults without PD (1). This version of the UPDRS has been modified specifically to make it applicable to persons without PD, and to be administered and scored by both physicians and nonphysician clinic staff (19). This score is based on the assessment of four cardinal domains: bradykinesia, rigidity, tremor, and axial motor signs (walking and balance); midline nonwalking motor items, including speech and facial expression were also assessed (20). UPDRSm scores range from 0 to 100 with higher scores indicating greater presence of motor impairments; the scores in our analytic sample ranged from 0 to 27. The UPDRSm has excellent test–retest reliability, with an intraclass correlation coefficient of 0.90 (21). Variables summarizing presence/absence of bradykinesia, rigidity, tremor and axial motor symptoms, as well as a composite score summing the total number of signs ≥1 were computed.

Independent Variables

The main independent variable is chronological age in years, self-reported at time of enrollment and served as our primary predictor of interest. Participant age ranged from 20 to 85 years in our sample. Candidate explanatory factors of the association between age and parkinsonian signs are listed below.

Striatal DAT binding level (DAT)

[^{11}C]-β-CFT (2-β-carbomethoxy-3β-(4-fluorophenyl) tropane) or [^{11}C]-WIN 35,428 is a specific radioligand for the DAT (22). As previously described (13), Dynamic PET scanning was performed for 90 minutes, following a bolus intravenous injection of 370 MBq of [^{11}C]- β-CFT. Sequential three-dimensional emission scans were obtained using an ECAT HR + tomograph (CTI PET Systems, Knoxville, TN), which acquires 63 transaxial slices (axial field-of-view 15.2 cm; slice thickness 2.4 mm with an in-plane resolution of 4.1 mm). A thermoplastic mask was made for each subject to minimize head movement. The scanner gantry was equipped with a Neuroinsert (CTI PET Systems) to reduce contribution of scattered photon events. PET emission data were corrected for attenuation, scatter, and radioactive decay.

Regional cerebral [^{11}C]-β-CFT binding potential (BP) was calculated using a two-parameter multilinear reference tissue model approach (MRTM2) (23). The cerebellum was selected as a reference region because it contains negligible levels of dopamine, providing an estimate of nonspecific binding and free tracer concentration. Regional measurements of DAT binding were calculated as a ratio of the amount of DA in each region compared to the cerebellum (see

reference (13) for details). Specifically, for this paper, DAT was of interest, and was calculated as the sum in the left and right caudate nucleus and putamen. We examined both the continuous version of this variable and a tertile cutoff version of this variable. Tertile cutoffs occurred at 2.63 and 3.27.

White matter hyperintensities (WMH)

A volumetric spoiled gradient recall (SPGR) MRI was collected for each participant using a Signa 1.5 Tesla scanner (GE Medical Systems, Milwaukee, WI) with a standard head coil. The coronal SPGR sequence (echo time = 5, repetition time = 25, Xip angle = 40°, number of excitations = 1, slice thickness = 1.5 mm, image matrix = 256 × 192, filed of view = 24 cm) was acquired to maximize contrast among gray matter, white matter, and cerebral spinal fluid and provide high-resolution delineation of cortical and subcortical structures. The MR data was cropped in preparation for alignment with the PET data using Analyze AVW software (BIR, Mayo Foundation, Rochester, MN). Registration of the MR and dynamic PET images was performed using a modification of the automated image registration algorithm of Woods et al. Striatal regions of interest (ROIs) were drawn on the MR to include the head of the caudate nucleus, putamen of each hemisphere, and the cerebellum. All MR-drawn ROIs were transferred to the PET data for regional sampling of radioactivity using in-house developed software (UPMC Roitool). Fast fluid-attenuated inversion recovery (FLAIR) (repetition time/echo time 9,002/56 msec effectively, inversion time 2,200 msec, number of excitations 1, slice thickness 5 mm) in axial sequences with a 24-cm field of view and a 192 × 256-pixel matrix were also obtained for assessment of WMH using a semiquantitative scale (24). This scale grades the total volume of periventricular and subcortical white matter signal abnormalities by comparing the findings on any particular scan with sets of complete scans that demonstrated successively increasing changes from absent (grade 0) or barely detectable (grade 1) to extensive and confluent (grade 8).

