Parkinsonism and Related Disorders 62 (2019) 68–72

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

Physical activity mediates the association between striatal dopamine transporter availability and cognition in Parkinson's disease

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ARTICLE INFO

Keywords:
Single photon emission computerized tomography
Exercise
Cognitive function
Mediation models
Parkinson's disease

ABSTRACT

Objective: Associations between cognition and nigrostriatal dopaminergic deficits in Parkinson's disease have been documented in the literature, but are incompletely understood. Here we studied the extent to which physical activity mediates the relationship between striatal dopamine transporter availability and global cognition among patients with Parkinson's disease.

Methods: Data from 174 patients from a multi-center study were analyzed using regression-based mediation analysis. Striatal dopamine transporter binding ratio (SBR), Physical Activity Scale for Elderly (PASE), and Montreal Cognitive Assessment (MoCA) were used to evaluate patients' dopamine transporter availability (DAT), physical activity, and global cognition respectively at the time of testing. Confidence intervals (CI) of 95% were established using a bootstrapping approach to test the statistical significance of the direct, indirect (i.e., mediation), and total effects of the mediation model.

Results: As hypothesized, the positive mediating effect of physical activity in the association between DAT and global cognition was significant, while adjusting for age (95% CI [0.0030, 0.3942]). Specifically, higher SBRs were positively associated with PASE scores, which in turn, were positively associated with MoCA scores. Secondary analyses revealed a similar positive mediation effect of physical activity for DAT in the caudate and putamen separately (95% CI [0.0377, 0.4231] and [0.0211, 1.1000], respectively).

Conclusion: We report that the relationship of dopamine transporter availability with global cognition in Parkinson's disease is mediated by physical activity. Pending further research for specific recommendations, interventions to increase physical activity as tolerated should be considered in patients with Parkinson's disease.

1. Introduction

It is widely acknowledged that Parkinson's disease (PD) is often associated with a range of non-motor symptoms [1]. Cognitive impairment, in particular, is common in PD [2], and is known to contribute adversely to the patients' quality of life [3]. Research has shown that more than 25% of PD patients develop cognitive impairment [4], even in early stages of the disease [5].

Multiple studies have shown that cognitive function in PD, at least in part, is related to the nigrostriatal dopaminergic deficits characterizing this disease [6,7]. However, the mechanisms that underlie the link between dopaminergic depletion and cognition in PD remain unclear. Physical activity, among other modifiable factors, has been shown to have a substantial influence on cognition. Studies in both human and animal models have shown that physical activity promotes cognitive functioning across the lifespan [8], presumably through induction of neuroplasticity [9]. In PD, physical activity and physical exercise interventions positively impact cognitive function [10–13], while also improving motor symptoms and health-related quality of life [14,15]. Moreover, epidemiologic evidence suggests that moderate to vigorous exercise may reduce the risk of developing PD [16]. Thus, physical activity can be considered as a plausible potential mediator in the association between dopaminergic disruption and cognition in PD.

Altogether, research in PD points to strong associations between cognitive function and dopaminergic mechanisms [6,7], while also demonstrating strong associations between cognition and physical activity [12,13]. A framework that ties these distinct factors together has not been tested to the best of our knowledge. Here, we set out to analyze a well-defined sample of PD patients and test the linkage among nigrostriatal dopaminergic deficits, physical activity, and cognition.

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https://doi.org/10.1016/j.parkreldis.2019.01.027
Received 26 July 2018; Received in revised form 20 December 2018; Accepted 29 January 2019

Based on the statistical framework of mediation analysis, our objective was to examine the extent to which the association between dopamine transporter (DAT) availability in the striatum and global cognition in PD is mediated by physical activity.

2. Methods

2.1. Participants

All data were obtained from the Parkinson's Progression Markers Initiative (PPMI), an international, multi-center, observational study. Detailed study aims, design, methodology, participant selection criteria, and other relevant information can be found online (http://www.ppmi-info.org/). All subjects provided written informed consent and the procedures were all approved by the Institutional Review Boards of each participating center.

