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CLINICAL INVESTIGATIVE STUDY

Cortico-striatal functional connectivity and cerebral small vessel disease: Contribution to mild Parkinsonian signs

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ABSTRACT

Background and Purpose: Mild Parkinsonian signs (MPS) are common in older adults.
We hypothesized that MPS are associated with lower functional connectivity (FC) in
dopamine-dependent cortico-striatal networks, and these associations vary with white
matter hyperintensity (WMH), a risk factor for MPS.

Methods: We examined resting-state functional MRI in 266 participants (mean age 83;
57% female; 41% African American) with data on MPS (Unified Parkinson's Disease
Rating Scale), demographics, cognition, muscle-skeletal, and cardiometabolic health. FC
between cortex and striatum was examined separately for sensorimotor, executive, and
limbic functional subregions. Logistic regression tested the association of FC in each net-
work with MPS, adjusted for covariates. Interactions of FC by WMH were tested; and
analyses were repeated stratified by WMH above/below the median.

Results: Compared to those without MPS, those with MPS had lower cortico-striatal FC in
the left executive network (adjusted odds ratio [95% confidence interval], p-value: 0.188
[0.043, 0.824], .027). The interaction with WMH was $p = .064$; left executive FC was
inversely associated with MPS for high WMH (0.077 [0.010, 0.599], .014) but not low
WMH participants (1.245 [0.128, 12.132], .850).

Conclusions: MPS appear related to lower executive network FC, robust to adjustment
for other risk factors, and stronger for those with higher burden of WMH. Future longi-
tudinal studies should examine the interplay between cerebral small vessel disease and
connectivity influencing MPS.

KEYWORDS
cortico-striatal network, functional connectivity, mild Parkinsonian signs, white matter hyperinten-
sities

INTRODUCTION

Mild Parkinsonian signs (MPS) in older adults have become the focus of
intense study to determine whether they represent prodromal signs of
other neurological diseases, including Parkinson's disease (PD), or non-
specific consequences of aging. If MPS were a prodromal stage of neu-
rological diseases, it could have important implications for early identi-
fication of older adults at greater risk for neurodegenerative diseases.

However, few studies have characterized the neural substrates that
distinguish individuals with compared to those without MPS in the
absence of prototypical PD. Prior neuroimaging studies have been
limited to overt, somewhat advanced stages of structural abnormali-
ties, including regional brain volumes[1] and white matter hyperintensity
(WMH).[2]

Integrity of the cortico-striatal dopaminergic network appears rel-
evant as we recently showed the integrity of nigrostriatal nerve

terminals was lower in older adults with MPS compared to those without in the absence of PD-specific PET binding changes and PD diagnosis.[3] Postmortem studies of non-PD older adults with MPS suggest nigral cell losses, although mixed pathological findings were seen, including beta-amyloid deposition and cerebral small vessel disease (cSVD).[4,5] Neuroimaging markers of structural connectivity indicate an inverse relationship, with lower connectivity observed for those with MPS.[6–8] Although one of these studies suggested that periventricular connectivity was most affected in the frontal lobe, other studies did not provide information on the spatial distribution of connectivity abnormalities related with MPS.[8] Two neuroimaging studies of gray matter volumes found no associations between striatum and MPS,[9,10] perhaps because volumetric measures only capture more advanced changes compared to functional markers.

Resting-state (RS) connectivity reflects the earliest detectable changes in brain parenchyma, prior to radiologically overt structural abnormalities.[11,12] A recent study of RS and MPS found reduced intrastriatal connectivity but no significant association between cortico-striatal connectivity and MPS.[13] Impaired RS is considered an early sign of neuropathological changes in several neurodegenerative conditions, including PD,[14–16] Alzheimer's disease,[17–19] Huntington's disease,[20–22] amyotrophic lateral sclerosis,[23] and Lewy body dementia.[24] Thus, RS alterations may have utility as early markers of these conditions.

Unlike other radiologically overt signs, lower RS is reversible and may respond to exercise interventions.[25,26] Recent multimodal imaging combining RS functional (f) MRI and ^{18}F-DOPA-PET reveals that lower dopaminergic signaling in the striatum correlates with lower cortico-striatal functional connectivity (FC), suggesting that FC may respond to L-DOPA administration.[27] This is supported by pharmacological studies in PD patients, whereby decreased cortico-striatal connectivity is partially restored after receiving L-DOPA.[28–31] This suggests that strategies improving RS connectivity, like exercise and pharmacological interventions, may translate to improved motor performance.

Here, we characterized the RS connectivity between sensorimotor, executive, and limbic subregions of striatum and corresponding regions of cortex. We focus on these networks because they regulate sensorimotor, executive control, and mood/motivation domains, which are critical for mobility control.[32] We hypothesized that MPS would be associated with lower connectivity in all networks, after controlling for locomotor risk factors and WMH burden, as WMH is a predictor of MPS[2,3] and related to lower connectivity.[33]

METHODS

Participants

Participants of the Health Aging and Body Composition Study were recruited from Pittsburgh, Pennsylvania and Memphis, Tennessee in 1997-1998 and were ages 70-79 when enrolled. Of participants who returned for an in-person visit in Pittsburgh in 2006-2008 (ages 79-90), 325 were recruited for an MRI study if they met inclusion criteria: could walk without assistive devices, no hospitalization for major clinic events (physical or psychiatric) in the previous 3 months, no metal present in body, no claustrophobia, less than 250 lbs, and had mobility measured at their last visit.[34] Of the 325 participants, 314 completed 3T MRI; of these, 42 were excluded due to incomplete scan data and 6 were excluded due to incomplete Unified Parkinson's Disease Rating Scale data, yielding $n = 266$.

Protocols were approved by the University of Pittsburgh institutional review board. Participants provided informed consent at each visit.

Outcome

MPS were determined via the Unified Parkinson's Disease Rating Scale Part III motor examination, which included subdomains of bradykinesia, tremor, rigidity, balance, and gait disturbances. MPS was defined as either (1) two or more items with a score of one, indicating mild symptoms; (2) one item with a score of at least two, indicating moderate to severe symptoms; or (3) rest tremor score of one without meeting diagnostic criteria for PD.[2] Bradykinesia was considered present if slowing or hesitation was detected in either right or left extremities during finger tapping, fist clench, pronation-supination, toe, or heel tapping. Gait and postural disturbances were considered present if an abnormality was detected for any of the following: rising from a chair with arms folded across the chest, postural stability test, posture, or gait. Tremor of the upper extremities was considered present if either facial or hand tremor was observed at rest or during an action.[10] Few participants (12%) had tremor in this cohort; hence, this sign was not included in the analyses.[10] Six participants met clinical diagnostic criteria for PD (asymmetry in distal limb bradykinesias associated with other cardinal motor domain features), were taking PD medications, or had an existing PD diagnosis. Sensitivity analyses are repeated excluding these six individuals. Subscores of bradykinesia and gait disturbance were also evaluated.[9,10]

Predictors

Selected demographic and physiological covariates are known to correlate with impairments of balance, gait, and other movement outcomes.[35] To control for these factors when modeling the relationship between MPS and cortico-striatal connectivity, we included the variables described below. We also included cognitive and psychological measures that are sometimes correlated with MPS and health status.

