Dietary Caffeine and Brain Dopaminergic Function in Parkinson Disease

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Objective: This study was undertaken to investigate the effects of dietary caffeine intake on striatal dopamine function and clinical symptoms in Parkinson disease in a cross-sectional and longitudinal setting.
Methods: One hundred sixty-three early Parkinson disease patients and 40 healthy controls were investigated with [^{123}I]FP-CIT single photon emission computed tomography, and striatal dopamine transporter binding was evaluated in association with the level of daily coffee consumption and clinical measures. After a median interval of 6.1 years, 44 patients with various caffeine consumption levels underwent clinical and imaging reexamination including blood caffeine metabolite profiling.
Results: Unmedicated early Parkinson disease patients with high coffee consumption had 8.3 to 15.4% lower dopamine transporter binding in all studied striatal regions than low consumers, after accounting for age, sex, and motor symptom severity. Higher caffeine consumption was further associated with a progressive decline in striatal binding over time. No significant effects of caffeine on motor function were observed. Blood analyses demonstrated a positive correlation between caffeine metabolites after recent caffeine intake and dopamine transporter binding in the ipsilateral putamen.
Interpretation: Chronic caffeine intake prompts compensatory and cumulative dopamine transporter downregulation, consistent with caffeine's reported risk reduction in Parkinson disease. However, this decline does not manifest in symptom changes. Transiently increased dopamine transporter binding after recent caffeine intake has implications for dopaminergic imaging guidelines.

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Caffeine (1,3,7-trimethylxanthine) is the most extensively consumed psychostimulant worldwide.[1] Together with its various acute effects on wakefulness, motor coordination, and blood pressure,[2] regular consumption has been hypothesized to reduce the risk of Parkinson disease (PD).[3] This caffeine-induced risk reduction seems dose-dependent and has been observed in both case–control[4,5] and epidemiological studies, including prospectively followed cohorts.[6–10] Experiments with animal models, such as the 1-methyl-4-phenyl 1,2,3,6-tetrahydropyridine (MPTP) neurotoxin and alpha-synuclein models, have additionally provided evidence of the neuroprotective effects of caffeine in PD-type neurodegeneration.[11,12] Notably, decaffeinated coffee fails to provide the same protective benefits, highlighting the specific mechanistic role of caffeine itself rather than other chemical compounds present in coffee and caffeine-containing products.[13]

Although the positive effects of caffeine on PD prevention are well documented, the impact of caffeine on symptomatic individuals already diagnosed with PD is unclear despite several studies on this topic. In one controlled randomized trial of PD patients undergoing 6–18 months of treatment with caffeine, there was no clinical improvement, but there was increased dyskinesia, leading to the conclusion that caffeine cannot be recommended as symptomatic therapy for parkinsonism.[14] However, this trial focused on symptomatic therapy and did not address the potential of caffeine for disease modification. On the other hand, a meta-analysis of 4 studies with follow-up periods ranging from 4 to 10 years suggested that caffeine consumption in patients with early PD may slow disease progression.[15] Nevertheless, only 4 studies were included in the meta-analysis, and there was substantial heterogeneity in the parameters used to assess both caffeine consumption and PD progression in these studies, which limits the generalizability of their findings.

Caffeine-induced modification of the nigrostriatal dopamine system could be one of the underlying factors in the possible protection against PD. Caffeine modulates dopaminergic function in the central nervous system by interacting with adenosine receptors, which are colocalized and functionally interact with dopamine receptors.[16,17] This adenosine–dopamine interaction has been proposed to play a role in the pathogenesis and treatment of PD,[11,18,19] leading to the testing of multiple adenosine A_{2A} receptor antagonists as potential PD treatments.[20] Human dopaminergic functional imaging studies focusing on caffeine have indicated that typical dietary doses of caffeine can increase postsynaptic dopamine D2/D3 receptor availability.[21,22] However, the results of presynaptic dopamine transporter (DAT) imaging studies in PD patients have yielded mixed results, with one study reporting no significant changes in striatal DAT binding after chronic coffee consumption,[23] whereas another has observed lower caudate nucleus DAT binding in coffee-drinking PD patients than in nonconsumers.[24] The long-term effects of caffeine consumption on brain presynaptic dopamine function or PD progression have not yet been examined.

Our study was designed to test the hypothesis that caffeine improves dopaminergic function in PD patients and enhances motor function in the long term. To elucidate this matter, we conducted a study to investigate the dopaminergic effects of caffeine in PD patients in a cross-sectional and longitudinal setting using conventionally available brain DAT imaging.

Subjects and Methods

Participants

Part I. The cross-sectional part of the study included 163 patients diagnosed with PD and 40 healthy controls. PD patients underwent [^{123}I]-N-(3-fluoropropyl)-2β-carboxymethoxy-3β-(4-iodophenyl) nortropane ([^{123}I]FP-CIT) single photon emission computed tomography (DAT-SPECT) imaging for diagnostic purposes, and all PD patients had abnormal, reduced striatal DAT binding. The imaging sites were Turku University Hospital and Helsinki University Medical Imaging Center in Finland as part of the NMDAT project (ClinicalTrials.gov NCT02650843). Of the 163 PD patients, 115 were de novo unmedicated, 47 were receiving antiparkinsonian dopaminergic medications at the time of imaging, and one patient did not have medication data and was excluded from the unmedicated group (Table 1). For the medicated patients, the median L-dopa equivalent daily dose was 300.0mg (interquartile range [IQR] = 305.0mg). PD diagnoses were clinically confirmed by two movement disorder specialists after a median follow-up of 3.0 years (range = 0.1–5.9 years) based on the symptoms, signs, progression, L-dopa response, and DAT-SPECT results. The exclusion criteria for healthy controls were current medications acting on the central nervous system, current neurological symptoms, or any relevant prior neurological or psychiatric diseases. PD and control participants with moderate or severe dementia (Mini-Mental State Examination [MMSE] < 18) were excluded from the study.[25]