Data from participants' 10th (approximately 48 months after the study's baseline visit) and 12th visits (approximately 60 months after the study's baseline visit) were used in the current study, which were the latest visits with sufficient data points in the three variables of interest (i.e., striatal DAT availability, physical activity, and global cognition). We reasoned that data from a later visit would allow us to find more variance in participants' cognitive measures. 423 participants were initially enrolled in the PPMI, but data from 249 participants were unavailable due to attrition or missing values in at least one of the variables of interest. Therefore, our analyses were based on data from 174 participants (56 Females; 118 Males, mean Age = 65.79 yrs, SD = 9.48).

2.2. Primary outcome measures

2.2.1. Striatal dopamine transporter binding ratio

Striatal binding ratio (SBR) has shown to be highly correlated with other measures of PD severity and progression, such as the Unified Parkinson Disease Rating Scale and Hoehn and Yahr (H&Y) stage [17]. To confirm DAT deficits, all PPMI participants underwent a Single Photon Emission Computerized Tomography (SPECT) imaging scan to determine their eligibility for the study at the screening visit and had additional scans according to the PPMI protocol in subsequent visits. These SPECT images underwent quality control both technically and scientifically. SBR of left and right caudate and putamen were obtained from the PPMI database. Average scores from these 4 structures were calculated. Regional caudate and putamen data were additionally calculated for secondary analyses. Detailed procedures and information regarding PPMI's SPECT imaging protocol can be found on the PPMI website.

2.2.2. Physical activity

The Physical Activity Scale for the Elderly (PASE) [18] was used to assess participants' physical activity at the time of testing. The PASE is a brief questionnaire, specifically designed to measure physical activity in older adults in large epidemiologic studies. The PASE has been shown as a valid and reliable instrument for measuring physical activity [18]. Scores from this questionnaire are highly correlated with objective measures of physical activity such as a portable accelerometer [19].

2.2.3. Global cognition

Global cognition was assessed using the Montreal Cognitive Assessment (MoCA) [20]. The MoCA was designed as a brief screening tool for mild cognitive impairment, assessing a variety of cognitive domains (i.e., attention, memory, executive function, visuospatial ability, and language). The MoCA is a valid and reliable instrument in PD [20] and has been listed as a recommended instrument for assessing global cognition in this population.

As a multi-center, longitudinal study, the PPMI did not administer all tests and assessments at each visit. All measures and scores used in the current study were obtained at the 12th visit, except for SBRs, which were obtained at the 10th visit (approximately 12 months apart), the most recent session at which SPECT imaging data has been acquired. However, given the slow and linear rates of change for DAT documented at this stage [21], we expect this time difference to have minimal influence over the results.

2.3. Statistical analysis

We examined the extent to which the association between average striatal DAT availability and global cognition in PD is mediated by physical activity by fitting a mediation model with observational data from the PPMI. In these models, SBR was the independent variable, PASE score was the mediator, and MOCA score was the dependent variable. Pearson and Spearman correlation coefficients were used to evaluate the linear relationship between the variables of interest and potential confounding variables. Ordinary least squares (OLS) regression was used to test the proposed mediation models. In order to test the statistical significance of the total, direct, and indirect (i.e., mediation) effects, 95% confidence intervals (CI) were established by using a bootstrapping approach with 10,000 samples. Effects were considered statistically significant if the value '0' fell outside the 95% CI. We additionally performed an exploratory analysis where we tested if disease severity, as measured with the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part III (motor examination) moderated the paths in the proposed mediation model. This analysis relied on a moderated mediation model. All statistical analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC) and the "PROCESS" macro developed by Hayes (http://www.processmacro.org/index.html). Statistical significance was set at $\alpha = 0.05$.

