

Striatal DAT binding fully mediates caffeine's effect on motor progression in Parkinson disease

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Abstract

Background

Parkinson's disease (PD) is characterized by decreased striatal dopamine transporter (DAT) binding and progressive motor impairment. The role of caffeine in patients with established PD remains controversial, and the pathway linking caffeine intake, DAT levels and motor symptoms has not been fully elucidated.

Purpose

This study aimed to examine the influence of caffeine consumption on striatal DAT binding and core motor symptoms in PD. We also explored whether altered DAT binding mediated the relationship between caffeine and motor dysfunction, and evaluated the long-term effect of caffeine on the progression of motor symptoms.

Methods

Data of 83 healthy controls and 261 idiopathic PD patients were retrieved from the PPMI database and grouped by caffeine intake status. Striatal specific binding ratio (SBR) was measured using [^{123}I] FP-CIT SPECT. Correlation and mediation analyses were performed based on the full cohort of 261 PD patients. Longitudinal progression was assessed via generalized estimating equations (GEE) in 207 PD patients with valid 1–4 years follow-up data.

Results

Caffeine intake significantly reduced striatal DAT binding across all participants. In the PD cohort, lower DAT binding correlated with severe rigidity and bradykinesia, and fully mediated the adverse effects of caffeine on these two symptoms. Longitudinal analysis in PD patients confirmed that caffeine intake accelerated the progression of rigidity and bradykinesia, with no significant effect on resting tremors.

Conclusion

Caffeine consumption downregulates striatal DAT binding in PD, which further exacerbates rigidity and bradykinesia progression. Unlike its potential preventive effect on PD onset, sustained caffeine intake acts as an unfavorable lifestyle factor for established PD. This finding provides novel mechanistic evidence for individualized lifestyle intervention in PD management.

Introduction

Parkinson's disease (PD) is the second most prevalent neurodegenerative disorder worldwide, characterized by progressive degeneration of nigrostriatal dopaminergic neurons and reduced striatal dopamine transporter (DAT) availability, which ultimately leads to the core cardinal motor symptoms of rigidity, bradykinesia, and resting tremor ^{1,2}. The progressive deterioration of motor function severely impairs patients' quality of life and imposes a substantial socioeconomic burden on global healthcare systems. Despite decades of research, the modifiable environmental factors that influence PD pathogenesis and disease progression remain incompletely elucidated, hindering the development of effective intervention strategies to delay motor deterioration ^{3–5}.

Caffeine, one of the most widely consumed psychoactive substances globally, has been extensively investigated for its potential neuroprotective or neuromodulatory effects on PD ^{6–8}. Existing epidemiological studies have proposed conflicting

associations between caffeine intake and PD risk, with most observational studies suggesting a reduced incidence of PD among regular caffeine consumers^{9–11}. However, emerging preclinical and clinical evidence has challenged this conventional protective view, indicating that caffeine may exert complex regulatory effects on the nigrostriatal dopaminergic system, and its long-term impact on the progression of established PD remains controversial^{12, 13}. Notably, few studies have systematically explored the direct link between caffeine consumption, striatal DAT dysfunction, and the longitudinal progression of core motor symptoms in PD patients, and the underlying molecular and neural mechanisms mediating this association are still unclear^{13, 14}.

Striatal DAT, a key biomarker of nigrostriatal dopaminergic integrity, is responsible for dopamine reuptake and regulates synaptic dopamine homeostasis^{15–17}. Reduced striatal DAT binding, as quantitatively detected by [¹²³I] FP-CIT single photon emission computed tomography (SPECT), is a well-validated pathological hallmark of PD and is closely correlated with the severity and progression of PD motor symptoms^{18, 19}. Accumulating evidence indicated that exogenous environmental factors could modulate striatal DAT availability, which might serve as a critical intermediate pathway linking lifestyle factors to PD motor dysfunction^{20, 21}. Nevertheless, whether caffeine consumption modulates PD motor symptoms and their progression by altering striatal DAT binding has not been empirically verified in human longitudinal cohorts.

Accordingly, the present study utilized high-quality longitudinal data from the Parkinson's Progression Markers Initiative (PPMI) database to systematically investigate the effects of caffeine consumption on striatal DAT binding and core motor symptoms in both healthy controls and PD patients. We further adopted mediation analysis to clarify the mediating role of striatal DAT dysfunction in the association between caffeine intake and PD motor abnormalities and employed generalized estimating equations (GEE) to explore the longitudinal impact of caffeine consumption on motor symptom progression. This study aims to clarify the complex regulatory effect of caffeine on PD pathogenesis and progression, provide objective imaging and clinical evidence for the caffeine-DAT-motor symptom regulatory pathway, and offer novel insights for lifestyle intervention and disease progression management in PD patients.

Materials and methods

Subjects

Data used in the present study were retrieved from the Parkinson's Progression Markers Initiative (PPMI) database (www.ppmi-info.org). A total of 83 healthy controls (HC) and 261 patients with idiopathic Parkinson's disease (PD) with available demographic, clinical, and [¹²³I] FP-CIT SPECT imaging data were included. All participants had completed questionnaires regarding caffeine consumption, which were obtained from the PPMI database. Based on caffeine intake status, participants were classified into three groups: current consumers (CC), former consumers (FC), and never consumers (NC). Participants who had regularly consumed caffeinated coffee at least once weekly for 6 months or longer were defined as CC if they continued drinking coffee, and FC if they had stopped. Accordingly, the HC group (n = 83) was subdivided into HC-CC (n = 54), HC-FC (n = 16), and HC-NC (n = 13). The PD group (n = 261) was divided into PD-CC (n = 123), PD-FC (n = 76), and PD-NC (n = 62). For longitudinal analyses, follow-up data from 1 to 4 years were downloaded for these PD patients. Only patients with at least two time points were included, yielding a final longitudinal sample of 207 PD patients (PD-CC, n = 96; PD-FC, n = 63; PD-NC, n = 48). A flowchart of participant inclusion was presented in Fig. 1. The PPMI study protocol was registered on June 8, 2010 (ClinicalTrials.gov identifier: NCT01141023)²².