Part II. The longitudinal prospective part of the study was conducted in Turku University Hospital, Finland. PD patients who had participated in Part I and were treated in Turku University Hospital (n = 105) were contacted, and 44 PD patients volunteered to participate in Part II, with 29 patients having been unmedicated at Part I. Thus, PD patients of Part II underwent examination and scanning twice, with a median interval of 6.1 years (range = 2.3–7.6 years). At the Part II visit, patients were again clinically examined 2–4 hours prior to imaging, using the same tests and questionnaires as in Part I.

Clinical Evaluation Procedures

All participants underwent several clinical examinations 2–4 hours before imaging. The examinations included a clinical interview and administration of Part III of the International

TABLE 1. Demographic and Clinical Characteristics of the Cross-Sectional Cohort in Part I (unmedicated PD patients and healthy controls)

	Low Coffee Consumers (0–3 cups/day)	High Coffee Consumers (>3 cups/day)	*p* (low vs high coffee consumers)
Unmedicated PD patients			
n	57	58	–
Coffee consumptions			
Coffee, cups/day	2.0 [2]	5.0 [3]	<0.001***
Demographics			
Age, yr	66.0 [16]	67.0 [13]	0.80
Sex, M/F	20/37	33/25	0.019*
Motor symptoms			
Hoehn and Yahr stage	2.0 [1]	2.0 [1]	0.49
Motor symptom duration, mo	15 [14]	18 [24]	0.62
MDS-UPDRS motor	34.5 (15.0)	36.5 (15.1)	0.50
Nonmotor symptoms			
NMSS total	34.5 [48]	43.0 [56]	0.50
PDQ-8	6.3 [25]	9.4 [22]	0.97
MMSE	28 [3]	27 [3]	0.27
BDI	6.0 [8]	6.0 [8]	0.45
Alcohol and nicotine			
Alcohol, drinks/wk	1.0 [3]	1.0 [6]	0.13
Daily nicotine use, yes/no[a]	4/53	7/51	0.36
Striatal DAT binding			
Caudate right	2.27 [0.68]	2.00 [0.58]	0.004**
Caudate left	2.16 [0.90]	1.98 [0.75]	0.049*
Putamen right	1.49 [0.93]	1.26 [0.62]	0.049*
Putamen left	1.44 [0.83]	1.23 [0.58]	0.015*
Healthy controls			
n	22	18	-
Coffee consumptions			
Coffee, cups/day	2.0 [1]	6.0 [5]	<0.001***
Demographics and motor function			
Age, yr	69.1 (9.1)	64.0 (8.3)	0.073
Sex, M/F	10/12	11/7	0.32
MDS-UPDRS motor	7.0 [9]	4.5 [6]	0.53
Nonmotor symptoms			
NMSS total	11.5 [14]	8.0 [18]	0.86
MMSE	29 [3]	28 [3]	1.0
BDI	1.0 [2]	0 [6]	0.72
Alcohol and nicotine			
Alcohol, drinks/wk	2.0 [6]	1.0 [4]	0.76
Daily nicotine use, yes/no[a]	1/21	2/16	0.58
Striatal DAT binding			
Caudate right	2.50 (0.28)	2.60 (0.34)	0.29
Caudate left	2.59 (0.36)	2.64 (0.38)	0.69
Putamen right	2.33 (0.31)	2.37 (0.33)	0.75
Putamen left	2.29 (0.35)	2.36 (0.35)	0.53

Note: Values are n, median [interquartile range] or mean (standard deviation). *P* values are from chi-squared or Fisher exact tests, Mann–Whitney *U* tests, or independent samples *t* tests.

Abbreviations: BDI = Beck Depression Inventory; DAT = dopamine transporter; F = female; M = male; MDS-UPDRS = Movement Disorder Society's Unified Parkinson's Disease Rating Scale; MMSE = Mini-Mental State Examination; PD = Parkinson disease; PDQ-8 = Parkinson's Disease Questionnaire.

[a]Cigarettes, snus, or nicotine from other sources.

*$p < 0.05$;

**$p < 0.01$;

***$p < 0.001$.

Parkinson and Movement Disorder Society's Unified Parkinson's Disease Rating Scale (MDS-UPDRS),[26] the MMSE,[27] the Non-Motor Symptoms Scale,[28] the Parkinson's Disease Questionnaire (PDQ-8),[29] and the Beck Depression Inventory (BDI).[30] The MDS-UPDRS Training Program and Exercise was completed successfully by all examiners. Among the PD patients, one patient had missing data regarding the MDS-UPDRS motor score. The examinations for Part I were conducted between 2014 and 2019. Data for Part II were collected during the years 2021–2022.

Ethics and Informed Consent

The study was approved by the ethics committee of the Turku University Hospital (decision No. 3/1801/2021) and was conducted following the principles of the Declaration of Helsinki. Informed consent was obtained from all participants in Parts I and II.

SPECT Imaging and Image Preprocessing

Participants were injected with 185MBq of the radiopharmaceutical [^{123}I]FP-CIT 3 hours before SPECT imaging. To protect the thyroid from radiation, participants were administered either 250 or 300mg of potassium perchlorate or potassium iodine tablets (130mg) 30–60 minutes prior to the radiopharmaceutical injection.