Age, gender, race, and education (no high school degree or General Educational Diploma, high school completion, and post-secondary completion) were collected via self-report at study entry. Measures associated with mobility were collected at the time of scan, including: body mass index (kg/m^2), quadriceps strength, via Kin-Com isokinetic
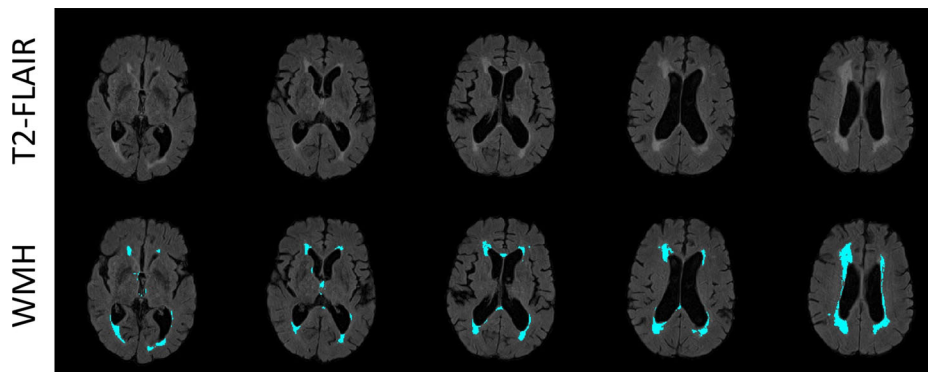
FIGURE 1 White matter hyperintensity segmentation by fuzzy connectedness algorithm. The top row shows five axial slices of T2-FLAIR data from one participant with white matter hyperintensities (WMHs). The second row shows the same five axial slices overlaid by the WMH segmentation (cyan) obtained from the fuzzy connectedness algorithm of Wu et al[38]

dynamometer, musculoskeletal pain (self-report for presence/absence of any pain in any knee or hip or in the back), vision (six-point self-report scale of 1-excellent to 6-completely blind), and proprioception was measured by vibratory stimulus on the toe during standard neurological examination.

Cardiovascular and metabolic burden was evaluated as follows. Diabetic status was determined by self-report of diabetes, medication use, fasting plasma glucose >126 mg/dl, or 2-hour post-challenge plasma glucose >200 mg/dl. Self-report and/or medication records were used to assess cerebrovascular diseases (including stroke and transient ischemic attack), congestive heart failure, or chronic obstructive pulmonary disease. Peripheral artery disease was based on ankle-brachial index below 0.9. A participant was considered hypertensive if they exhibited systolic blood pressure >140 mmHg or diastolic pressure >90 mmHg.

Cognitive and psychological measures included the Modified Mini-Mental State Examination (3MSE),[36] the Center for Epidemiologic Studies Depression Scale Revised 10 (CESD-10),[37] and digit symbol substitution test (DSST).

MRI acquisition

Scanning was conducted at the University of Pittsburgh, on a 3T Siemens Magnetom TIM Trio MRI scanner with a Siemens 12-channel head coil. Prior to scanning, participants were instructed to remain as still as possible; padding for head and neck reduced head motion. The following sequences were acquired: an axial, whole-brain T1-weighted structural Magnetization Prepared Rapid Acquisition Gradient Echo (MPRAGE) (Repetition Time [TR] = 2300 ms, Echo Time [TE] = 3.43 ms, Flip Angle [FA] = 9^0, Field of View [FOV] = 224×256, 1 mm^3 isotropic resolution, no acceleration); an axial, whole-brain T2-weighted Fluid-attenuated inversion recovery (FLAIR) volume (TR = 9160 ms, TE = 90 ms, FA = 150^0, FOV = 212×156, 1×1×3 mm resolution, 3 mm gap between slices, no acceleration); and a 5-minute echo-planar imaging sequence (TR = 2000 ms, TE = 34 ms, FA = 90^0, FOV = 128×128, 2×2×3 mm resolution) to assess RS blood-oxygen level-dependent

response. During scanning, there was no fixation cross or other presented stimuli.

Image processing

Image processing was conducted using Matlab R2104a (MathWorks, Inc., Natick, MA), SPM12 (Wellcome Center for Human Neuroimaging, London, UK), and FSL6.00 (Functional Magnetic Resonance Imaging of the Brain Analysis Group, Oxford, UK). We used SPM for each participant: the FLAIR volume was coregistered to the MPRAGE (12-DOF search, normalized mutual information cost function), and then MPRAGE and FLAIR volumes were segmented into air, soft tissue, skull, cerebrospinal fluid (CSF), gray and white matter (GM, WM). Default segmentation parameters were used except the number of WM Gaussians was set to two to avoid excluding WMH voxels. Brain masks were defined as the union of the CSF, WM, and GM segmentation maps after thresholding at 0.1 probability, followed by image filling and closing using Matlab. MPRAGE volumes were warped into Montreal Neurological Institute space using FMRIB's Nonlinear Image Registration Tool (FNIRT) in FSL.

WMHs were identified from FLAIR volumes using a procedure that identifies seeds above a specified standard deviation of intensity and uses fuzzy connectedness to grow the seeds.[38] Following segmentation, a trained analyst confirmed WMH maps. Figure 1 illustrates the fuzzy connectedness algorithm applied to one participant's T2-FLAIR data. WMH volume (normalized to total brain volume) was grouped into high and low based on the median split.

Slice-timing and motion correction for RS data was performed in SPM (6-DOF search, mutual information cost function) and images were smoothed with an 8 mm full width at half maximum (FWHM) kernel. Skull-stripping was conducted using FSL's Brain Extraction Tool. Skull-stripped RS volumes were aligned to anatomical volumes using the FMRIB's Linear Image Registration Tool with boundary-based registration.

Cortical regions-of-interest (ROIs) were obtained from the Multimodal Parcellation atlas,[39] using a volumetric projection of the

surface parcellation (https://identifiers.org/neurovault.image:24150), and then categorized as sensorimotor, executive control function (ECF), and limbic regions. Sensorimotor ROIs were Brodmann areas 1, 2, 3a, 3b, 4, 6v, frontal eye fields, premotor eye fields, and supplementary and cingulate eye fields. ECF ROIs were Brodmann areas 46, 9-46d, a9-46v, and p9-46v. Limbic ROIs were Brodmann areas a24 and s32, orbital frontal cortex (OFC), and posterior OFC. Striatal ROIs were obtained from the Oxford-GSK-Imanova Striatal Connectivity atlas,[40] which divides striatum into sensorimotor, executive, and limbic regions. Because striatal outputs feed back to cortex via thalamocortical fibers, we consider the thalamus, obtained from the CIC atlas.[41] We consider left and right hemispheres separately.