Other risk factors

Lower-limb large-fiber sensory function was assessed by using a 128 Hz tuning fork to measure the duration of perception of vibratory sensations in the right ankle. Grip strength was assessed on participants' dominant hand, using an isometric dynamometer (Jamar, Bolingbrook, IL), while sitting with the arm resting on a table and elbow at approximately a 90° angle, and was measured in kilograms. Participants self-reported a history of diabetes, any heart problems, hypertension, stroke, or transient ischemic attack. The number of comorbidities thus identified was computed.

Other Population Characteristics

Self-reported completed years of education, sex, and race were collected. Weight (in pounds) and height (in inches) were used to calculate body mass index (BMI; [weight in lbs × 0.45]/[height in inches × 0.025]^2). The MMSE, indicative of global cognitive function was administered; MMSE scores range from 0 to 30, with higher scores indicating better cognitive function (17). Presence of depressive symptoms was collected at clinical assessment by self-report and also using the Center for Epidemiological Studies Depression (CES-D) scale (25).

Statistical Analyses

Because age, WMH, and UPDRSm are non-normally distributed variables, nonparametric tests were used. Median and interquartile ranges were reported. All models were adjusted for sex.

To identify the candidate explanatory variables of the age-UPDRSm association, sex-adjusted spearman correlations were computed between age, DAT, WMH, and other factors with UPDRSm. Squared partial correlation coefficients provided estimates of the variance explained by that variable. Sex-adjusted correlations with UPDRSm were also computed for other population characteristics to identify additional measures that could potentially influence UPDRSm; a Sidak correction factor with an adjusted p value = .0046 ($\alpha = 0.05$, 11 comparisons) was used to correct for type I error for these additional analyses. Sensitivity analyses tested the associations with individual UPDRS signs.

To identify the explanatory variables with a statistically significant influence on the age-UPDRSm association, age- and sex- adjusted negative binomial regression models included DAT, WMH, or other risk factors (grip strength, vibratory sensitivity, comorbidities) each entering a separate model, without and with an interaction of Age × Candidate explanatory factor.

To further illustrate how the age-UPDRSm association varied by levels of the candidate explanatory factor(s) identified in the above steps, sex-adjusted negative binomial models were repeated stratified by presence/absence of that factor; tertiles were used for DAT. A contrast statement tested for a linear trend association of the main independent variable with UPDRSm across levels of each candidate explanatory factor.

To estimate the influence of the candidate explanatory factor(s) on the age-UPDRSm associations identified in the above steps, we examined each explanatory variable in fully-adjusted mediation models with bootstrapped 95% confidence intervals (CI). These models tested the significance of the indirect effect of age (main independent variable) on UPDRSm through each candidate explanatory factor; the effect size of the attenuation was computed as the ratio of indirect to total effect multiplied by 100, and reported as the percent mediation effect.

For all models, fit was assessed with the deviance (value/degrees of freedom) value, and it was consistently between 1 and 1.5, indicating good model fit. Analyses were performed with SAS version 9.4 and IBM SPSS Statistics version 25.

Results

Of 87 participants, about half were female, and over two thirds were white; median age was 62 years. As observed in other studies of non-PD adults, UPDRSm scores ranged between 0 and 25, with most participants having values between 1 and 6 (interquartile range); signs primarily included gait and postural modest impairments; about 50% of the sample had 2 or more parkinsonian signs (Table 1). The distribution of parkinsonian signs in this sample was not driven by a particular subcategory; among those with 1+ axial (gait/balance) impairments, all except for two persons had associated rating for tremors, bradykinesia, or rigidity. Of note, abnormal facial or speech items were not found in this non-PD population. Cognitive function was high and the prevalence of comorbid conditions was low, reflective of this generally healthy, community-dwelling sample. As expected, older age significantly correlated with lower DAT levels and presence of other risk factors (sex-adjusted $p \leq .001$ for all); higher DAT levels were significantly associated with less WMH ($p < .0001$) but not with the other factors (Supplementary Table 1).