SPECT imaging acquisition for Part I was performed using one of 6 SPECT/computed tomography (CT) devices. Prior to the study, all SPECT/CT devices were calibrated using a striatal phantom (RSD; Radiology Support Devices, Long Beach, CA) following a recommended calibration procedure.[31,32] All follow-up images for Part II were obtained with one device (Symbia T6 Series SPECT/CT; Siemens Healthineers, Erlangen, Germany). The SPECT images were reconstructed using HybridRecon Neurology version 3.0.1. (Hermes Medical Solutions, Stockholm, Sweden), with 3-dimensional ordered-subsets expectation maximization algorithm. The SPECT imaging protocol was implemented in accordance with the recommendation of the European Association of Nuclear Medicine.[33]

Region of Interest Analyses

The reconstructed SPECT images for both parts were analyzed using BRASS analysis software (version 2.6; Hermes Medical Solutions, Stockholm, Sweden). Specific binding ratios (SBRs) of DAT were calculated for each of the 6 subregions of the striatum, namely, the left and right anterior putamen, posterior putamen, and caudate (regions of interest [ROIs]), using the occipital cortex as the reference tissue. SBRs were calculated using the following formula:

$$\mathrm{SBR} = \left(\mathrm{SBR}_{\text{caudate or putamen}} - \mathrm{SBR}_{\text{occipital}}\right)/\mathrm{SBR}_{\text{occipital}}.$$

To obtain the mean level of DAT binding in the putamen, the SBRs of the anterior and posterior putamen were averaged. For the analysis of Part II, baseline and follow-up DAT images were reconstructed at the same time using identical preprocessing settings. Age, sex, and MDS-UPDRS motor scores or changes in MDS-UPDRS motor scores (Part II) were used as covariates in the analyses. In Part II, both absolute and yearly adjusted changes in DAT binding were investigated.

Voxelwise Analyses

The reconstructed and preprocessed DAT-SPECT images were averaged, and nonlinearly registered to MNI space using a [^{123}I] FP-CIT template in MNI space using both the ANTs[34] linear registration function and SPM[35] "Old Normalize" function. These transformations were applied to each individual SPECT image. The images were smoothed with an 8mm full width at half maximum Gaussian kernel. Cluster-level familywise error-corrected p values < 0.05 were considered significant. For details, see Supplementary Methods.

Evaluation of Caffeine Consumption

In both Part I and Part II of the study, coffee consumption was assessed on the day of DAT imaging by asking the participants to self-report their average daily intake of cups or mugs of coffee (where one mug equals two cups). For Part II, the sizes of cups and mugs were also clarified using visual aids, including pictures and volumes specified in the form (1 cup = 1.25dl, 1 mug = 2.5dl), and caffeine consumption was additionally assessed with a 2-week diary in which participants completed a questionnaire about their consumption of 31 specific caffeine-containing products, known as the Caffeine Consumption Questionnaire-Revised (CCQ-R; Supplementary Methods).[36,37]

Blood Measurements

Whole blood samples were collected from the participants in Part II for targeted metabolite profiling analysis. Blood was drawn immediately before tracer injection, and participants were provided with explicit instructions to abstain from consuming coffee or any products containing caffeine for a minimum of 3 hours prior to blood sampling and thereafter until DAT-SPECT imaging. The blood sampling procedure was conducted at 11:00 AM, 1.5 hours prior to radiopharmaceutical injection and 4.5 hours prior to imaging, and the samples were sent to the LC–MS Metabolomics Center, Biocenter Kuopio, University of Eastern Finland for analysis. Three patients had missing data for the blood analysis.

The quantification of caffeine and its 3 main metabolites (paraxanthine, theobromine, and theophylline) was conducted using liquid chromatography and high-resolution mass spectrometry, following a previously published method.[38] The analysis utilized a liquid chromatograph (Vanquish UPLC system; Thermo Fisher Scientific, Waltham, MA), a mass spectrometer (Q- Exactive Focus orbitrap mass spectrometer; Thermo Fisher Scientific, Bremen, Germany), and XCalibur 4.1.31.9 and TraceFinder 4.1 software tools (Thermo Fisher Scientific).

Statistical Analyses

Statistical analysis was performed using IBM SPSS Statistics (version 29; SPSS, Chicago, IL). The normality of variables was assessed using histograms and Shapiro–Wilk tests. The data are presented as the mean (standard deviation [SD]), median [IQR], or n. Group differences were calculated using chi-squared or Fisher exact tests for categorical variables and Mann–Whitney U tests or independent samples t tests for continuous variables. The differences in demographic and clinical characteristics between baseline and follow-up were analyzed with McNemar test for binary variables and Wilcoxon signed rank test or paired-samples t test for continuous variables. An analysis of covariance model was employed to investigate the relationships between coffee/caffeine intake and striatal DAT binding, with age, sex, and MDS-UPDRS motor score or disease duration serving as covariates. The level of statistical significance was set at $p < 0.05$. To account for multiple comparisons, false discovery rate (FDR) adjustment according to Benjamini–Hochberg was performed for striatal subregions.