Prior to connectivity analysis, all ROIs were warped into participant native space using inverse deformation fields from FNIRT. RS time courses were extracted from all ROI voxels, with first five TRs discarded to account for drift. To address scanner, motion, and physiological noise, we regressed out motion parameters, mean WM signal, mean CSF signal, the first five eigenvariates (accounting for approximately 90% of the variance) of WM signal after subtracting the mean, and the first five eigenvariates of CSF signal after subtracting the mean.

The relationship between connectivity and MPS was evaluated two ways. At a super-regional level, we examined whole-network cortico-striatal connectivity and tested its association with MPS status. This allowed us to look for network-wide relationships with MPS. At the ROI level, we computed the correlation between each cortical ROI with the corresponding striatal ROI and tested whether these correlations were stronger for those without compared to those with MPS status. This provided a better spatial resolution, at the level of individual ROIs.

In the super-regional approach, mean signal from each cortical network was correlated with mean signal from the corresponding striatal region. For example, to compute left sensorimotor cortico-striatal correlation, mean signal from all left hemisphere sensorimotor cortical voxels was correlated with mean signal of left hemisphere sensorimotor striatal voxels. This Pearson correlation was Fisher Z-transformed for subsequent statistical analysis. To compute striatal-thalamic connectivity, we obtained the Pearson correlations for sensorimotor striatum and thalamus, executive striatum and thalamus, and limbic striatum and thalamus; these values were Fisher Z-transformed and averaged to give mean striatal-thalamic FC.

In the ROI-by-ROI analysis, we evaluated the pairwise Pearson correlations between cortical ROIs, and corresponding striatal ROIs. For example, to compute the connectivity between right Brodmann area 1 and right sensorimotor striatum, we took the mean signal of all voxels in right Brodmann area 1 and correlated it with the mean signal of all voxel in right sensorimotor striatum. These correlations were Fisher Z-transformed for subsequent statistical analysis.

Statistical analysis

Bivariate associations of participants' characteristics with MPS, bradykinesia, and gait disturbances were examined using independent t-tests for continuous variables or χ^2 t-tests for categorical variables.

Logistic regression models examined whether RS connectivity of each network predicted MPS, bradykinesia, or gait disturbances. Models were built in three steps to address confounding and prevent overfitting: (1) adjusted for age; (2) from step 1, sex, race, musculoskeletal pain, quadriceps strength, congestive heart failure, diabetes, peripheral arterial disease, pulmonary diseases/conditions, and cardiovascular diseases were entered with forward stepwise conditional approach; and (3) from step 2, further adjusted for WMH burden. Subsequently, the interaction of FC by WMH was tested. Analyses were repeated stratified by WMH. Logistic regression models also examined whether pairwise RS connectivity for each cortico-striatal connection predicted MPS after adjusting for age. Analyses were completed in SAS9.4 (SAS Institute, Cary, NC) with two-tailed significance set at $p < .05$.

As this is the first study examining these associations, and given that our analyses relied on ROIs identified a priori (via literature review to assess biological plausibility), we were more concerned with erroneously ruling out potential findings than with false positives.[42] Accordingly, we did not use multiple comparison correction.

RESULTS

Participant age ranged from 79 to 90 years (mean 83 years) at the time of MRI. Participants were 41.3% Black (the remainder of this sample were White). 84.9% of participants had completed at least high school education. Of the $n = 266$ participants in the sample, $n = 117$ were classified as having MPS. Compared to those without MPS, those with MPS (Table 1) walked more slowly, had lower DSST score, were more likely to have joint pain, and had higher WMH volume (all $p < .05$). Associations were similar for subscores of bradykinesia and gait disturbances; those with bradykinesia also had significantly lower 3MSE scores (age-adjusted $p = .039$) and significantly lower CES-D (age-adjusted $p = .0032$). For full summary, see Table 2.

Averaged across all participants, cortico-striatal FC varied by network, being highest for the limbic network and lowest for the sensorimotor network; trends were similar for both hemispheres and both MPS groups. WMH volume was inversely associated with RS connectivity in the cortico-striatal executive network (right: $r = -0.045$, $p = .0207$; left: $r = -0.046$, $p = .0323$); associations with the sensorimotor or limbic networks were not statistically significant ($p > .05$). Sensorimotor, ECF, and limbic networks showed high connectivity between regions within networks (Figure 2A, red, green, and blue lines). Substantial internetwork connections were present between ECF cortex and sensorimotor cortex (Figure 2A, black lines).

In our super-regional approach, MPS was associated with cortico-striatal RS connectivity in the executive network, but not sensorimotor or limbic networks. The MPS-related executive difference appeared more pronounced in the left (5%, $p = .022$) than the right hemisphere (3%, $p = .098$); associations with bradykinesia showed a similar pattern (left: 7%, $p = .003$; right: 3%, $p = .11$).

In our ROI-by-ROI analysis, MPS was significantly associated with cortico-striatal RS connectivity within ROIs the left executive network (Brodmann areas 46, $p = .034$ and 9-46d, $p = .030$) consistent with

TABLE 1 Demographics and health characteristics for cohort and stratified by presence/absence of any Parkinsonian sign, bradykinesia, and gait disturbances