This study was conducted in accordance with the Declaration of Helsinki. All data used in this study were obtained from the PPMI database. The original PPMI study was reviewed and approved by the PPMI Institutional Review Board. Written informed consent was obtained from all participants enrolled in the original PPMI study prior to data collection.

Clinical Data

All participants enrolled in the PPMI cohort underwent a standardized battery of clinical assessments. Demographic variables (age and sex) were collected, along with clinical measures including Hoehn and Yahr (H&Y) stage, Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) total scores, and sub-scores for rigidity, bradykinesia, and rest tremor amplitude. These sub-scores were computed as summed item scores for the total body and separately for the left and right sides. All clinical scale evaluations were performed while participants were in the medication-off state.

Striatal DAT Processing

Dopamine transporter (DAT) imaging was acquired using [¹²³I] FP-CIT single-photon emission computed tomography (SPECT) at PPMI imaging centers. SPECT datasets were sent to the Institute for Neurodegenerative Disorders for standardized processing. Detailed procedures are publicly available on the PPMI website (<https://www.ppmi-info.org/access-data-specimens/download-data/>). Striatal regions of interest (ROIs) were placed on the caudate and putamen as target regions, and the occipital cortex as the reference region²³. Count densities were extracted for each striatal ROI, and specific binding ratios (SBR) were calculated as:

$$\text{SBR} = (\text{target region counts} / \text{reference region counts}) - 1$$

Mean SBR values of the caudate and putamen were then computed for subsequent analyses.

Statistical analysis

All statistical analyses were performed using SPSS (Version 28.0, IBM Corporation) and MATLAB (R2025a, MathWorks, Inc.). Baseline demographic characteristics were compared between patients with PD and HC using independent t-tests or Mann–Whitney U tests for continuous variables and chi-square tests for categorical variables. The D'Agostino–Pearson omnibus test was applied to assess the normality of data distribution, and a two-tailed $p < 0.05$ was defined as the threshold for statistical significance.

General linear models (GLMs) were adopted for group comparisons of striatal DAT binding, including independent t-tests, one-way analysis of variance (ANOVA), and post hoc analyses, with age and gender included as covariates. The Bonferroni correction was applied to adjust for multiple comparisons.

Partial Spearman correlation analyses, adjusted for age and gender, were conducted to examine the associations between striatal DAT binding and unilateral motor symptom severity, including left- and right-sided extremity rigidity, bradykinesia, and rest tremor amplitude.

Mediation analysis was performed to explore the potential effect of caffeine consumption on the three cardinal motor symptoms of PD. In each mediation model, caffeine consumption grouping was treated as the categorical predictor, with the NC group defined as the reference group. Striatal SBR was specified as the mediating variable, and the individual scores of extremity rigidity, bradykinesia, and rest tremor amplitude were separately set as the outcome variables.

Generalized estimating equations (GEEs) were utilized for longitudinal analyses to evaluate the impact of caffeine consumption on the progression of PD cardinal motor symptoms. The grouping variable was included as the independent variable (NC group: reference, coded 0; CC group: experimental group, coded 1). Age at each follow-up was incorporated as the within-subject factor, and all participants had longitudinal data from at least two time points. The total score of each motor symptom was treated as the corresponding dependent variable. For all analyses, statistical significance was established at $p < 0.05$ (two-tailed).

Results

Demographics and clinical variables

Baseline demographic and clinical characteristics were compared between the PD group and the HC group. There were no significant between-group differences in age or sex (all $p > 0.05$) (Table 1).

Table 1
Demographic and clinical data

Age	PD	HC	T/ χ^2	P-value
	61.75 $\pm$ 0.5615	59.96 $\pm$ 1.140	1.511	0.1316
Gender (F/M)	91/170	28/55	2.658	0.103
HY	1.623 $\pm$ 0.03108	/		
UPDRS-III	22.24 $\pm$ 0.6218	/		
Rigidity (L/R/Total)	1.632 $\pm$ 0.09440 (L)	1.870 $\pm$ 0.09321 (R)	4.287 $\pm$ 0.1776 (Total)	/
Bradykinesia (L/R/Total)	4.701 $\pm$ 0.2324 (L)	3.877 $\pm$ 0.2010 (R)	10.05 $\pm$ 0.3552 (Total)	/
Rest tremor (L/R/Total)	1.552 $\pm$ 0.1139 (L)	1.594 $\pm$ 0.1138 (R)	4.575 $\pm$ 0.2162 (Total)	/
The data for subjects with successfully registered imaging data are presented. Abbreviations: HC=healthy control; PD=Parkinson's disease; HY=Hoehn & Yahr stage; and UPDRS= Unified Parkinson's Disease Rating Scale.				

Caffeine exerted PD-like effects by reducing striatal DAT binding

We first examined the pathological impact of PD on striatal DAT binding in the human brain. Relative to HC participants, PD patients exhibited significantly reduced DAT binding in all striatal subregions, including the bilateral caudate nucleus and putamen (all $p < 0.0001$) (Fig. 2A).

We next investigated the effects of caffeine on striatal DAT binding. One-way ANOVA revealed significant differences among caffeine subgroups within both the PD cohort and the HC cohort. Post hoc analyses in the PD cohort showed that CC displayed significantly lower DAT binding in the bilateral caudate and left putamen compared with NC ($p = 0.0058$, $p = 0.0234$, $p = 0.0307$, respectively; **Fig. 2BCE**). FC also exhibited significantly lower DAT binding in the left putamen relative to NC ($p = 0.0349$) (Fig. 2E).