Results

Cross-Sectional Analysis (Part I)

The median coffee consumption of all participants was 3 cups per day (IQR = 3, range = 0–16 cups per day), and this level was used as the threshold for classifying the participants into high and low caffeine intake groups. The demographic and clinical characteristics of the unmedicated PD patients are presented in Table 1, and the characteristics of the entire PD sample are provided in Supplementary Table S1. There were no differences in demographic characteristics between the groups apart

from a higher proportion of male PD patients in high consumers (57%) compared to low consumers (35%; see Table 1). Additionally, there was no difference in nicotine use or MMSE scores between unmedicated PD patients with high and low coffee consumption. MMSE scores did not correlate with striatal DAT binding ($p > 0.13$). Unmedicated de novo PD patients with high coffee consumption (>3 cups per day, median = 5 cups per day; n = 58) had lower DAT binding in all studied striatal regions compared to unmedicated de novo PD patients with low coffee consumption (0–3 cups per day, median = 2 cups per day; n = 57), both without considering covariates (Fig 1) and after controlling for the effects of age, sex, and MDS-UPDRS motor score (right putamen: $F[1, 109] = 5.43$, $p = 0.022$; left putamen: $F[1, 109] = 8.26$, $p = 0.005$; right caudate: $F[1, 109] = 9.76$, $p = 0.002$; left caudate: $F[1, 109] = 4.67$, $p = 0.033$). High coffee consumption was also associated with lower tracer binding in the raphe nucleus ($F[1, 109] = 5.12$, $p = 0.026$), but not in the nucleus accumbens ($p = 0.24$). The relative differences were 7.2% for the raphe nucleus and 8.3 to 15.4% for the striatum, with the largest difference observed in the right caudate, in which there was 15.4% lower DAT binding in patients with high coffee consumption than in those with low coffee consumption. The adjusted mean differences are presented in Supplementary Table S2. No significant hemispheric differences were observed (ie, between left vs right, higher DAT vs lower DAT, and ipsilateral vs contralateral). The striatal results retained significance after applying FDR correction.

Although no significant differences were found in the medicated PD patients alone (n = 47), similar results to the unmedicated PD patients were observed in the entire PD sample (n = 163) when considering the same covariates (Supplementary Results). No significant differences were found in the healthy controls (n = 40). Additionally, no differences were observed between tremor-predominant and imbalance predominant PD subtypes (Supplementary Results).

Longitudinal Analysis (Part II)

The demographic and clinical characteristics of the longitudinal cohort are presented in Table 2. In initially unmedicated PD patients (n = 29), a high daily caffeine intake was associated with a greater annual decrease in DAT binding in the right putamen when controlling for age at baseline, sex, and annual change in MDS-UPDRS motor score ($F[1, 24] = 7.83$, $p = 0.010$). Similar results were observed in the left putamen ($F[1, 24] = 6.14$, $p = 0.021$) and the left caudate ($F[1, 24] = 5.09$, $p = 0.033$) but not in the right caudate ($p > 0.19$). This finding is consistent with the results presented in Table 3 from Spearman correlation tests. The adjusted regression coefficients can be found in Supplementary Table S3. The effect of caffeine on DAT binding in the right putamen was also significant without considering covariates (Fig 2). The primary results remained the same after FDR correction (DAT change in the right putamen: $p = 0.040$, the left putamen: $p = 0.041$, the right caudate $p = 0.20$, the left caudate $p = 0.045$). Using disease duration, sex, and age as covariates, results were similar. However, also the association between the annual change in the left caudate DAT binding and daily caffeine consumption showed statistical significance when disease duration was used as a covariate instead of the change in MDS-UPDRS motor score ($p = 0.016$ vs $p > 0.05$). There were no significant associations observed between daily caffeine intake and annual changes in tracer binding in either the raphe nucleus or the nucleus accumbens ($p > 0.51$).

In the entire longitudinal PD sample (n = 44), associations did not remain statistically significant after FDR correction. In medicated patients (n = 15), when L-dopa equivalent dose, sex, and age were used as covariates, the results remained nonsignificant ($p > 0.18$). Inclusion of the baseline SPECT imaging device as a covariate did not change the main results (eg, right putamen unmedicated patients: $F[1, 22] = 11.7$, $p = 0.002$; full sample: $F[1, 37] = 5.55$, $p = 0.024$). Annual rates of motor progression (change in MDS-UPDRS motor score) did not associate with caffeine intake or concentrations of caffeine and its metabolites ($p > 0.15$).

Voxelwise Analyses

Voxelwise analyses confirmed the ROI findings, showing widespread lower SBRs in the entire striatum (Fig 3A) and faster SBR decline during the follow-up in almost all striatal voxels (see Fig 3B), and no specific striatal subregions were significantly associated with caffeine intake in either of these analyses.

Blood Analyses

The concentrations of paraxanthine, theophylline, and theobromine are presented in Supplementary Table S4. The concentrations of paraxanthine and theophylline positively correlated with DAT binding in the putamen ipsilateral to the predominant motor symptoms of PD (theophylline: $r = 0.45$, $p = 0.005$; paraxanthine: $r = 0.39$, $p = 0.017$). A similar correlation of these concentrations with higher DAT binding was observed in the putamen (paraxanthine: $r = 0.318$, $p = 0.045$; theophylline: $r = 0.387$, $p = 0.014$). The positive correlation between theophylline concentration and ipsilateral putamen DAT binding was significant also when the effects of