Sex-adjusted correlations with UPDRSm were statistically significant and in the expected direction for age, DAT, WMH, strength, vibratory sensitivity, and comorbid conditions (Table 2). Sex-adjusted effect sizes were larger for age (24%), muscle strength, and vibratory

sensitivity (15%) as compared to DAT or WMH (8%–9%). Among other population characteristics, only MMSE was associated with UPDRSm (Table 2), but the association did not survive adjustment for multiple testing (Sidak corrected $p = .0046$).

In sex-adjusted binomial models, the association of age with UPDRSm was robust to adjustment for each candidate explanatory variable (Table 3). Higher DAT, but not WMH or other factors, remained significantly associated with better UPDRSm independent of age or sex (Table 3). Higher DAT remained associated with better UPDRSm score also independently of WMH and other factors ($p \leq .01$, Supplementary Table 2). When associations with the four UPDRSm signs were examined, we found both age and DAT had stronger associations with axial signs (rho [p value]: –.43 [<.001] and –.44 [<.001]) and bradykinesia (.40[<.0001] and –.22 [$p = .05$]), as compared to tremor, or rigidity ($p \geq .2$ for all).

DAT positively interacted with age on UPDRSm (risk ratio = 0.98, 95% CI: 0.96, 0.99, $\chi^2 = 5.37$, $p = .02$), while WMH ($p = .35$), grip strength ($p = .17$), vibratory sensitivity ($p = .86$), or comorbidities ($p = .36$) did not. Sex-adjusted negative binomial models stratified by DAT tertile (Table 4) revealed the association between age and UPDRSm was stronger (larger parameter estimates, smaller p) in the lowest and middle tertile of DAT, as compared to the highest tertile of DAT (Table 4); the test of trend across tertiles was statistically significant ($p = .0002$).

In mediation models adjusted for sex, WMH, strength, vibration, and comorbid conditions, there was a significant indirect effect of age on UPDRSm through DAT (indirect effect: 0.027, bootstrapped 95% CI: 0.0007, 0.074). DAT accounted for 30.4% of the total effect of age on UPDRSm (effect size = 0.304). The indirect effect of age on UPDRSm was not statistically significant for WMH or any other factors ($p > .1$ for all).

Table 1. Participants' Characteristics ($n = 87$)

Characteristics	*N* (%) or Median (IQR)
Age, years	66 (IQR: 52–78.5)
Sex, female	50 (57.47%)
White matter hyperintensities (0–9 points)	1.50 (IQR: 0.50–5.00)
Hand grip strength[b], kg	25.50 (IQR: 21–36)
Ankle vibration sensitivity[b], seconds	10 (IQR: 7–13)
Number of comorbidities[c]	
0	45 (52.33%)
1	27 (31.40%)
2	10 (11.63%)
3	3 (3.49%)
4	1 (1.16%)
5	0 (0.00%)
DAT	2.92 (IQR: 2.48–3.42)
UPDRSm	2 (IQR: 1.0–6.0)
UPDRS Axial	21 (25.30%)
UPDRS Bradykinesia	49 (56.32%)
UPDRS Tremor	37 (44.60%)
UPDRS Rigidity	21 (25.30%)
Two or more Parkinsonian signs	46 (52.87%)
Race, white	75 (86.21%)
Education (years)	14 (IQR: 13–16)
Body mass index (kg/m^2)	27.02 (IQR: 23.42–30.16)
MMSE score, points	30 (IQR: 29–30)
Depression[a]	13 (14.94%)

Note: DAT = Dopamine transporter binding levels; IQR = Interquartile range; MMSE = Mini-Mental State Examination; UPDRS-m = Unified Parkinsonian Disease Rating Scale, motor.

[a]By self-report; [b]right side. [c]By self-report, comorbidities include: TIA, stroke, diabetes, hypertension, heart problems.