Consistently, in the HC cohort, CC participants showed markedly reduced DAT binding in the bilateral caudate and putamen compared with NC ($p = 0.0035$, $p = 0.0033$, $p = 0.0007$, $p = 0.0094$, respectively; **Fig. 2BCDE**). Furthermore, CC had significantly lower DAT binding in the bilateral caudate than FC ($p = 0.014$, $p = 0.0242$, respectively) (Fig. 2BC).

Collectively, these findings revealed that caffeine, similar to the pathological changes in PD, reduced striatal DAT binding.

Close associations existed between striatal DAT binding and the three cardinal motor symptoms

Subsequently, we revealed the association between striatal DAT binding and three major motor symptoms. It should be noted that motor function in the human body is controlled by the contralateral cerebral hemisphere. Thus, whether DAT binding associated with each cardinal motor symptom (rigidity, bradykinesia, and rest tremor) on both sides of the body were evaluated separately. Consistent with previous studies, both left- and right-side rigidity, bradykinesia, and rest tremors

were all found that had significant negative associations with contralateral striatal DAT binding (Fig. 3). Besides, rest tremors of both body sides were also positive associated with DAT binding in the ipsilateral striatum (Fig. 3). This suggested that the striatum on both sides jointly influenced resting tremors through opposite modulatory effects.

The effect of caffeine on motor symptoms was fully mediated by striatal DAT binding

Given the effects of caffeine on the striatum and the close link between the striatum and motor function, it is natural to further explore the potential association between caffeine and motor symptoms. Thus, mediation analysis was performed to explore the potential effect of caffeine consumption on the three cardinal motor symptoms of the PD cohort. It should be noted that in the mediation effect analysis of this study, only CC and NC were included. The exposure status of the FC group was unstable due to the cumulative effects of previous caffeine intake and lag effects after caffeine cessation, which could not reflect the stable pathway of current caffeine intake affecting motor symptoms through the mediator variable striatal DAT binding. Therefore, the mechanism analysis was only conducted in the current stable exposure population to ensure the biological rationality and reliability of the mediation model. Furthermore, considering that the CC group exhibited significantly decreased DAT binding in the bilateral caudate nucleus and left putamen compared with the NC group, only the above striatal regions were included as mediator variables.

When the aforementioned striatal DAT binding was included as the mediator, caffeine showed regulatory effects on the three motor symptoms in a complete mediation pattern ($a*b$: 95% CI did not cross zero, c' : $p > 0.05$) (Fig. 4) (Table 2). Specifically, coffee consumption exerted a positive effect on rigidity and bradykinesia scores ($a*b$: $\beta > 0$ and $p < 0.05$). In other words, caffeine intake exacerbated rigidity and bradykinesia. In addition, we also observed contradictory effects of caffeine intake on resting tremors (negative effects on ipsilateral tremor scores ($a*b$: $\beta < 0$) and positive effects on contralateral tremor scores ($a*b$: $\beta > 0$)). Although the overall effect tended to be positive (caffeine intake aggravated resting tremor), neither of the two indirect effects was statistically significant ($a*b$: $p > 0.05$). Furthermore, in each mediation model, we repeated the analysis by replacing the binary caffeine intake variable (coded 1 for CC and 0 for NC) with a continuous measure of weekly coffee consumption (actual weekly cups in CC participants and 0 in NC participants). Consistent results were obtained (**Supplementary Materials**).

Table 2
Mediation analysis

Independent Variable	Mediator	Dependent Variable	a*b:β	a*b:95% CI		a*b:T	P-values			
				lower limit	upper limit		a*b	c'	a	b
Caffeine Consumption Grouping	Right Caudate SBR	Scores of left rigidities	0.232	0.074	0.427	2.577	0.01	0.557	0.006	<0.001
		Scores of left bradykinesias	0.621	0.205	1.128	2.617	0.009	0.626	0.006	<0.001
		Scores of left rest tremors	0.174	0.034	0.382	1.943	0.052	0.372	0.006	0.006
	Left Caudate SBR	Scores of right rigidities	0.194	0.035	0.399	2.122	0.034	0.124	0.023	<0.001
		Scores of right bradykinesias	0.389	0.067	0.802	2.067	0.039	0.578	0.023	<0.001
		Scores of left rest tremors	-0.123	-0.307	-0.007	-1.587	0.113	0.94	0.023	0.016
		Scores of right rest tremors	0.134	0.021	0.312	1.817	0.069	0.509	0.023	0.003
	Left Putamen SBR	Scores of right rigidities	0.139	0.017	0.303	1.929	0.054	0.084	0.031	<0.001
		Scores of right bradykinesias	0.422	0.047	0.89	1.986	0.047	0.618	0.031	<0.001
		Scores of left rest tremors	-0.146	-0.357	-0.01	-1.607	0.108	0.878	0.031	0.003
		Scores of right rest tremors	0.098	0.006	0.264	1.444	0.149	0.43	0.031	0.024

Bold values indicate significant differences. In each mediation model, caffeine consumption grouping was treated as the categorical predictor, with the NC group defined as the reference group. Bilateral caudate SBRs and left putamen SBR were specified as the mediating variable, respectively, and the individual scores of extremity rigidity, bradykinesia, and rest tremor amplitude were separately set as the outcome variables. a*b represented indirect effect; c' represented direct effect.

Caffeine intake exacerbated the progression of rigidity and bradykinesia

Following the identification that caffeine exerted a regulatory effect on motor function via complete mediation, we performed a longitudinal analysis to explore the direct evidence underlying the impact of caffeine on motor progression in PD. Of note, the total scores for each of the three motor symptom domains (rigidity, bradykinesia, and tremor) were used as dependent variables. The total rigidity score was derived from the sum of ratings for bilateral limbs and the neck. The total bradykinesia score included ratings for bilateral limbs, rising from a seated position, and global spontaneous movements. The total tremor score consisted of ratings for bilateral limbs, lips, chin, and persistence of tremors.