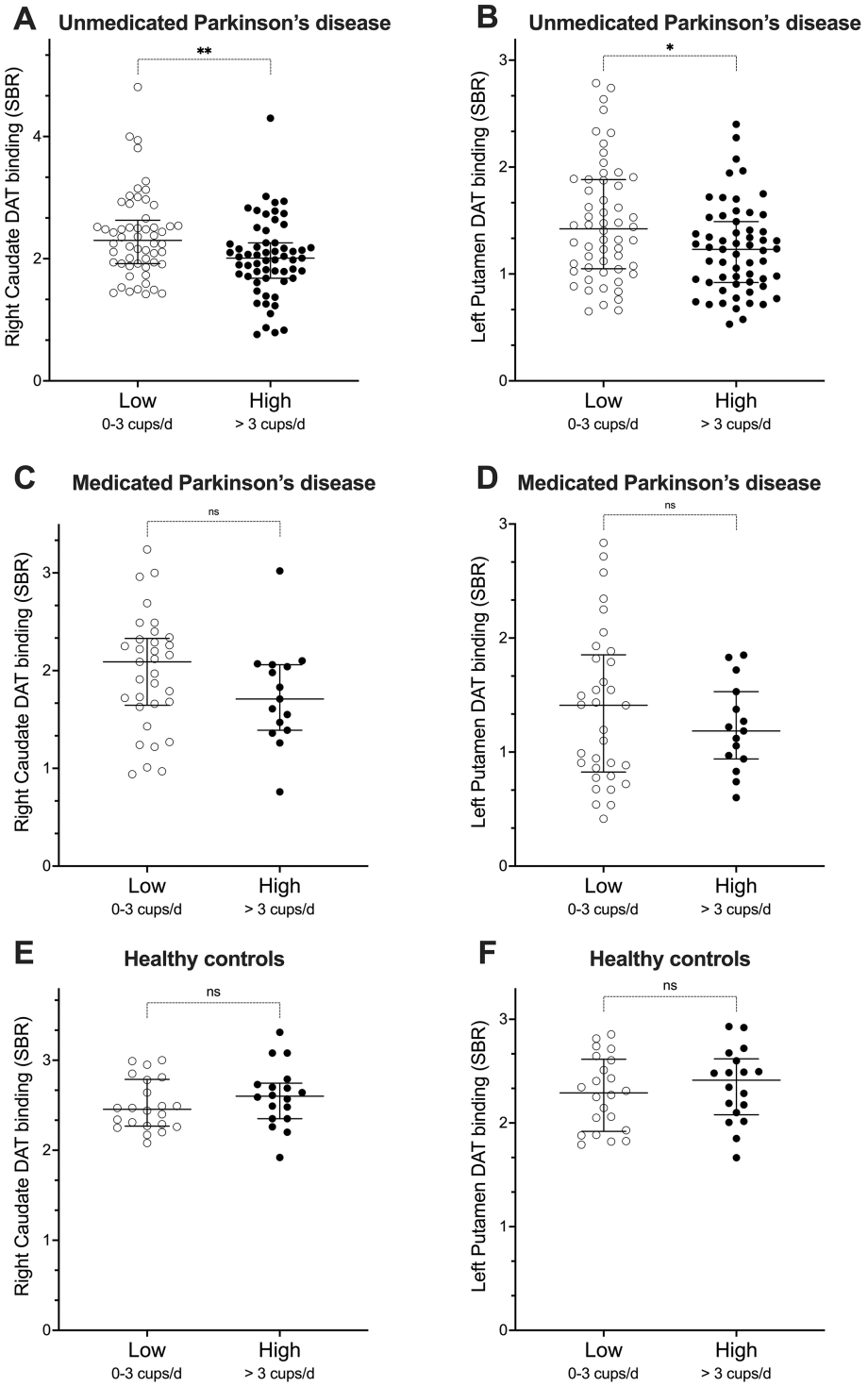

FIGURE 1: Dopamine transporter (DAT) binding differences in individuals with high and low daily coffee consumption (Part I). (A) DAT specific binding ratios (SBRs) in the right caudate of unmedicated Parkinson disease (PD) patients. (B) DAT binding in the left putamen of unmedicated PD patients. (C) DAT binding in the right caudate of medicated PD patients. (D) DAT binding in the left putamen of medicated PD patients. (E) DAT binding in the right caudate of healthy controls. (F) DAT binding in the left putamen of healthy controls. *$p < 0.05$, **$p < 0.01$; ns = nonsignificant.

age, sex, and MDS-UPDRS were accounted for ($F[1, 32] = 8.67$, $p = 0.006$). No significant correlations were observed with the contralateral/lower putamen or the caudate nucleus of either hemisphere ($r < 0.25$, $p > 0.12$; Fig 4).

The median concentration of caffeine in the blood was 1,012.7ng/ml (range = 1.0–4,044.6ng/ml). There were positive correlations between caffeine, paraxanthine, and theophylline concentrations and daily coffee consumption

TABLE 2. Demographic and Clinical Characteristics of the Longitudinal Cohort in Part II