3. Results

Descriptive statistics regarding participants' demographic and clinical characteristics are presented in Table 1. In addition, bivariate correlations between SBR, PASE, and MoCA scores and potential confounding variables are presented in Table 2. SBR, PASE scores, MoCA scores, "off" MDS-UPDRS part III scores, and H&Y stages were significantly correlated with each other (all p *values* < 0.05). Age was significantly correlated with PASE scores, MoCA scores, and MDS-UPDRS part III scores. PD duration was not significantly correlated with any of the other variables (all p *values* > 0.05), except with the PASE scores ($p < 0.05$).

The OLS regression analyses for testing the proposed mediation

Table 1
Descriptive statistics for participants' demographic characteristics and clinical measures.

	Age (years)	Gender (F/M)	MDS-UPDRS part III	H&Y Stages	PD duration (months)	Striatum	Caudate	Putamen	PASE	MoCA
N	174	174	174	174	174	174	174	174	174	174
Mean	65.79	56/118	29.94	1.96	67.05	1.03	1.50	0.56	157.34	26.93
SD	9.48	–	11.13	0.39	6.46	0.35	0.53	0.21	90.12	3.01

Note. MDS-UPDRS part III = Movement disorder society Unified Parkinson's Disease Rating Scale part III; H&Y Stages = Hoehn and Yahr Stages; PD duration = Parkinson's disease duration; Striatum = Striatal Dopamine Transporter Binding Ratio; Caudate = Dopamine Transporter Binding Ratio in caudate; Putamen = Dopamine Transporter Binding Ratio in putamen; PASE = Physical Activity Scale for Elderly; MoCA = Montreal Cognitive Assessment.

Table 2
Bivariate correlations between variables of interest and potential confounding variables.

	Striatum	PASE	MoCA	Age	MDS-UPDRS part III	H&Y Stages	PD duration
Striatum	1.0000						
PASE	0.2037**	1.0000					
MoCA	0.1964**	0.2267**	1.0000				
Age	−0.1222	−0.2270**	−0.4045***	1.0000			
MDS-UPDRS part III	−0.2514***	−0.1679*	−0.2414**	0.2022**	1.0000		
H&Y Stages	−0.3317***	−0.2638***	−0.1717*	0.0798	0.4889**	1.0000	
PD duration	−0.1380	−0.1498*	−0.0813	0.0958	0.1096	0.0798	1.0000

Note[1]. All abbreviations are as in Table 1. Note[2]. Pearson product correlation was used for testing the correlation between the Age and PD duration variables; Spearman's rank-order correlation was used in all other correlation tests. Note[3]. * < 0.05, ** < 0.01, *** < 0.001. Note[4]. Sample size = 174.

Table 3
Estimated model coefficients for mediation models.

		Consequent						
		PASE				MoCA		
		Coeff.	SE	p		Coeff.	SE	p
Striatum	a	44.9738	19.1681	0.0201	c'	1.2688	0.6377	0.0482
PASE		–	–	–	b	0.0070	0.0025	0.0058
constant	i_1	111.1091	20.8252	< .0001	i_2	24.5227	0.7363	< 0.0001
		R^2 = 0.0310				R^2 = 0.0766		
		F (1,172) = 5.5051, p = 0.0201				F (2,171) = 7.0877, p = 0.0011		
Caudate	a	29.9632	12.7526	0.0199	c'	0.9136	0.4235	0.0324
PASE		–	–	–	b	0.0069	0.0025	0.0062
constant	i_1	112.4010	20.2797	< .0001	i_2	24.4681	0.7196	< 0.0001
		R^2 = 0.0311				R^2 = 0.0802		
		F (1,172) = 5.5205, p = 0.0199				F (2,171) = 7.4563, p = 0.0008		
Putamen	a	64.0828	32.6757	0.0515	c'	1.3512	1.0844	0.2145
PASE		–	–	–	b	0.0074	0.0025	0.0036
constant	i_1	121.7031	19.3923	< .0001	i_2	25.0104	0.7056	< 0.0001
		R^2 = 0.0219				R^2 = 0.0637		
		F (1,172) = 3.8462, p = 0.0515				F (2,171) = 5.8144, p = 0.0036		