The GEE results demonstrated that disease progression of motor function differed significantly between the CC group and the NC group (Fig. 5) (Table 3). Specifically, participants in the CC group exhibited significantly faster progression of rigidity and bradykinesia over time compared with those in the NC group ($\beta = 0.863$, $z = 1.977$, $p = 0.048$ and $\beta = 2.503$, $z = 3.078$, $p = 0.002$). However, no significant group difference was observed in the longitudinal progression of tremor ($\beta = 0.599$, $z = 1.152$, $p = 0.249$).

Table 3
Longitudinal progress comparison of motor scores

Motor score progression		β	z	P-values
CC vs NC	Scores of total rigidities	0.863	1.977	0.048
	Scores of total bradykinesias	2.503	3.078	0.002
	Scores of total tremors	0.599	1.152	0.249

Bold values indicate significant differences. Generalized estimating equations (GEEs) were utilized for longitudinal analyses to evaluate the impact of caffeine consumption on the progression of PD cardinal motor symptoms. CC=current caffeine consumers; NC=never caffeine consumers.

Discussion

The present study systematically explored the effects of caffeine consumption on striatal DAT availability and core motor symptoms in PD patients based on cross-sectional and longitudinal PPMI cohort data and clarified the mediating mechanism of striatal DAT binding underlying caffeine-induced motor dysfunction. Our key findings demonstrated that long-term current caffeine consumption significantly reduced striatal DAT binding in both healthy individuals and PD patients, an effect similar to the dopaminergic depletion seen in PD pathology. Furthermore, reduced striatal DAT binding was tightly correlated with the severity of contralateral rigidity and bradykinesia, and showed divergent associations between ipsilateral and contralateral resting tremors. Mediation analysis further confirmed that striatal DAT dysfunction completely mediated the adverse effects of caffeine intake on rigidity and bradykinesia. Longitudinal GEE analysis ultimately verified that caffeine consumption accelerated the progressive deterioration of rigidity and bradykinesia in PD patients, while exerting no significant effect on resting tremor progression.

PD is pathologically characterized by impaired nigrostriatal dopaminergic function^{24, 25}. In line with this, we observed markedly reduced DAT binding in the bilateral caudate nucleus and putamen among PD patients relative to healthy controls. This finding agrees with prior neuroimaging reports and further supports the reliability of [¹²³I] FP-CIT SPECT for assessing nigrostriatal dopaminergic lesions^{26, 27}. Notably, our study found that caffeine consumption induced a PD-like pathological change of reduced striatal DAT binding in both HC and PD cohorts, suggesting that caffeine is an important environmental factor interfering with striatal dopaminergic function. Previous studies mostly focused on the preventive effect of caffeine on PD onset in healthy populations, while our findings innovatively revealed the adverse modulatory effect of sustained caffeine intake on established PD pathology, indicating that the role of caffeine in PD is stage-dependent: caffeine may reduce the risk of PD occurrence in the prodromal stage, but aggravates dopaminergic dysfunction in diagnosed PD patients^{13, 28}.

A major innovation of this study was the clarification of the complete mediating role of striatal DAT binding in the association between caffeine intake and PD motor symptoms. We found that current caffeine consumption significantly decreased DAT binding in bilateral caudate and left putamen, and these dopaminergic deficits further exacerbated the severity of rigidity and bradykinesia. The contralateral dominant correlation between striatal DAT binding and limb motor symptoms observed in our study was consistent with the classic neuroanatomical principle of contralateral motor control by the cerebral cortex and striatum^{29, 30}. Intriguingly, resting tremors showed dual correlations with ipsilateral and contralateral DAT binding, indicating that tremor regulation was mediated by bilateral striatal networks with opposite

modulatory effects, which might explain why caffeine showed no significant longitudinal effect on tremor progression in subsequent analyses. The unstable mediating effect of caffeine on resting tremor further suggests that the pathological mechanism of PD tremor was more complex than that of rigidity and bradykinesia, and might involve non-dopaminergic pathways such as the cerebellar-thalamic circuit ^{31–33}.

Longitudinal analysis was the most robust evidence for verifying the causal effect of caffeine on PD progression. Our GEE results demonstrated that regular caffeine intake significantly accelerated the progression of rigidity and bradykinesia over 1–4 years of follow-up, providing direct clinical evidence for the adverse impact of caffeine on PD disease progression. Rigidity and bradykinesia were the most typical motor symptoms dominated by nigrostriatal dopaminergic lesions, which are highly dependent on striatal DAT function and dopamine synaptic homeostasis ^{34–36}. Combined with the mediation results, we could conclude that long-term caffeine intake continuously reduced striatal DAT availability, impaired dopamine reuptake function, aggravated dopaminergic synaptic disorder, and ultimately accelerated the progressive deterioration of rigidity and bradykinesia in PD patients.

Notably, this study excluded former caffeine consumers in the mediation mechanism analysis, considering the residual and lagging effects of previous caffeine exposure, which ensured the stability and biological credibility of the causal pathway between current caffeine intake, DAT dysfunction, and motor symptoms ^{37–39}. This rigorous grouping strategy avoids the confounding bias of irregular caffeine exposure, making our mechanistic conclusions more reliable. In addition, the consistent results obtained by replacing binary caffeine grouping with continuous weekly coffee consumption further validated the dose-dependent adverse effect of caffeine on PD motor dysfunction and striatal dopaminergic damage.

This study has several strengths. First, the study was based on the multicenter, large-sample PPMI cohort with standardized clinical assessment and SPECT imaging processing protocols, ensuring the accuracy and reproducibility of data. Second, we combined cross-sectional correlation analysis, mediation mechanism exploration, and longitudinal progression verification, forming a complete evidence chain from phenotypic correlation to internal mechanism and causal progression.