Patients	Baseline	Follow-up	*p* (baseline vs follow-up)
Unmedicated at baseline			
Demographics			
Age, yr	63.3 (10.1)	68.9 (10.0)	<0.001***
Sex, M/F	12/17		–
Coffee consumption			
Coffee, cups/day	4 [4]	3 [4]	0.22
Motor symptoms			
Hoehn and Yahr stage	2.0 [1]	2.0 [0]	0.059
LEDD, mg	0 (0)	510 (298)	<0.001***
MDS-UPDRS motor	31.9 (12.6)	26.6 (16.7)	0.048*
Nonmotor symptoms			
NMSS total	40.0 [35]	43.0 [33]	0.81
PDQ-8	6.3 [15.6]	12.5 [24.3]	0.034*
MMSE	28 [2]	28 [3]	0.27
BDI	5.0 [8.0]	5.0 [5.0]	1.0
Alcohol and nicotine			
Alcohol, drinks/wk	1 [4]	0 [2]	0.022*
Daily nicotine use, yes/no[a]	2/27	1/28	1.0
Striatal DAT binding			
Caudate right	2.08 (0.44)	1.52 (0.34)	<0.001***
Caudate left	2.23 (0.53)	1.58 (0.40)	<0.001***
Putamen right	1.26 (0.33)	0.90 (0.31)	<0.001***
Putamen left	1.31 (0.44)	0.96 (0.31)	<0.001***
Medicated at baseline			
Demographics			
Age, yr	64.2 (9.1)	69.1 (9.0)	<0.001***
Sex, M/F	9/6		–
Coffee consumption			
Coffee, cups/day	4 [3]	2 [2]	0.50
Motor symptoms			
Hoehn and Yahr stage	2.0 [0]	2.0 [2]	0.11
LEDD, mg	393 (218)	791 (401)	<0.001***
MDS-UPDRS motor	40.9 (13.8)	36.8 (17.9)	0.30
Nonmotor symptoms			
NMSS total	38.0 [56]	61.0 [63]	0.28
PDQ-8	15.6 [15.6]	9.0 [38]	0.41
MMSE	28 [2]	27 [5]	0.048*
BDI	6.0 [10]	8.0 [5]	0.71
Alcohol and nicotine			
Alcohol, drinks/wk	1 [5]	0 [3]	0.034*
Daily nicotine use, yes/no[a]	1/14	0/15	1.0
Striatal DAT binding			
Caudate right	1.79 (0.42)	1.33 (0.31)	<0.001***
Caudate left	1.96 (0.55)	1.48 (0.47)	<0.001***
Putamen right	1.11 (0.33)	0.82 (0.17)	0.002**
Putamen left	1.18 (0.51)	0.91 (0.27)	0.011*

Note: Median time interval between examinations = 73 months (6.1 years; IQR, range = 32, 28–91 months). Motor symptom duration at baseline (median [IQR]): unmedicated = 15 months [13]; medicated = 48 months [84]. Values are median [IQR], mean (standard deviation) or n. *P* values are from related-samples Wilcoxon signed rank tests, paired-samples *t* tests, McNemar tests, or Fisher exact tests.

Abbreviations: BDI = Beck Depression Inventory; DAT = dopamine transporter; F = female; IQR = interquartile range; LEDD = L-dopa equivalent dose; M = male; MDS-UPDRS = Movement Disorder Society's Unified Parkinson's Disease Rating Scale; MMSE = Mini-Mental State Examination; NMSS = Non-Motor Symptoms Scale; PDQ-8 = Parkinson's Disease Questionnaire.

[a]Cigarettes, snus or nicotine from other sources.

*$p < 0.05$;

**$p < 0.01$;

***$p < 0.001$.

(caffeine: $r = 0.32$, $p = 0.043$; paraxanthine: $r = 0.59$, $p < 0.001$; theophylline: $r = 0.43$, $p = 0.006$; Supplementary Table S5, Fig 4).

Discussion

This study aimed to assess the effects of caffeine consumption on striatal dopaminergic function and clinical symptoms in PD patients cross-sectionally and longitudinally.

TABLE 3. Correlations between Caffeine Consumption and Longitudinal Changes in Part II

Patients	Change per year mean (SD)	Correlation with caffeine consumption, Spearman *r*	*p*
Unmedicated at baseline			
Motor symptoms			
Hoehn and Yahr stage	0.06 (0.16)	−0.03	0.89
LEDD, mg	95 (53)	−0.21	0.27
MDS-UPDRS motor	−0.9 (3.4)	0.18	0.35
Nonmotor symptoms			
NMSS total	0.8 (9.5)	−0.07	0.72
PDQ-8	1.9 (4.6)	−0.17	0.40
MMSE	−0.09 (0.46)	0.14	0.47
BDI	0.02 (1.63)	−0.30	0.13
Alcohol and nicotine			
Alcohol, drinks/wk	−0.19 (1.21)	−0.17	0.39
Striatal DAT binding			
Caudate right	−0.10 (0.08)	−0.24	0.22
Caudate left	−0.12 (0.06)	−0.37	0.045*
Putamen right	−0.06 (0.06)	−0.50	0.006**
Putamen left	−0.06 (0.06)	−0.50	0.005**
Medicated at baseline			
Motor symptoms			
Hoehn and Yahr stage	0.08 (0.19)	−0.18	0.52
LEDD, mg	79 (67)	0.38	0.16
MDS-UPDRS motor	−0.44 (3.83)	−0.14	0.62
Nonmotor symptoms			
NMSS total	4.8 (15.7)	0.20	0.48
PDQ-8	0.64 (4.2)	0.064	0.82
MMSE	−0.32 (0.62)	0.14	0.61
BDI	−0.12 (1.61)	−0.47	0.076
Alcohol			
Alcohol, drinks/wk	−0.17 (0.33)	0.03	0.92
Striatal DAT binding			
Caudate right	−0.09 (0.07)	0.09	0.75
Caudate left	−0.09 (0.06)	−0.24	0.40
Putamen right	−0.06 (0.07)	−0.33	0.23
Putamen left	−0.05 (0.08)	0.39	0.16

Note: Change per year = (follow-up – baseline)/years of follow-up.