Note. Coeff = coefficient; Caudate = Dopamine transporter binding ratio in caudate; Putamen = Dopamine transporter binding ration in putamen; Other abbreviations are as in Table 1.

model are summarized in Table 3 and the estimated regression coefficients are superimposed on the statistical diagram of the proposed mediation model in Fig. 1.

We first assessed whether the association between striatal DAT availability and global cognition is mediated by physical activity (Fig. 1a). The direct effect between striatal DAT availability and global cognition (i.e., path c') was statistically significant ($\hat{\beta}_{c'}$ = 1.2688, SE = 0.6377, 95% CI [0.0100, 2.5275]). Thus, while holding PASE scores constant, higher SBR scores were associated with higher MoCA scores. The indirect effect in the model (i.e., path ab), expressing the positive mediating role of physical activity in the association between SBR and global cognition, reached statistical significance as hypothesized ($\hat{\beta}_{ab}$ = 0.3140, SE = 0.1517, 95% CI [0.0532, 0.6452]). The completely standardized indirect effect was 0.0368 (95% CI [0.0065, 0.0738]), indicating a small-to-moderate effect size [22]. Thus, we found that the positive association between SBRs and MoCA scores was mediated at least in part by PASE scores. Finally, the total effect (i.e., path c, which equals to c' + ab) reached statistical significance ($\hat{\beta}_{c}$ = 1.5828, SE = 0.6400, 95% CI [0.3194, 2.8461]). Thus, greater SBRs were associated with higher MoCA Scores. Note that the mediating effect of physical activity in the association between striatal DAT availability and global cognition was still present while controlling for participants' age ($\hat{\beta}_{ab}$ = 0.1593, SE = 0.1018, 95% CI [0.0030, 0.3942], completely standardized indirect effect = 0.0186 (95% CI [0.0003, 0.0458]).

Next, we tested whether the averaging of SBR values across the caudate and putamen masked results which are specific to any of these two structures. More specifically, we examined whether physical activity mediated the relationship between SBR and global cognition, when considering DAT availability from the caudate and putamen separately (Fig. 1b–c, also see Table 3 for model coefficient estimation). Mediation analyses showed consistent and similar indirect effects of physical activity on the DAT binding ratio of caudate and putamen with global cognition ($\hat{\beta}_{ab}$ = 0.2070, SE = 0.0987, 95% CI [0.0377, 0.4231] and $\hat{\beta}_{ab}$ = 0.4739, SE = 0.2737, 95% CI [0.0211, 1.1000]; completely standardized indirect effect = 0.0364 (95% CI [0.0067, 0.0724]) and 0.0327 (95% CI [0.0015, 0.0725]), for caudate and putamen, respectively).

In an exploratory analysis, we further investigated whether disease severity, as measured with MDS-UPDRS part III moderated the relationship between the variables in each of the paths reported above, using a moderated mediation model. Results from this analysis (Supplemental Fig. 1) indicated that MDS-UPDRS III scores did not moderate any of the paths in the proposed mediation model ($\hat{\beta}_{Int\_a}$ = 1.0866, SE = 1.6826, 95% CI [-2.2348, 4.4081], $\hat{\beta}_{Int\_b}$ = 0.0003, SE = 00.0002, 95% CI [-0.0001, 0.0007], and $\hat{\beta}_{Int\_c'}$ = 0.0858, SE = 0.0560, 95% CI [-0.0247, 0.1963], for paths a, b, and c', respectively). In other words, none of the paths in the proposed mediation model were contingent upon the level of disease severity, as assessed with MDS-UPDRS part III scores.