		All cohort	Parkinsonian signs		Bradykinesia		Gait disturbances	
			Absent	Present	Absent	Present	Absent	Present
Number (%)		266	149 (56.02)	117 (43.98)	202 (75.94)	64 (24.06)	199 (74.81)	67 (25.19)
Demographic	Age, years	83.00 ± 2.79	82.59 ± 2.55	83.52 ± 3.00	82.79 ± 2.77	83.65 ± 2.78	82.65 ± 2.53	84.03 ± 3.27
	Women, N (%)	150 (56.82)	83 (55.70)	67 (58.26)	114 (56.44)	36 (58.06)	111 (55.78)	39 (60.00)
	Black, N (%)	109 (41.29)	59 (39.60)	50 (43.48)	82 (40.59)	27 (43.55)	82 (41.21)	27 (41.54)
	Education≥ HS, N (%)	225 (84.91)	129 (87.16)	96 (82.05)	170 (84.58)	55 (85.94)	170 (85.86)	55 (82.09)
Overall function	Modified Minimental	93.10 ± 6.60	93.87 ± 6.34	92.12 ± 6.82	93.64 ± 6.35	91.42 ± 7.11	93.49 ± 6.32	91.96 ± 7.28
	Digit Symbol Substitution Test, mean (SD)	36.90 ± 13.653	39.74 ± 12.72	33.26 ± 13.71	38.13 ± 13.50	33.08 ± 12.97	38.82 ± 13.03	31.18 ± 13.45
	CES-D	6.83 ± 6.23	6.16 ± 5.48	7.67 ± 7.00	6.17 ± 5.90	8.88 ± 6.83	6.43 ± 5.97	7.99 ± 6.86
	BL gait speed	0.90 ± 0.19	0.94 ± 0.17	0.852 ± 0.204	0.917 ± 0.183	0.845 ± 0.194	0.928 ± 0.178	0.814 ± 0.191
	Musculoskeletal pain, present/absent, N (%)	81 (30.45)	31 (20.81)	50 (42.74)	52 (25.74)	29 (45.31)	50 (25.13)	31 (46.27)
	BL BMI	27.51 ± 4.51	27.16 ± 4.01	27.96 ± 5.08	27.35 ± 4.29	28.02 ± 5.19	27.34 ± 4.23	28.05 ± 5.32
	Quadriceps muscle strength	81.29 ± 29.88	84.06 ± 29.98	77.62 ± 29.48	82.72 ± 29.02	76.32 ± 32.49	83.18 ± 29.50	75.27 ± 30.52
Vascular risk factors and conditions	Systolic blood pressure, mmHG	134.86 ± 19.46	133.24 ± 18.26	136.92 ± 20.79	133.71 ± 18.06	138.44 ± 23.10	134.17 ± 19.83	136.87 ± 18.35
	Diabetes, N (%)	31 (11.74)	15 (10.07)	16 (13.91)	25 (12.38)	6 (9.68)	21 (10.55)	10 (15.38)
	Cerebrovascular disease, N (%)	10 (3.79)	5 (3.36)	5 (4.35)	5 (2.48)	5 (8.06)	9 (4.52)	1 (1.54)
	Peripheral arterial disease, N (%)	6 (2.27)	2 (1.34)	4 (3.48)	5 (2.48)	1 (1.61)	5 (2.51)	1 (1.54)
	Chronic obstructive and pulmonary disease, N (%)	21 (9.17)	11 (8.21)	10 (10.53)	20 (11.24)	1 (1.96)	13 (7.60)	8 (13.79)
	Congestive heart failure, N (%)	0	0	0	0	0	0	0
Brain MRI	High WMH volume, N (%)	132 (50)	61 (41.50)	71 (60.68)	91 (45.50)	41 (64.06)	91 (46.19)	41 (61.19)
	Gray matter volume[a], mm³ normalized by intracranial volume	0.383 ± 0.0248	0.386 ± 0.0219	0.378 ± 0.028	0.385 ± 0.023	0.375 ± 0.027	0.385 ± 0.023	0.375 ± 0.027

Note: All data represent mean±standard deviation unless otherwise indicated.

Abbreviations: BL, baseline; BMI, body mass index; CES-D, Center for Epidemiologic Studies Depression Scale; HS, high school; N, number.

[a] Normalized by volume of total brain X100.

FUNCTIONAL CONNECTIVITY AND PARKINSONIAN SIGNS

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TABLE 2 Associations of demographics and health characteristics with RS connectivity

		RS connectivity between:							
		Striatum and thalamus		Sensorimotor striatum and sensorimotor cortex		Limbic striatum and limbic cortex		ECF striatum and ECF cortex	
		Right	Left	Right	Left	Right	Left	Right	Left
Demographic	Age	–	–	–	–	–	–	–	–
	Women versus men	0.003	0.005	−0.019	0.0002	0.078*	0.055*	0.013	−0.015
	Black versus White	−0.013	−0.012	−0.033	−0.011	0.017	−0.024	−0.007	−0.056*
	Education≥ HS versus all other levels	0.016	0.005	0.030	0.018	−0.029	−0.039	−0.059*	−0.013
Overall function	Modified Minimental	0.002	0.087	0.034	0.021	0.007	0.038	−0.029	0.070
	Digit Symbol Substitution Test	0.051	0.040	0.073	0.042	0.022	−0.015	−0.020	0.041
	CES-D	−0.005	0.181*	0.006	−0.030	−0.051	0.042	0.000	0.017
	BL gait speed	0.100	0.018	−0.023	0.027	0.013	0.062	−0.078	−0.010
	Musculoskeletal pain	−0.009	−0.023	0.005	0.020	−0.025	−0.060*	−0.007	−0.024
	BL BMI	0.180*	0.155*	0.101	−0.119	−0.004	0.049	0.064	0.010
	Quadriceps muscle strength	−0.029	−0.063	0.036	−0.060	−0.099	−0.055	0.008	0.009
Vascular risk factors and conditions	Systolic blood pressure	0.020	−0.019	−0.127	−0.020	−0.158*	−0.087	−0.179	−0.183
	Diabetes	0.008	0.033	0.041	−0.007	−0.012	−0.051	0.002	−0.021
	Cardiovascular disease	−0.075*	−0.039	−0.007	−0.016	0.033	0.127*	0.041	0.027
	Peripheral arterial disease	0.006	−0.028	−0.034	−0.075	0.031	0.094	0.069	0.114
	Chronic obstructive and pulmonary disease	0.002	−0.055*	0.007	0.060	−0.001	−0.047	−0.009	0.050
	Congestive heart failure	–	–	–	–	–	–	–	–
Brain MRI	High WMH volume	−0.038*	−0.022	−0.007	−0.042*	−0.031	−0.038	−0.045*	−0.046*
	Gray matter volume[a]	0.026	0.009	−0.135*	−0.045	−0.007	0.093	0.110	0.093

Note: Age-adjusted correlations and mean differences are reported for continuous and categorical variables, respectively.
Abbreviations: BL, baseline; BMI, body mass index; CES-D, Center for Epidemiologic Studies Depression Scale; ECF, executive control function; HS, high school; RS, resting-state; WMH, white matter hyperintensity.
[a]Normalized by volume of total brain X100.
*Age-adjusted *p*-value of comparison is <.05.

the super-regional approach (Figure 2B). In addition to these left ECF connections, two connections were significantly associated with MPS. Cortico-striatal connectivity of a right ECF network ROI, a9-46v (*p* = .040), may drive the nonsignificant right ECF trend found in the super-regional approach. Additionally, cortico-striatal connectivity of a lone sensorimotor region, right 6v (*p* = .035), is associated with MPS. Results of ROI-by-ROI analysis are consistent with the super-regional analysis, finding that cortico-striatal connections within ECF (predominantly in the left hemisphere) are associated with MPS.