Abbreviations: BDI = Beck Depression Inventory; DAT = dopamine transporter; LEDD = L-dopa equivalent dose; MDS-UPDRS = Movement Disorder Society's Unified Parkinson's Disease Rating Scale; MMSE = Mini-Mental State Examination; NMSS = Non-Motor Symptoms Scale; PDQ-8 = Parkinson's Disease Questionnaire; SD = standard deviation.

*$p < 0.05$;

**$p < 0.01$.

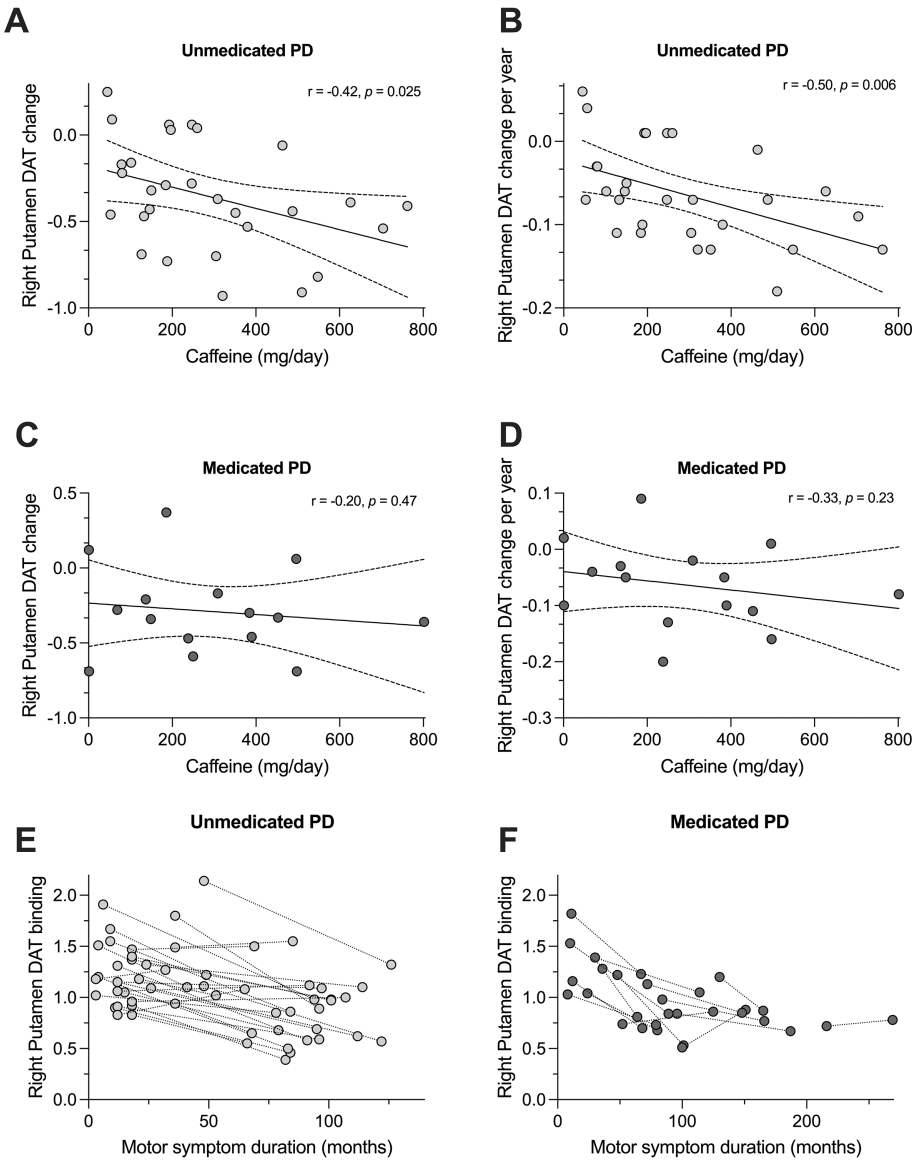

FIGURE 2: Longitudinal dopamine transporter (DAT) binding changes in Parkinson disease (PD) patients in relation to caffeine intake and motor symptom duration (Part II). (A) Negative correlation between right putamen DAT change and daily caffeine intake in unmedicated PD patients ($p = 0.025$). (B) Same correlation as that shown in panel A but considering the DAT change per year rather than the net change ($p = 0.006$). (C) Correlation between right putamen DAT change and daily caffeine intake in medicated PD patients ($p = 0.47$). (D) Same correlation as shown in panel C, but considering the DAT change per year rather than the net change ($p = 0.23$). (E) Individual changes in right putamen DAT binding between baseline and follow-up in relation to motor symptom duration in unmedicated PD patients. (F) Individual changes in medicated PD patients. Dashed lines delineate 95% confidence intervals; r = Spearman rank correlation coefficient.

The results indicate that high coffee (and therefore caffeine) consumption in PD patients is linked to lower striatal DAT binding compared to those with minimal coffee intake. Longitudinal analysis supports these findings, revealing that prolonged caffeine consumption is associated with a greater decline in striatal DAT binding in PD patients over time. Additionally, the investigation of caffeine and its metabolites revealed a positive correlation between recent caffeine intake and DAT binding in PD patients, which should be considered during diagnostic analysis, as it could complicate the interpretation of clinical DAT imaging outcomes. Whereas a recent dose of caffeine temporarily enhances striatal DAT binding, chronic use is associated with an overall reduction, highlighting the complex dynamics of caffeine's impact on dopaminergic pathways in PD.