Several limitations of this study should also be acknowledged. First, caffeine intake information was obtained from self-reported questionnaires, which might have inherent reporting bias. Second, this study only focused on coffee-derived caffeine intake and failed to distinguish the effects of different caffeine sources (tea, energy drinks, etc.) and other coffee components, which may interfere with the results. Third, although we confirmed the longitudinal progression effect of caffeine, the follow-up duration was limited to 4 years, and longer-term cohort data are needed to verify the persistent impact of caffeine on PD prognosis. Finally, this study was a clinical observational study, and further basic experimental studies were required to clarify the molecular mechanism by which caffeine regulates DAT expression and function.

In conclusion, the present study demonstrated that long-term current caffeine consumption induced striatal DAT reduction similar to PD pathological changes, and striatal dopaminergic dysfunction completely mediates the adverse effects of caffeine on PD rigidity and bradykinesia. Regular caffeine intake significantly accelerated the longitudinal progression of rigidity and bradykinesia in PD patients. These findings challenged the traditional protective view of caffeine in PD, suggested that caffeine was a harmful lifestyle factor for disease progression in diagnosed PD patients, and provided novel evidence for individualized lifestyle guidance and disease progression management for PD populations.

Abbreviations

PD

Parkinson's disease

DAT

dopamine transporter

PPMI

Parkinson's Progression Markers Initiative

HC
healthy controls
CC
current consumers
FC
former consumers
NC
never consumers
SPECT
single photon emission computed tomography
ROIs
regions of interest
SBR
specific binding ratios
GLMs
General linear models
ANOVA
analysis of variance
GEEs
Generalized estimating equations
H&Y
Hoehn and Yahr
UPDRS
Unified Parkinson's Disease

Declarations

Author's Roles

All authors of the paper have made significant contributions and are consistent with the content of the manuscript. Zhengye Cao and Na Wang were in charge of project design; Chao Wang, Hongying Zhang, and Song'an Shang was responsible for the inclusion of subjects; Zhengye Cao and Na Wang were in charge of data gathering and paper writing; Hongjie Hu, Na Wang, and Zhengye Cao was in charge of data analyses.

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Author Contribution

All authors of the paper have made significant contributions and are consistent with the content of the manuscript. Zhengye Cao and Na Wang were in charge of project design; Chao Wang, Hongying Zhang, and Song'an Shang was responsible for the inclusion of subjects; Zhengye Cao and Na Wang were in charge of data gathering and paper writing; Hongjie Hu, Na Wang, and Zhengye Cao was in charge of data analyses.

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Data and code availability statement

Some or all data, models, or code generated or used during the study are available from the corresponding author by request.