4. Discussion

PD patients frequently experience cognitive impairment in the course of their disease. Both motor symptoms and cognitive impairment

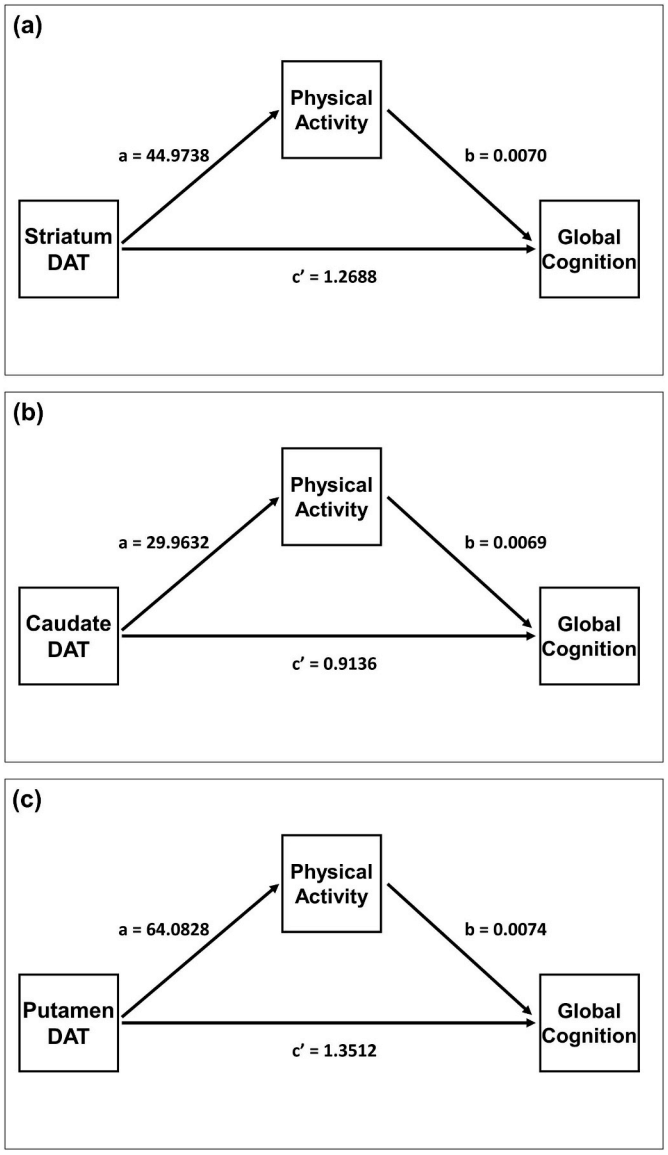

Fig. 1. Mediation models testing whether physical activity mediates the association between DAT binding ratio and global cognition. Separate models were tested based on average striatal binding ratio (a) and based on regional binding ratio in the caudate (b) and putamen (c).

have been suggested to be associated with the underlying dopaminergic disruption in PD [23], and both appear to be positively affected by physical activity [14,15,24]. Associations between cognitive function and dopaminergic denervation, and between cognition and physical activity, as reported here, fit in well with previous reports [6,7,12,13]. Adding to the current state of knowledge, we further demonstrate that the association between striatal DAT binding ratio and global cognition in PD patients is partially mediated by physical activity. In secondary analyses, we found that the mediation model yielded similar results when considering DAT binding ratios in both the caudate and the putamen. These results are in line with previous results reporting similar associations between cognitive function and DAT availability in these two structures [6]. Additionally, none of the paths in the proposed mediation model were moderated by disease severity, as assessed by MDS-UPDRS III scores.