Table 2. Sex-Adjusted Spearman Correlation Coefficients and p Values Between Population Characteristics and UPDRSm

	Spearman Correlation Coefficients (p value)
Age	0.490 ($p < .0001$)
DAT	–0.298 ($p = .006$)
WMH	0.277 ($p = .010$)
Hand grip strength, kg	–0.390 ($p < .0001$)
Ankle vibration sensitivity, seconds	–0.399 ($p < .0001$)
Comorbidities	0.228 ($p = .036$)
Race, white	–0.020 (0.85)
Education (years)	–0.180 (0.10)
Body mass index (kg/m^2)	–0.110 (0.33)
MMSE score, points	–0.250 (0.025)
Depression[a]	0.201 (0.080)

Note: DAT = Dopamine transporter binding levels; MMSE = Mini-Mental State Examination; UPDRS-m = Unified Parkinsonian Disease Rating Scale, motor; WMH = White matter hyperintensities.

[a]By self-report.

Discussion

In this sample of neurologically intact adults aged 20–85 years, the associations of older age with worse UPDRSm score was robust to adjustment for several risk factors. DAT was the only factor that significantly influenced and in fact reduced the association of age with parkinsonian signs, albeit only up to 30%. Longitudinal studies are needed to better understand the relationships between age, DAT, vascular, and locomotor risk factors and the development of age-related parkinsonian signs.

Among the risk factors hereby examined, DAT was the only factor predicting UPDRSm independent of sex and age, with

Table 3. Results of Sex-Adjusted Negative Binomial Regression Models Estimating the Associations of Age with UPDRSm, Further Adjusted for Candidate Explanatory Factors: DAT, WMH, Strength, Vibratory Sensitivity, or Comorbidities

		Risk Ratio (95% confidence interval), χ^2, p value
Model 1	Age, years	1.04 (1.02, 1.05), 19.53, $p < .0001$
	DAT	0.61 (0.45, 0.82), 10.14, $p = .002$
Model 2	Age	1.04 (1.03, 1.06), 23.70, $p < .0001$
	WMH (0–9 points)	0.97 (0.87, 1.07), 0.47, $p = .50$
Model 3	Age	1.03 (1.02, 1.05), 13.73, $p = .0002$
	Hand grip strength, kg	0.98 (0.95, 1.01), 1.83, $p = .18$
Model 4	Age	1.03 (1.02, 1.05), 15.72, $p < .0001$
	Ankle vibration sensitivity, seconds	0.95 (0.90, 1.00), 3.53, $p = .06$
Model 5	Age	1.04 (1.03, 1.06), 27.72, $p < .0001$
	Comorbidities, number	0.99 (0.76, 1.30), 0.01, $p = .95$

Note: Risk ratio (95% CI), chi-square (χ^2), and p values are from separate models.

DAT = Dopamine transporter binding levels; UPDRS-m = Unified Parkinsonian Disease Rating Scale, motor; WMH = White matter hyperintensities.

Table 4. Results of Sex-Adjusted Negative Binomial Regression Models Estimating the Association of Age with UPDRS-m, Stratified by Tertile of DAT

	Tertile of DAT			
	1 ≤2.65 *n* = 28	2 2.66–3.27 *n* = 29	3 ≥3.28 *n* = 30	
	Risk ratio (95% confidence interval), χ^2, *p* value			Test for Trend Across Tertile of DAT χ^2 (*p* value)
Age, years	1.07 (1.03, 1.11), 15.50, $p < .0001$	1.05 (1.02, 1.07), 10.50, $p = .001$	1.02 (0.99, 1.04), 2.52, $p = .11$	14.33 (.0002)

Note: Risk ratio (95% CI), chi-square (χ^2), and *p* values are reported for each model (one for each tertile) and for the overall test of trend.

DAT = Dopamine transporter binding levels; UPDRS-m = Unified Parkinsonian Disease Rating Scale, motor.

associations stronger for axial (gait and balance) and bradykinesia signs as compared to other cardinal motor symptoms. We have previously reported on the significant association between age, striatal DAT and walking speed and balance in a subset of this cohort (13,14), but did not examine their combined effect on parkinsonian signs, nor did we account for WMH or other risk factors. In a separate study of very old adults (9), we have reported that the association of WMH with parkinsonian signs and gait speed was attenuated for those with a genotype related to higher synaptic DA availability. Taken together, our current and prior findings (9,13,14) suggest an important role of DA neurotransmission on parkinsonian signs, and in particular for walking and balance impairments, in the absence of PD. The nigrostriatal DA system regulates sensorimotor control and execution of overlearned motor skills, via engagement of sensorimotor cortex-striatal networks. In the absence of disease, higher nigrostriatal DA levels have a net effect of facilitating striatopallidum-thalamic excitatory outputs to primary sensorimotor regions, promoting ease and fluidity of movements, and initiation and execution of coordinated sequences of musculoskeletal activations (2). While loss of DA disrupts mobility control, with PD being an extreme example, its preservation may be critical to maintain physical function in older age.