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Figures

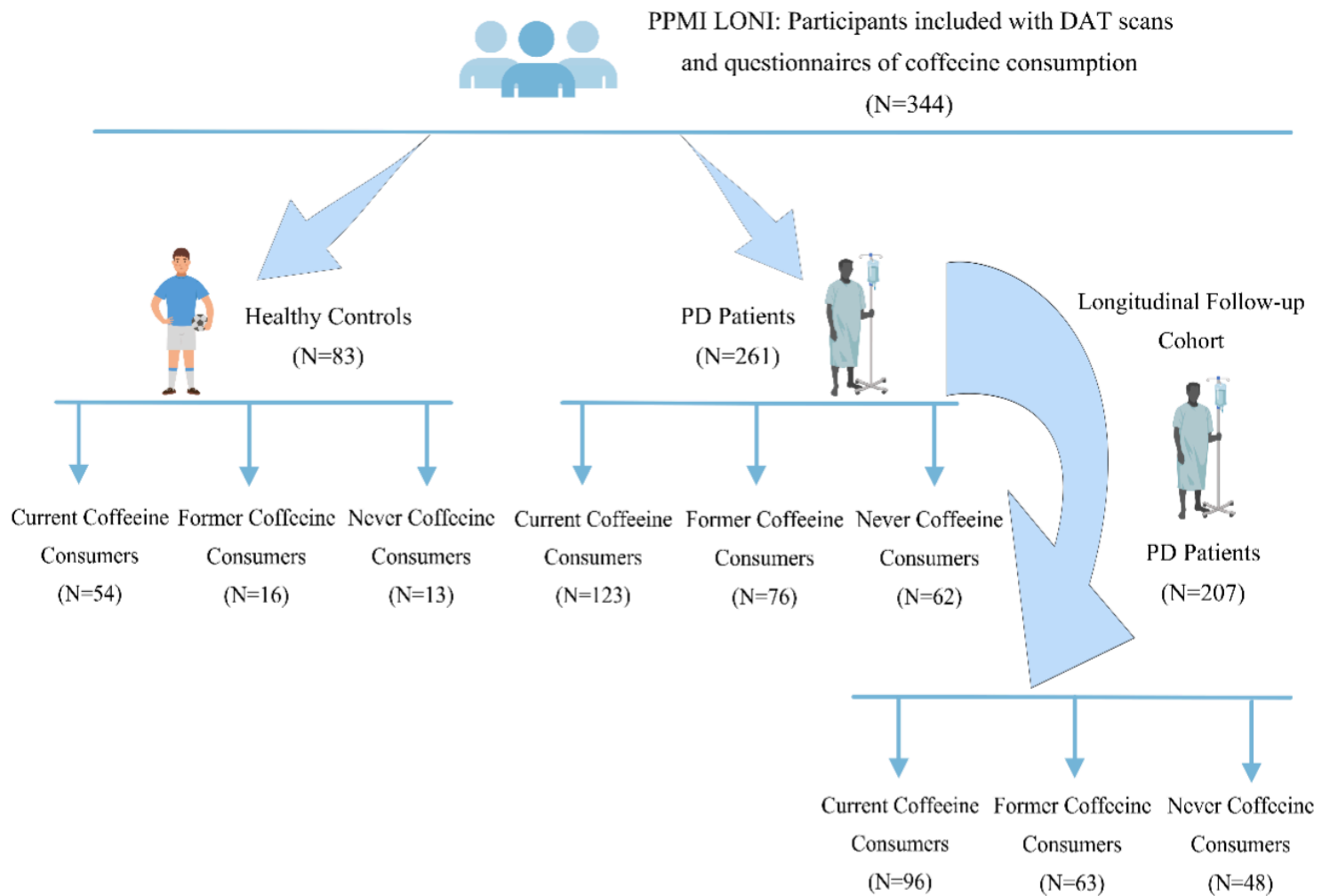


Figure 1

Flowchart shows participants' enrollment

The group comparisons were run with all patients with Parkinson's disease (PD) (N = 261) and healthy controls (N = 83). Longitudinal comparisons were run with 207 PD patients.

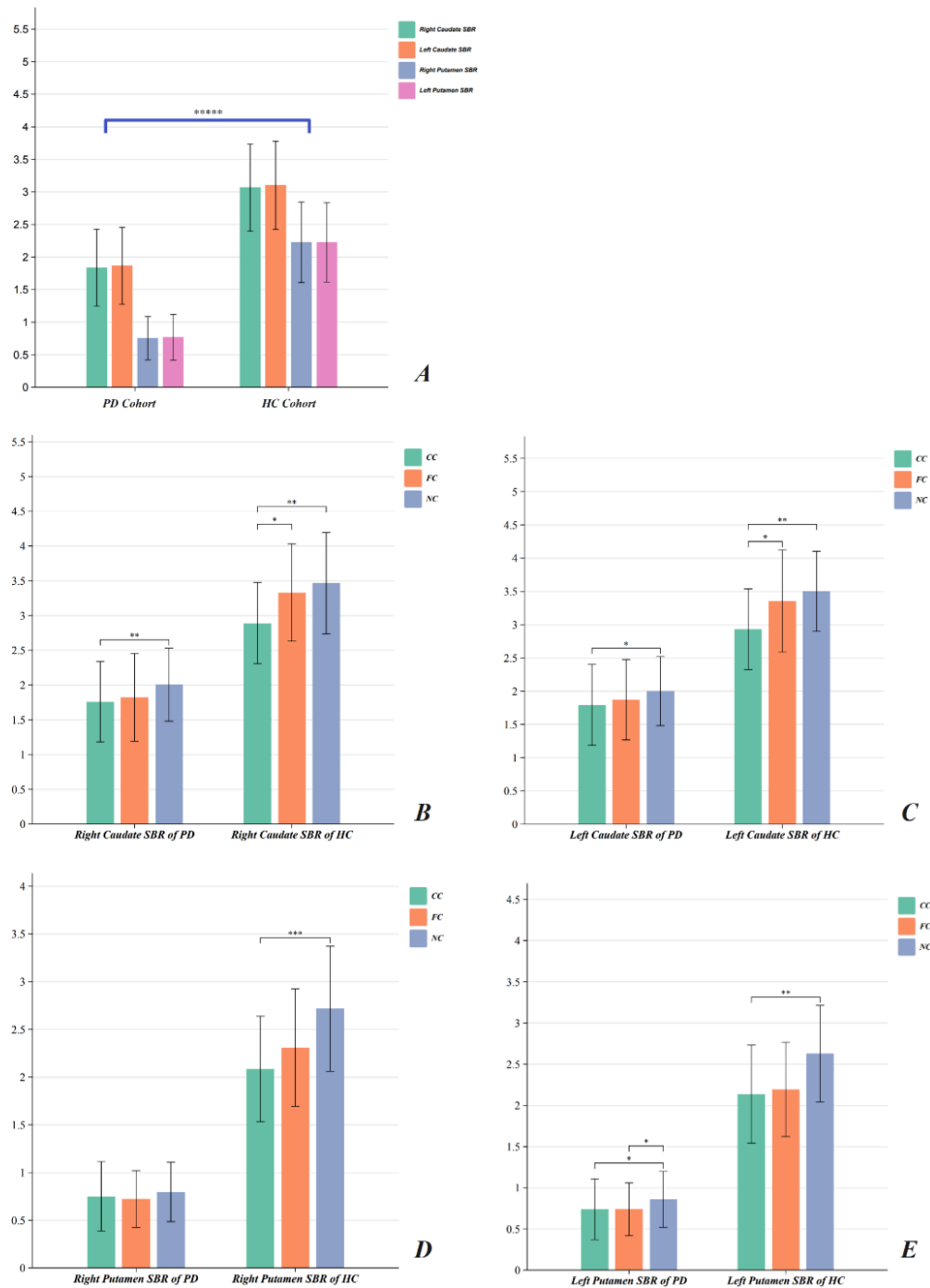


Figure 2

Striatal DAT binding comparisons

Relative to HC, PD patients exhibited significantly reduced DAT binding in all striatal subregions ($p < 0.0001$). In the PD cohort showed that CC displayed significantly lower DAT binding in the bilateral caudate and left putamen compared with NC ($p = 0.0058$, $p = 0.0234$, $p = 0.0307$). FC also exhibited significantly lower DAT binding in the left putamen relative to NC ($p = 0.0349$). In the HC cohort, CC participants showed markedly reduced DAT binding in the bilateral caudate and putamen compared with NC ($p = 0.0035$, $p = 0.0033$, $p = 0.0007$, $p = 0.0094$). Furthermore, CC had significantly lower DAT binding in

the bilateral caudate than FC ($p = 0.014$, $p = 0.0242$). CC=current caffeine consumer; FC=former caffeine consumer; NC=never caffeine consumer; SBR= specific binding ratios. *****, ***, **Bonferroni corrected; *Bonferroni uncorrected.