The association of MPS with left executive network FC remained significant in multivariable models adjusted for covariates, but not after additional adjustment for WMH burden (Table 3 and Figure 3A). In logistic regression models predicting bradykinesia, associations were significant after adjustment for covariates and for WMH burden (Table 3 and Figure 3B). Interaction of WMH by RS connectivity in the executive network was *p* = .064 for models predicting MPS and *p* = .060 for models predicting bradykinesia. In models stratified by median WMH burden, association between connectivity and MPS was significant for those with high but not low WMH burden (Table 4 and Figure 3C). Results were similar for bradykinesia (Table 4 and Figure 3D). Results were similar in sensitivity analyses excluding the six participants with potential prodromal PD (not shown).
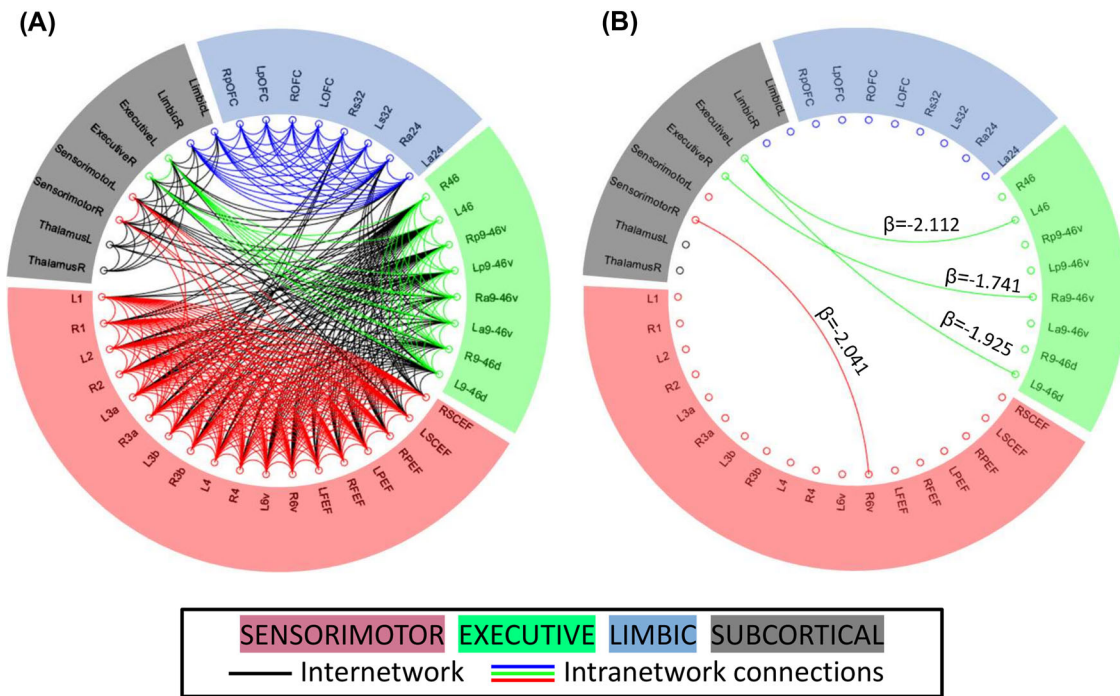
FIGURE 2 Global functional connectivity map and cortico-striatal association with mild Parkinsonian signs. Connectogram (A) shows the region-to-region pairwise connectivity within the sensorimotor (red region), executive (green region), and limbic (blue region) networks, averaged across participants. Subcortical regions of interest are denoted by the gray region. The threshold for the inclusion of an edge is the median pairwise correlation value. Intranetwork connections for sensorimotor (red), executive (green), and limbic (blue) are denoted by arcs within the connectogram. Internetwork connections are denoted by black arcs. Connectogram (B) illustrates pairwise cortico-striatal connections that are significantly correlated with mild Parkinsonian signs. Values listed correspond to logistic regression beta values for each edge with mild Parkinsonian signs after adjusting for age. Abbreviations: FEFs, frontal eye fields; L, left; OFC, orbital frontal cortex; PEFs, premotor eye fields; pOFC, posterior OFC; R, right; SCEFs, supplementary and cingulate eye fields

TABLE 3 Logistic regression models with RS connectivity of the left executive network as the main independent variable and presence/absence of Parkinsonian signs or bradykinesia, as dependent variables in separate models

	Model 1 adjusted for age	Model 2: further adjusted for covariates[a]	Model 3: model 2 further adjusted for WMH
Outcome: Parkinsonian signs	OR (95 % CI), *p*-value		
RS connectivity of the left executive network	0.188 (0.043, 0.824), .0267	0.162 (0.030, 0.874), .0343	0.219 (0.040, 1.199), .0800
Outcome: Bradykinesia	OR (95 % CI), *p*-value		
RS connectivity of the left executive network	0.080 (0.014, 0.461), .0047	0.061 (0.008, 0.465), .0070	0.077 (0.010, 0.604), .0147

Abbreviations: CI, confidence interval; OR, odds ratio; RS, resting-state; WMH, white matter hyperintensities.

[a]Variable entered in the model with forward stepwise conditional approach, to address overfitting: sex, race, musculoskeletal pain, quadriceps strength, gait speed, congestive heart failure, diabetes, peripheral arterial disease, pulmonary diseases/conditions, and cerebrovascular diseases.

DISCUSSION

In these community-dwelling older adults, those with MPS had significantly lower cortico-striatal FC in the executive network than those without MPS. While this association was robust to adjustment> for locomotor factors, it appeared significant only for those with high WMH burden, an indicator of cSVD.