The associations of striatal DAT, WMH, and comorbidities with UPDRSm were comparable in magnitude, suggesting that each may contribute similarly to this condition; however, they were weaker compared to the association of age with UPDRSm, as indicated by the size of the Spearman's correlation coefficients in Table 2. Given that the effect size of DAT on UPDRSm was smaller than that of age, the clinical relevance of our findings should be considered very cautiously. The interaction of age with DAT can also be interpreted in two ways. Our study raises interesting questions; for example, whether older adults with preserved DA neurotransmission would be protected against the effect of older age on parkinsonian signs. The DA system is an attractive target of interventions aimed at promoting physical function in the absence of PD. The DA system can respond to pharmacological, behavioral and/or physical activity interventions. However, most evidence to date is for cognition or mood (4,26–28). Future longitudinal studies should assess whether preserving DA neurotransmission late in life would protect from developing age-related parkinsonian signs in general, and walking and postural problems in particular.

We found that DAT remained associated with UPDRSm independently of age and WMH, but the opposite was not true. The association of WMH with UPDRSm was no longer significant after adjustment for age. This is in apparent contrast with previous reports of a predominantly vascular contribution toward parkinsonian signs (1,9) as compared to measures of DA signaling. A direct comparison between studies is challenging, due to differences both in the samples' age and the methodologies used to measure DA neurotransmission. Our study captured a wider range of nigral functionality across a wide age range, as compared to the binary measures of severe neuronal loss (1) or genetic (thus indirect) (9) measures of DA signaling in adults aged 70 years and older. It is also possible that our crude measures of WMH did not provide enough range of values to detect and association.

This study had several limitations of note. Our study focused on measures of nigrostriatal DA, and did not examine associative and reward networks, which are likely neural contributors to walking; however, their role in controlling parkinsonian signs is not yet as well established. We did not examine dopaminergic neurotransmission outside of the striatum; however, the striatum is the primary regions of DAT uptake. Second, we had a relatively small number of participants overall and in each tertile of DAT, which could limit power and precision of our estimates. Despite these limitations, we were able to detect statistically significant differences and mediation effects. Lastly, we did not have follow-up data, hence we could not ascertain incident PD. However, PD was excluded based on neurological examination and DAT scans inspection, and incident PD is rare in this age group. We (16) have previously shown age-related parkinsonian signs have a pattern of nigral abnormalities that is distinct from PD: bilateral and symmetric striatal loss without evidence of a predominant or asymmetric putaminal denervation gradient indicative of PD. These findings indicate that age-related DA loss is a distinct entity from prodromal or early PD.

In sum, our results indicate the DA system influences the detrimental effects of age on parkinsonian signs. The age-related associations with parkinsonian signs were not attenuated by WMH or other factors, indicating a specific role of striatal DA. Our results need to be replicated, and longitudinal data are needed. Interventions that target the dopaminergic system should be explored due to its potential role in enhancing motor and functional outcomes in older adults.

Supplementary Material

Supplementary data is available at *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences* online.

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Conflict of Interest

N.I.B. has received research support from the Michael J. Fox Foundation, Chase Pharmaceuticals, and Axovant Sciences. No other authors have any disclosures to make and have no relevant conflicts of interest.

Author Contributions

C.R.: Design and conceptualized study; drafted the manuscript for intellectual content; supervised and reviewed final analyses. A.L.M.: Analyzed the data; interpreted the data. A.L.R.: Interpreted the data; revised the manuscript for intellectual content. S.S.: Interpreted the data; revised the manuscript for intellectual content. N.I.B.: Study design and conceptualization; Major role in the acquisition of data.

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