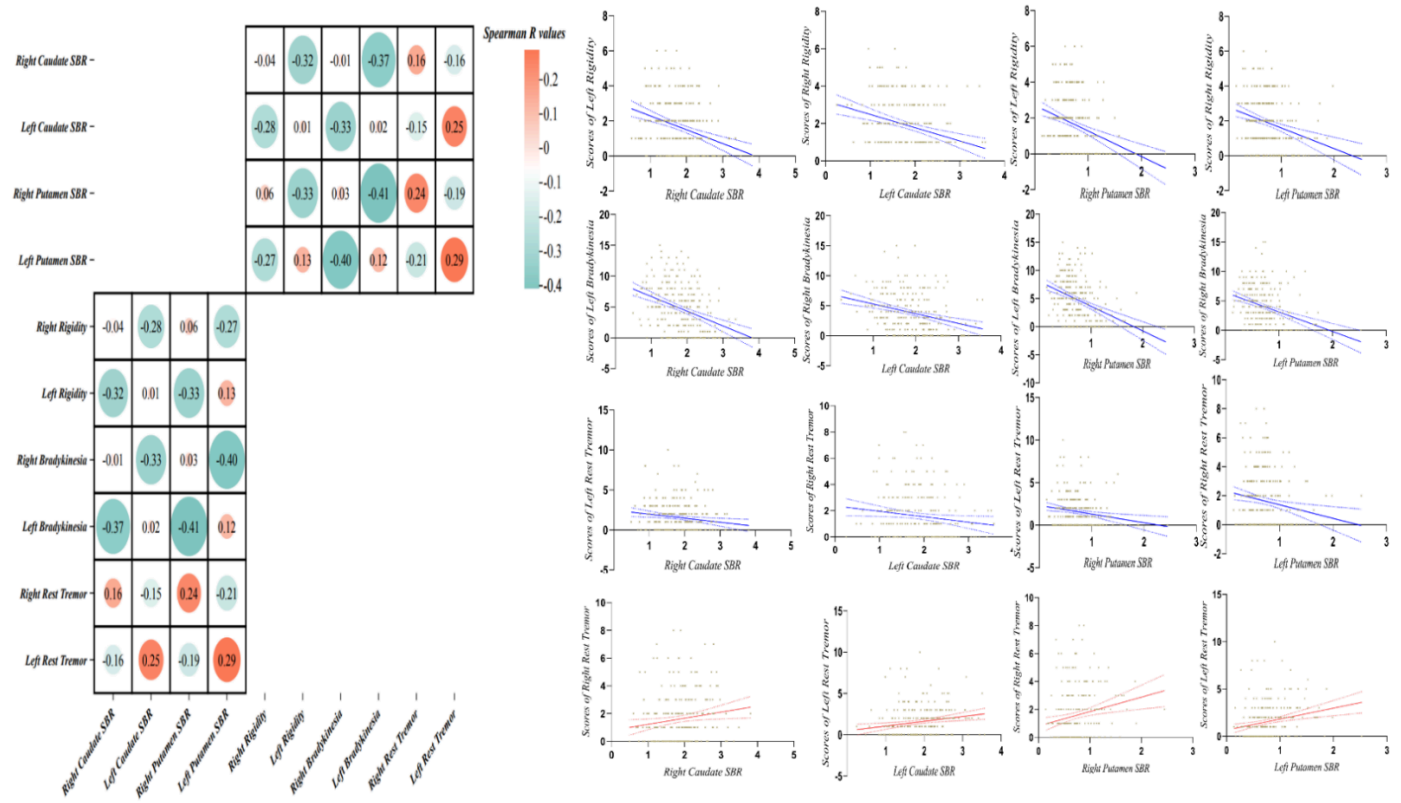


Figure 3

Association between cardinal motor symptom severity and striatal DAT binding

Both left- and right-side rigidity, bradykinesia, and rest tremors were all found that had significant negative associations with contralateral striatal DAT binding. Besides, rest tremors of both body sides were also positive associated with DAT binding in the ipsilateral striatum.