A common finding in aging adults without neurologically overt disease is a decrease in FC over time, especially in the default mode network.[43] Higher regional connectivity often correlates with higher performance across cognitive[44] and motor domains.[45] Thus, higher FC—due to higher initial connectivity or compensatory increases in connectivity—may be protective against age-related declines in performance. We observed a negative association between
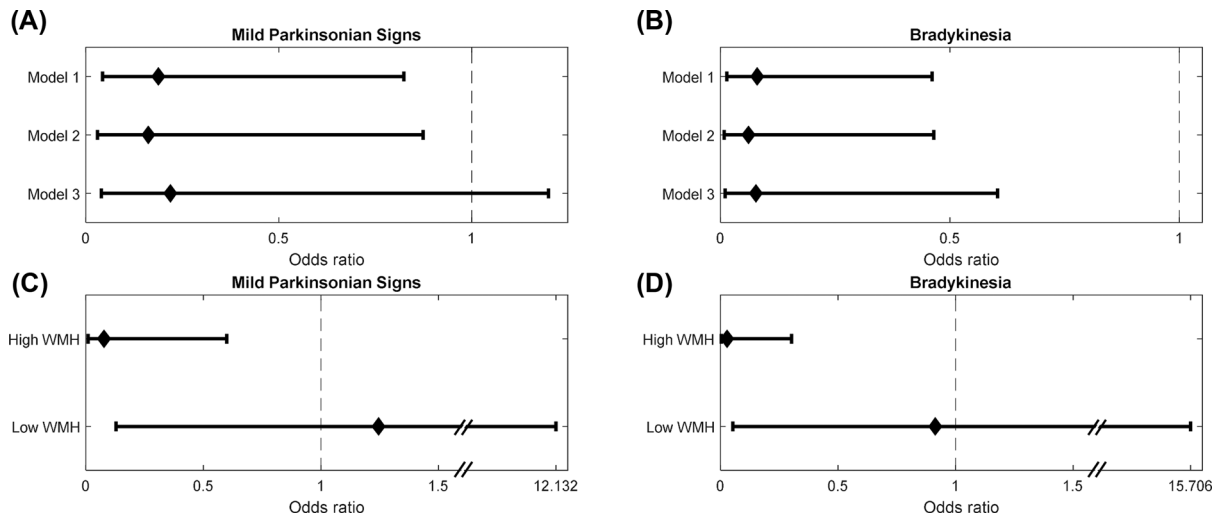
FIGURE 3 Odds ratios for logistic regression of left ECF connectivity and clinical status. (A) illustrates the odds ratios (ORs) for three logistic regression models relating left executive control function (ECF) cortico-striatal connectivity to mild Parkinsonian signs (MPS): model 1 is adjusted for age, model 2 is further adjusted for covariates (see Table 3 for details), and model 3 is further adjusted for white matter hyperintensity (WMH) burden. (B) illustrates the ORs for three logistic regression models relating left ECF cortico-striatal connectivity to bradykinesia; models are adjusted as in (A). (C) illustrates the ORs for logistic regression models relating left ECF cortico-striatal connectivity to MPS, stratified by WMH burden and adjusted for age. (D) illustrates the ORs for logistic regression models relating left ECF cortico-striatal connectivity to bradykinesia, stratified by WMH burden and adjusted for age

TABLE 4 Logistic regression models with RS connectivity of the left executive network as the main independent variable and presence/absence of Parkinsonian signs stratified by WMH volume above/below the median

	High WMH	Low WMH
Outcome: Parkinsonian signs	OR (95 % CI), *p*-value	
RS connectivity of the left executive network	0.077 (0.010, 0.599), .0143	1.245 (0.128, 12.132), .8503
Outcome: bradykinesia	OR (95 % CI), *p*-value	
RS connectivity of the left executive network	0.028 (0.003, 0.302), .0032	0.914 (0.053, 15.706), .9509

Note: All models adjusted for age.
Abbreviations: CI, confidence interval; OR, odds ratio; RS, resting-state; WMH, white matter hyperintensities.

executive FC and MPS status in participants with high but not low WMH burden, suggesting that this protective effect may be more pronounced for those with cSVD, another source of impaired motor control.

Our finding of lower RS connectivity in the presence of MPS is novel. Most previous neuroimaging studies of MPS have focused on dopamine binding quantification, volumetric analysis, and WMH quantification.[2,3] Collectively, these studies show that MPS is associated with reduced WM tract integrity in fronto-striatal areas (eg, due to WMH) and reduced dopaminergic signaling. It is possible that even early stages of structural abnormalities and/or reduced dopaminergic signaling would cause lower FC. Obtaining serial PET, structural and functional imaging can help address the evolution of the pathophysiology underlying reduced RS connectivity.

The causes of lower FC in aging are only partially understood;[46] even less is known about the drivers of reduced FC in MPS. For exam-

ple, it may be that Parkinson's pathology is present in these individuals and compromises RS connectivity. Studies of FC in PD show patterns of associations that are similar, but not identical, to those of our study. A meta-analysis of early-stage PD studies reveals lower connectivity between putamen and cortex in PD patients relative to controls.[14] PD-specific motor deficits correlate with lower connectivity in fronto-striatal[29,47,48] and default mode networks.[49] About 2% of participants (*n* = 6) received a PD diagnosis via retrospective assessment of medical history; this proportion is similar to that observed in other studies,[50] and our results were similar after excluding these participants. Although it cannot be completely ruled out, Parkinson-related pathology appears unlikely to have driven these results. MPS may reflect more general aging processes than PD-specific pathology.

In this cohort, MPS also appears to differ from PD in that there is no significant sex-related difference in MPS prevalence (Table 1). Conversely, there is significantly higher PD prevalence in men.[51] This is

also consistent with a nonsex-specific general aging process explaining MPS, rather than PD pathology.

Importantly, unlike WMH, FC is amenable to behavioral and pharmacological interventions that increase connectivity. Increased physical activity is a promising intervention that can influence RS. In animal studies, where chemical lesioning of dopaminergic neurons induces Parkinsonian symptoms, exercise partially restores FC and improves motor performance.[25] In an exercise study of PD patients, exercise intensity correlated with thalamocortical connectivity in primary motor cortex (another segment of the cortical-striatal-thalamic-cortical loop).[26] High intensity exercise is also associated with improved connectivity of substantia nigra and prefrontal cortex, which in turn led to increased quality of life scores in an exercise study of PD.[52] Together, these findings and our results suggest that FC may be a viable therapeutic target that may improve MPS.

It is important to note the limitations of our current study. Due to MRI exclusion criteria and self-selection bias, participants in imaging studies may be healthier and more educated than the populations from which they are drawn.[53] The fMRI protocol used in the Healthy Brain Project excluded coverage of the cerebellum; we could not evaluate whether RS abnormalities in cerebellar connectivity were also present in our MPS group. This protocol did not include fieldmaps, and uncorrected distortions may lead to false negatives in anterioventral limbic ROIs. The RS protocol was 5 minutes; subsequent studies have suggested that longer RS scans can improve reliability of network inference.[54] While longer times can yield more precise network correlations and can improve the reliability of network inference, it has been shown that the accuracy of network identification becomes stable at around 6 minutes.[54-56] In other words, longer scan times could have reduced noise in our connections and increased our statistical power; this might reveal additional significant associations, but we would still expect findings consistent with our results of associations between cortico-striatal network connection values and MPS status. Our sample size was relatively small, which could lead to imprecise estimates of our effect sizes, and our sample was cross-sectional. While increased FC appears protective against MPS, we are unable to determine whether this increase develops in response to cSVD (compensation) or whether it stems from higher initial connectivity (higher reserve). Though we use FC as a possible marker of dopaminergic signaling, we do not have direct measurements of dopamine via PET.

If replicated, our results could motivate studies investigating protective effects of higher initial FC against the influence of WMH on MPS over time. Adding dopamine nerve terminal PET or SPECT imaging would allow direct examination of the relationship between cortico-striatal FC and levels of dopaminergic signaling in the striatum, allowing dissection of the relative contributions of dopaminergic signaling and cSVD to MPS. Longitudinal studies of cSVD-FC interaction would provide two advantages: they would clarify whether protective FC is compensatory or present due to greater reserve and they would allow interventions to be administered, and their effects on MPS characterized.