Neuroprotective effects of physical activity in countering cognitive decline were demonstrated extensively in healthy older adults [25,26], and it has been suggested that similar effects may occur in PD patients [9,27]. The mechanisms by which physical activity ameliorates the symptoms of PD are not well-understood. However, a few putative biological mechanisms have been hypothesized and examined in animal models [28]. In particular, it has been suggested that physical activity may favorably alter the progression of PD through a reduction of nigrostriatal neurotoxicity, an increase in brain neurotrophic factors, and through an overall facilitation of neuroplasticity. The mediation model tested in the current study suggests that although disease severity, as measured by dopaminergic dysfunction, correlates strongly with cognitive dysfunction in PD, cognitive decline may not be directly attributable to disease severity per se, but rather also to the deleterious effects of a sedentary lifestyle related to the neuropathological progression of the disease.

Current medical treatment for the symptoms of PD focuses on improving function in activities of daily livings, employability, and preventing morbidity related to falls and other immediate consequences of poor mobility [29]. Classically, treatment of PD with levodopa has been limited due to concerns for eventual motor complications and fluctuations. The evidence from the current study may implicate an additional goal for the treatment of PD symptoms. Namely, if the relationship between striatal DAT binding ratio with cognitive scores in PD is mediated by physical activity, then treatment with a goal of increasing physical activity may be reasonable. However, research has consistently reported that PD patients are less active than age-matched individuals [30], thus strategies to promote physical activity in PD should be more consistently utilized. Future research should aim to study the cognitive benefits of early, more aggressive treatment of PD motor symptoms and promotion of physical activity in a prospective cohort.

While our findings clearly suggest that the relationship between striatal DAT binding ratio and global cognition is partially mediated by physical activity, the results should be interpreted with caution. First, the nature of the observational data prevented us from assessing causal relationships. Future research with more appropriate designs (e.g., randomized controlled trials) and statistical approaches will be needed in order to achieve more direct conclusions. Second, although PASE has been validated and widely used in elderly subjects [18,19], it was not designed specifically for, or validated in patients with PD. Independent validation of this questionnaire against quantitative measures of physical activity in PD should be studied in future research. Third, data used in the current study were from PD patients in earlier stages of the disease. With this limit in disease duration, we cannot generalize our findings to patients at other stages of the disease. The relative homogeneity of the sample studied here with respect to disease duration effectively minimized confounding effects related to this factor, but also prevented us from exploring meaningful associations between disease duration and other variables of interest. This homogeneity may have also prevented us from fully exploring the moderating effects of disease severity levels in the mediation model studied here. Future studies focusing on more heterogenous samples, are warranted in order to more fully delineate the role of physical activity in the association between DAT availability and cognition in PD.

In summary, we report that the relationship between striatal DAT binding ratio and global cognition in PD patients is mediated by physical activity. With physical activity being an accessible behavioral intervention, these results carry valuable implications for patients and medical providers. Future research with robust experimental designs and a focus on a more diverse group of PD patients will be needed in order to further understand the potential disease modifying effects of physical activity in this disease.

Authors' roles

Study conceptualization: ED, CS, MS; Data analysis: CS and KM; Original draft preparation: CS; Review and editing: KM, NB, MS, and ED.

Financial disclosures

Nina Browner received travel reimbursement and speaker fees from the Parkinson Foundation (formerly the National Parkinson Foundation). Miriam Sklerov reports previous funding from the National Institutes of Health (T32 NS07153) and the Parkinson Foundation (formerly the National Parkinson Foundation). All other authors have no financial disclosures.

Acknowledgement

Data were obtained from the Parkinson's Progression Markers Initiative (PPMI) database. For up-to-date information on the study, visit www.ppmi-info.org.

PPMI – a public-private partnership – is funded by the Michael J. Fox Foundation for Parkinson's Research and funding partners, including Abbvie, Avid Radiopharmaceuticals, Biogen, Bristol-Myers Squibb, Covance, GE healthcare, Genentech, GlaxoSmithKline, Lilly, Lundbeck, Merck, Meso Scale Discovery, Pfizer, Piramal, Roche, Servier, and UCB.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2019.01.027.

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