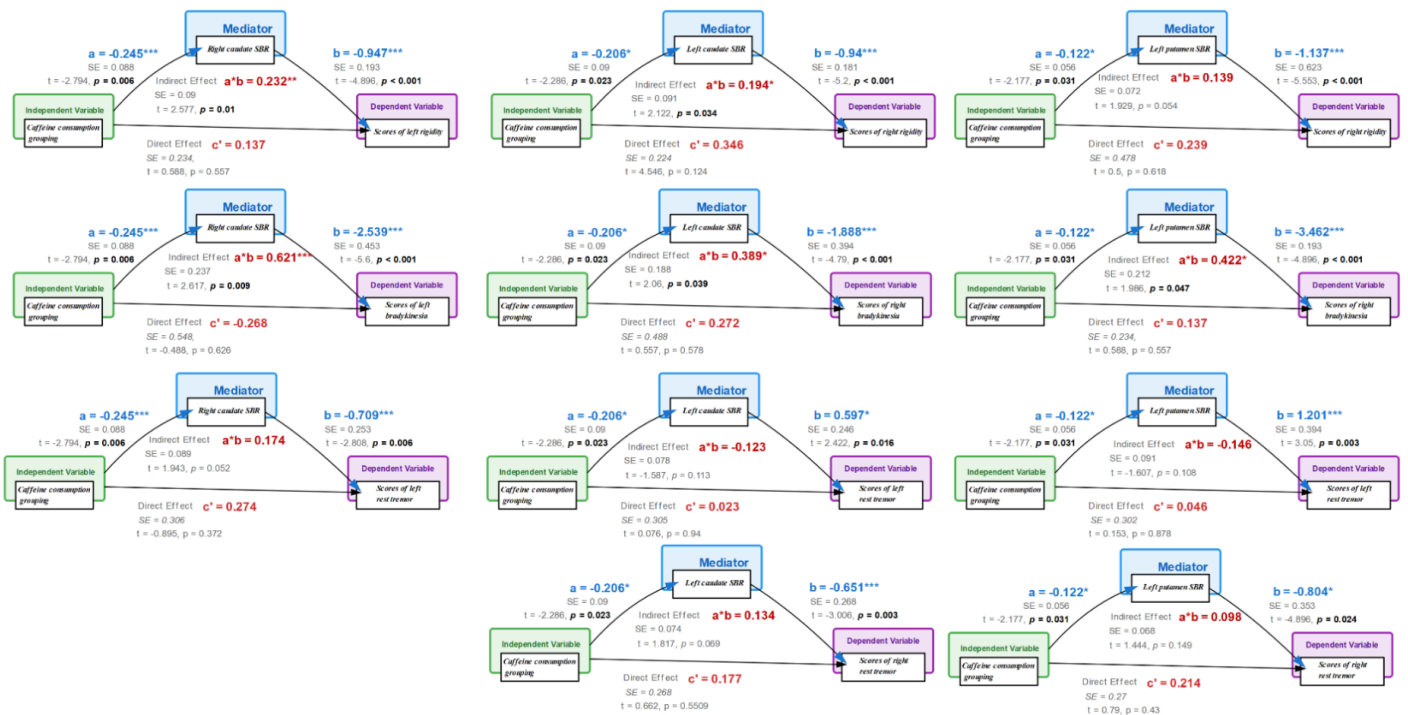


Figure 4

Mediation analysis

Caffeine showed regulatory effects on the three motor symptoms in a complete mediation pattern ($a*b$: 95% CI did not cross zero, c' : $p > 0.05$). CC exerted a positive effect on rigidity and bradykinesia scores ($a*b$: $\beta > 0$ and $p < 0.05$). In addition, we also observed contradictory effects of caffeine intake on resting tremors (negative effects on ipsilateral tremor scores ($a*b$: $\beta < 0$) and positive effects on contralateral tremor scores ($a*b$: $\beta > 0$)). However, neither of the two indirect effects were statistically significant ($a*b$: $p > 0.05$).

Fitted trend of average motor score progression between groups

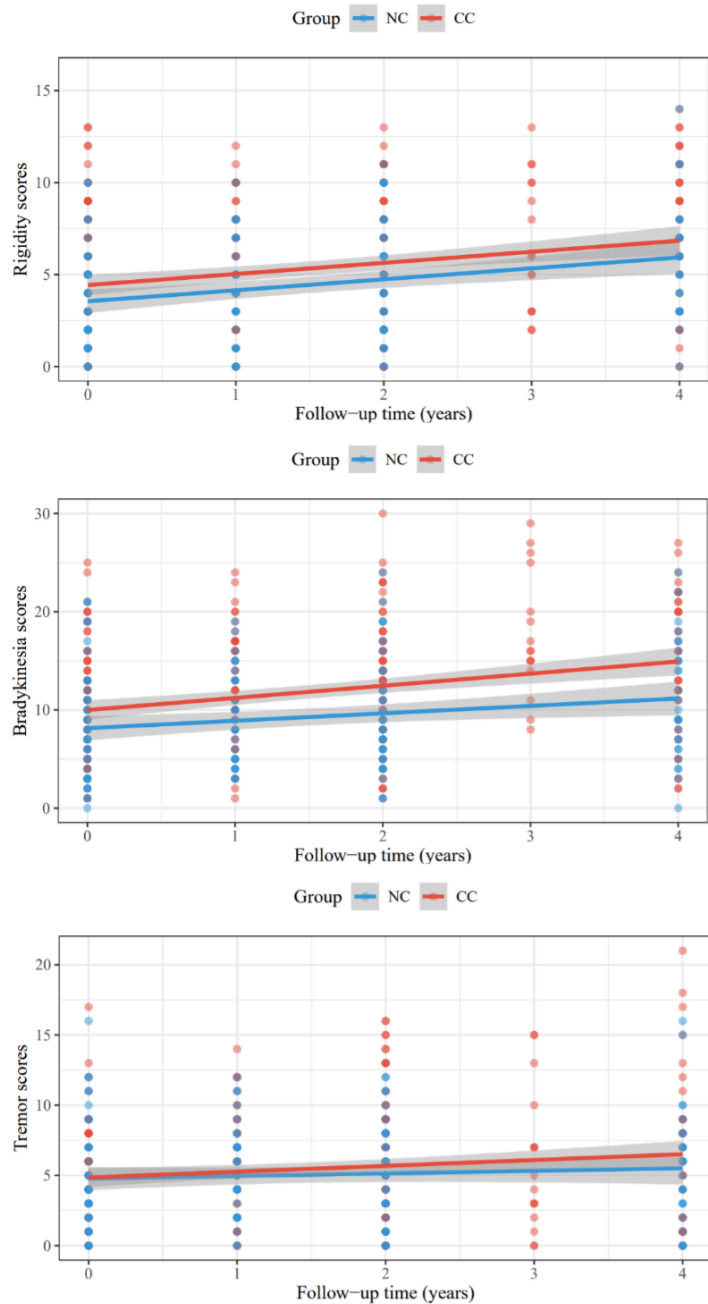


Figure 5

Progression of each cardinal motor symptom between CC and NC

Participants in the CC group exhibited significantly faster progression of rigidity and bradykinesia over time compared with those in the NC group. However, no significant group difference was observed in the longitudinal progression of tremor.

Supplementary Files

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- [SupplementaryMaterials.docx](#)