In conclusion, community-dwelling older adults with MPS had significantly lower cortico-striatal FC in the executive network when compared to those without MPS. This association was strongest in participants with high WMH burden. Future work should address the possible protective relationship of high cortico-striatal executive connectivity against cSVD-related MPS.

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REFERENCES

1. Camarda C, Torelli P, Pipia C, Battaglini I, Azzarello D, Rosano R, et al. Association between atrophy of the caudate nuclei, global brain atrophy, cerebral small vessel disease and mild Parkinsonian signs in neurologically and cognitively healthy subjects aged 45–84 years: a cross-sectional study. Curr Alzheimer Res. 2018;15:1013–26.

2. Rosso AL, Bohnen NI, Launer LJ, Aizenstein HJ, Yaffe K, Rosano C. Vascular and dopaminergic contributors to mild parkinsonian signs in older adults. Neurology. 2018;90:E223–9.

3. Rosano C, Metti AL, Rosso AL, Studenski S, Bohnen NI. Influence of striatal dopamine, cerebral small vessel disease, and other risk factors on age-related parkinsonian motor signs. J Gerontol - Ser A Biol Sci Med Sci. 2020;75:696–701.

4. Buchman AS, Leurgans SE, Yu L, Wilson RS, Lim AS, James BD, et al. Incident parkinsonism in older adults without Parkinson disease. Neurology. 2016;87:1036–44.

5. Ross GW, Petrovitch H, Abbott RD, Wilson RS, Lim AS, James BD, et al. Parkinsonian signs and substantia nigra neuron density in decendents elders without PD. Ann Neurol. 2004;56:532–9.

6. Hatate J, Miwa K, Matsumoto M, Sasaki T, Yagita Y, Sakaguchi M, et al. Association between cerebral small vessel diseases and mild parkinsonian signs in the elderly with vascular risk factors. Park Relat Disord. 2016;26:29–34.

7. De Laat KF, Van Norden AGW, Gons RAR, van Uden IWM, Zwiers MP, Bloem BR, et al. Cerebral white matter lesions and lacunar infarcts contribute to the presence of mild parkinsonian signs. Stroke. 2012;43:2574–9.

8. De Laat KF, van Norden AGW, van Oudheusden LJB, van Uden IWM, Norris DG, Zwiers MP, et al. Diffusion tensor imaging and mild parkinsonian signs in cerebral small vessel disease. Neurobiol Aging. 2012;33:2106–12.

9. Miller-Patterson C, Han J, Yaffe K, Rosso AL, Launer LJ, Kritchevsky SB, et al. Clinical and neuroimaging correlates of progression of mild parkinsonian signs in community-dwelling older adults. Park Relat Disord. 2020;75:85–90.

10. Rosano C, Bennett DA, Newman AB, Venkatraman V, Yaffe K, Harris T, et al. Patterns of focal gray matter atrophy are associated with bradykinesia and gait disturbances in older adults. J Gerontol - Ser A Biol Sci Med Sci. 2012;67 A:957–62.

11. Fox PT, Lancaster JL. Mapping context and content: the BrainMap model. Nat Rev Neurosci. 2002;3:319–21.

12. Smith SM, Fox PMT, Miller KL, Glahn DC, Fox PM, Mackay CE, et al. Correspondence of the brain's functional architecture during activation and rest. Proc Natl Acad Sci USA. 2009;106:13040–5.

13. Zitser J, Casaletto KB, Staffaroni AM, Sexton C, Weiner-Light S, Wolf A, et al. Mild motor signs matter in typical brain aging: the value of the UPDRS score within a functionally intact cohort of older adults. Front Aging Neurosci 2021;13.18.

14. Herz DM, Eickhoff SB, Løkkegaard A, Siebner HR. Functional neuroimaging of motor control in Parkinson's disease: a meta-analysis. Hum Brain Mapp. 2014;35:3227–37.

15. Dayan E, Browner N. Alterations in striato-thalamo-pallidal intrinsic functional connectivity as a prodrome of Parkinson's disease. Neuroimage Clin. 2017;16:313–8.

16. Rolinski M, Griffanti L, Piccini P, Roussakis AA, Szewczyk-Krolikowski K, Menke RA, et al. Basal ganglia dysfunction in idiopathic REM sleep behaviour disorder parallels that in early Parkinson's disease. Brain. 2016;139:2224–34.

17. Behfar Q, Behfar SK, von Reutern B, Richter N, Dronse J, Fassbender R, et al. Graph theory analysis reveals resting-state compensatory mechanisms in healthy aging and prodromal Alzheimer's disease. Front Aging Neurosci. 2020;12:1–13.

18. Koch K, Myers NE, Göttler J, Pasquini L, Grimmer T, Förster S, et al. Disrupted intrinsic networks link amyloid-β pathology and impaired cognition in prodromal Alzheimer's disease. Cereb Cortex. 2015;25:4678–88.

19. Contreras JA, Avena-Koenigsberger A, Risacher SL, West JD, Tallman E, McDonald BC, et al. Resting state network modularity along the prodromal late onset Alzheimer's disease continuum. Neuroimage Clin. 2019;22:101687.

20. Unschuld PG, Joel SE, Liu X, Shanahan M, Margolis RL, Biglan KM, et al. Impaired cortico-striatal functional connectivity in prodromal Huntington's disease. Neurosci Lett. 2012;514:204–9.

21. Koenig KA, Lowe MJ, Harrington DL, Lin J, Durgerian S, Mourany L, et al. Functional connectivity of primary motor cortex is dependent on genetic burden in prodromal Huntington disease. Brain Connect. 2014;4:535–46.

22. Kronenbuerger M, Hua J, Bang JYA, Ultz KE, Miao X, Zhang X, et al. Differential changes in functional connectivity of striatum-prefrontal and striatum-motor circuits in premanifest Huntington's disease. Neurodegener Dis. 2019;19:78–87.

23. Trojsi F, Di Nardo F, Siciliano M, Caiazzo G, Passaniti C, D'Alvano G, et al. Resting state functional MRI brain signatures of fast disease progression in amyotrophic lateral sclerosis: a retrospective study. Amyotroph Lateral Scler Front Degener. 2020;22(1–2):117–126.

24. Borroni B, Premi E, Formenti A, et al. Structural and functional imaging study in dementia with Lewy bodies and Parkinson's disease dementia. Park Relat Disord. 2015;21:1049–55.

25. Wang Z, Guo Y, Myers KG, Heintz R, Peng Y-H, Maarek J-MI, et al. Exercise alters resting-state functional connectivity of motor circuits in parkinsonian rats. Neurobiol Aging. 2015;36:536–44.

26. Shah C, Beall EB, Frankemolle AMM, Penko A, Phillips MD, Lowe MJ, et al. Exercise therapy for Parkinson's disease: pedaling rate is related to changes in motor connectivity. Brain Connect. 2016;6:25–36.

27. Ruppert MC, Greuel A, Tahmasian M, Schwartz F, Stürmer S, Maier F, et al. Network degeneration in Parkinson's disease: multimodal imaging of nigro-striato-cortical dysfunction. Brain. 2020;143:944–59.

28. Szewczyk-Krolikowski K, Menke RAL, Rolinski M, Duff E, Salimi-Khorshidi G, Filippini N, et al. Functional connectivity in the basal ganglia network differentiates PD patients from controls. Neurology. 2014;83:208–14.

29. Wu T, Long X, Zang Y, Wang L, Hallett M, Li K, et al. Regional homogeneity changes in patients with Parkinson's disease. Hum Brain Mapp. 2009;30:1502–10.

30. Yang W, Liu B, Huang B, Huang R, Wang L, Zhang Y, et al. Altered resting-state functional connectivity of the striatum in Parkinson's disease after levodopa administration. PLoS One. 2016;11:e0161935.

31. Festini SB, Bernard JA, Kwak Y, Peltier S, Bohnen NI, Müller MLTM, et al. Altered cerebellar connectivity in Parkinson's patients ON and OFF L-DOPA medication. Front Hum Neurosci. 2015;9:214.

32. Rosso AL, Studenski SA, Chen WG, Aizenstein HJ, Alexander NB, Bennett DA, et al. Aging, the central nervous system, and mobility. J Gerontol Ser A. 2013;68:1379–86.

33. Quandt F, Fischer F, Schröder J, Heinze M, Lettow I, Frey BM, et al. Higher white matter hyperintensity lesion load is associated with reduced long-range functional connectivity. Brain Commun. 2020;2:fcaa111.

34. Introducing the Health ABC study: the dynamics of health, aging, and body composition. Available at: https://healthabc.nia.nih.gov. Accessed April 27, 2021.

35. Rosso AL, Studenski SA, Longstreth WT, Brach JS, Boudreau RM, Rosano C. Contributors to poor mobility in older adults: integrating white matter hyperintensities and conditions affecting other systems. J Gerontol A Biol Sci Med Sci. 2017;72:1246–51.

36. Teng E, Chui H. The Modified Mini-Mental State (3MS) examination. J Clin Psychiatry. 1987;48:314–8.

37. Radloff LS. The CES-D scale. Appl Psychol Meas. 1977;1:385–401.

38. Wu M, Rosano C, Butters M, Whyte E, Nable M, Crooks R, et al. A fully automated method for quantifying and localizing white matter hyperintensities on MR images. Psychiatry Res - Neuroimaging. 2006;148:133–42.

39. Glasser MF, Coalson TS, Robinson EC, Hacker CD, Harwell J, Yacoub E, et al. A multi-modal parcellation of human cerebral cortex. Nature. 2016;536:171–8.

40. Tziortzi AC, Haber SN, Searle GE, Tsoumpas C, Long CJ, Shotbolt P, et al. Connectivity-based functional analysis of dopamine release in the striatum using diffusion-weighted MRI and positron emission tomography. Cereb Cortex. 2014;24:1165–77.

41. Tziortzi AC, Searle GE, Tzimopoulou S, Salinas C, Beaver JD, Jenkinson M, et al. Imaging dopamine receptors in humans with [11C]-(+)-PHNO: dissection of D3 signal and anatomy. Neuroimage. 2011;54:264–77.

42. Rothman K. No adjustments are needed for multiple comparisons. Epidemiology. 1990;1:43–6.

43. Ferreira LK, Regina ACB, Kovacevic N, da Graça Morais Martin M, Santos PP, de Godoi Carneiro C, et al. Aging effects on whole-brain functional connectivity in adults free of cognitive and psychiatric disorders. Cereb Cortex. 2016;26:3851–65.

44. Sheline YI, Raichle ME. Resting state functional connectivity in preclinical Alzheimer's disease. Biol Psychiatry. 2013;74:340–7.

45. Seidler R, Erdeniz B, Koppelmans V, Hirsiger S, Mérillat S, Jäncke L. Associations between age, motor function, and resting state sensorimotor network connectivity in healthy older adults. Neuroimage. 2015;108:47–59.

46. Sala-Llonch R, Bartrés-Faz D, Junqué C. Reorganization of brain networks in aging: a review of functional connectivity studies. Front Psychol. 2015;6:663.

47. Tessitore A, Amboni M, Esposito F, et al. Resting-state brain connectivity in patients with Parkinson's disease and freezing of gait. Park Relat Disord. 2012;18:781–7.

48. Shine JM, Moustafa AA, Matar E, Frank MJ, Lewis SJG. The role of frontostriatal impairment in freezing of gait in Parkinson's disease. Front Syst Neurosci. 2013;7:61.

49. Karunanayaka PR, Lee EY, Lewis MM, Sen S, Eslinger PJ, Yang QX, et al. Default mode network differences between rigidity- and tremor-predominant Parkinson's disease. Cortex. 2016;81:239–50.

50. Louis ED, Tang MX, Schupf N, Mayeux R. Functional correlates and prevalence of mild parkinsonian signs in a community population of older people. Arch Neurol. 2005;62:297–302.

51. Gillies GE, Pienaar IS, Vohra S, Qamhawi Z. Sex differences in Parkinson's disease. Front Neuroendocrinol. 2014;35:370–84.

52. Kelly NA, Wood KH, Allendorfer JB, Ford MP, Bickel CS, Marstrander J, et al. High-intensity exercise acutely increases substantia nigra and prefrontal brain activity in Parkinson's disease. Med Sci Monit. 2017;23:6064–71.

53. Ganguli M, Lee C, Hughes T, Snitz BE, Jakubcak J, Duara R, et al. Who wants a free brain scan? Assessing and correcting for recruitment biases in a population-based sMRI pilot study. Brain Imaging Behav. 2015;9:204–12.

54. Birn RM, Molloy EK, Patriat R, Parker T, Meier TB, Kirk GR, et al. The effect of scan length on the reliability of resting-state fMRI connectivity estimates. Neuroimage. 2013;83:550–8.

55. Fox MD, Snyder AZ, Vincent JL, Corbetta M, Van Essen DC, Raichle ME. The human brain is intrinsically organized into dynamic, anticorrelated functional networks. Proc Natl Acad Sci USA. 2005;102:9673–8.

56. Van Dijk KRA, Hedden T, Venkataraman A, Evans KC, Lazar SW, Buckner RL. Intrinsic functional connectivity as a tool for human connectomics: theory, properties, and optimization. J Neurophysiol. 2010;103:297–321.