High Levels of Caffeine Consumption Downregulate DAT in PD Patients

The finding of lower striatal DAT binding in PD patients with high caffeine consumption seems to conflict with epidemiological evidence of reduced PD risk in high

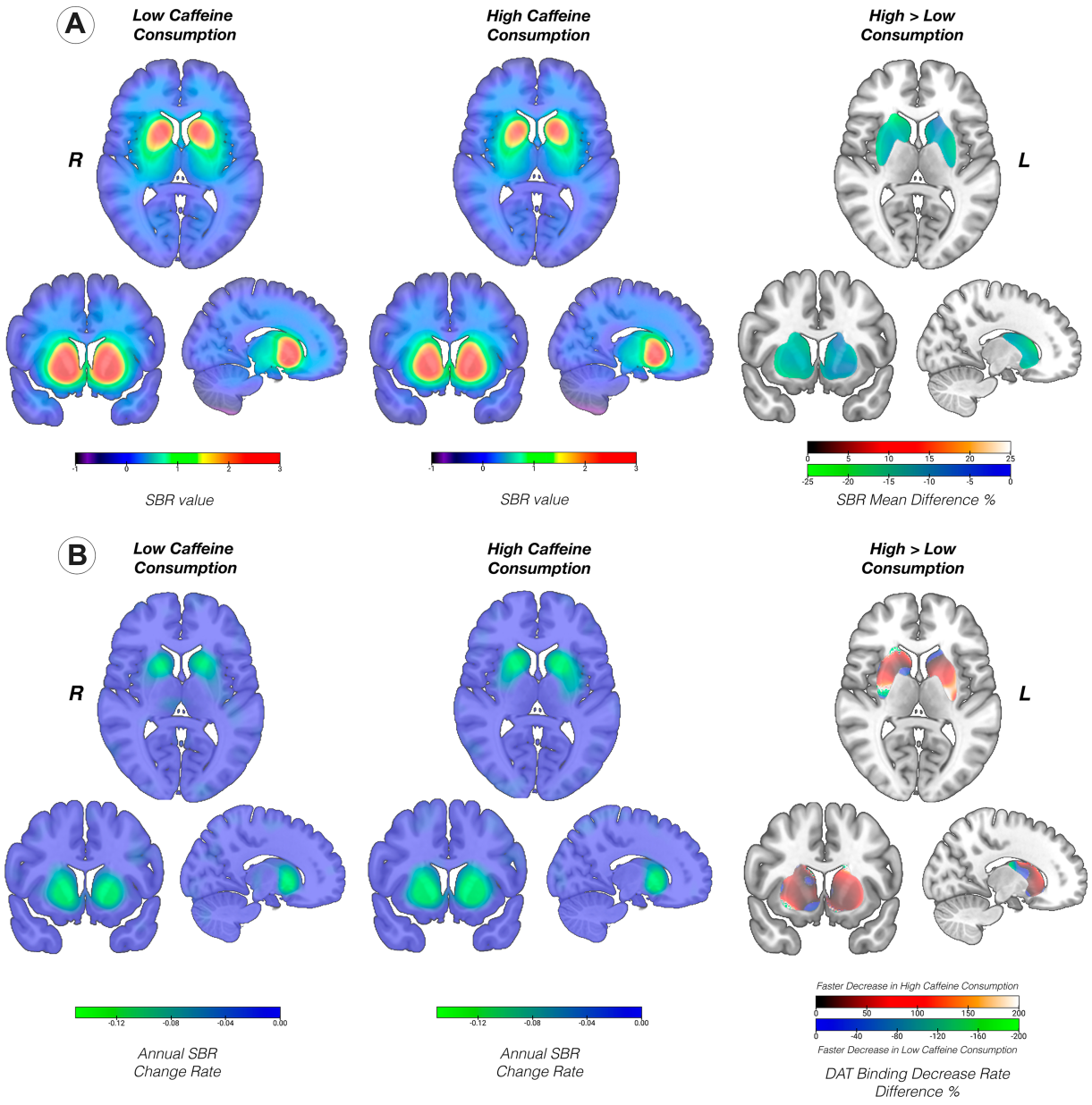

FIGURE 3: Voxelwise analyses of dopamine transporter (DAT) binding changes. (A) Cross-sectional cohort: voxelwise descriptive analyses of specific binding ratio (SBR) values for patients with low (left) and high coffee consumption (center) as well as their difference (right) for Part I. (B) Longitudinal cohort: voxelwise descriptive analyses of annual SBR value changes for patients with low (left) and high caffeine consumption (center) as well as their difference (right) for Part II.

caffeine consumers.[3–10] However, we interpret a decrease in striatal DAT binding as indicative of DAT downregulation, as DAT downregulation has been observed in users of other psychostimulants. There is compelling meta-analytical evidence demonstrating a generalized downregulation of the dopaminergic system in users of psychostimulant drugs.[39] Although these effects have been primarily observed in users of cocaine, amphetamine, and methamphetamine, the same mechanisms could be at play with consumption of less potent psychostimulants, such as nicotine and caffeine. Another meta-analysis of 7 studies comparing smokers and nonsmokers has shown similarly reduced DAT availabilities in smokers with a medium to large effect size.[40]

Reduced DAT binding could be assumed to indicate that there is a loss of nigrostriatal dopaminergic neuron count or density. However, our previous postmortem research showed no correlation between striatal DAT binding in PD patients and the number of nigral neurons or striatal axons, suggesting that DAT tracer binding primarily reflects the functional level of dopaminergic activity rather than neuron count.[41,42] Furthermore, in the case of methamphetamine users who show a similar but more pronounced reduction in DAT binding, detoxification

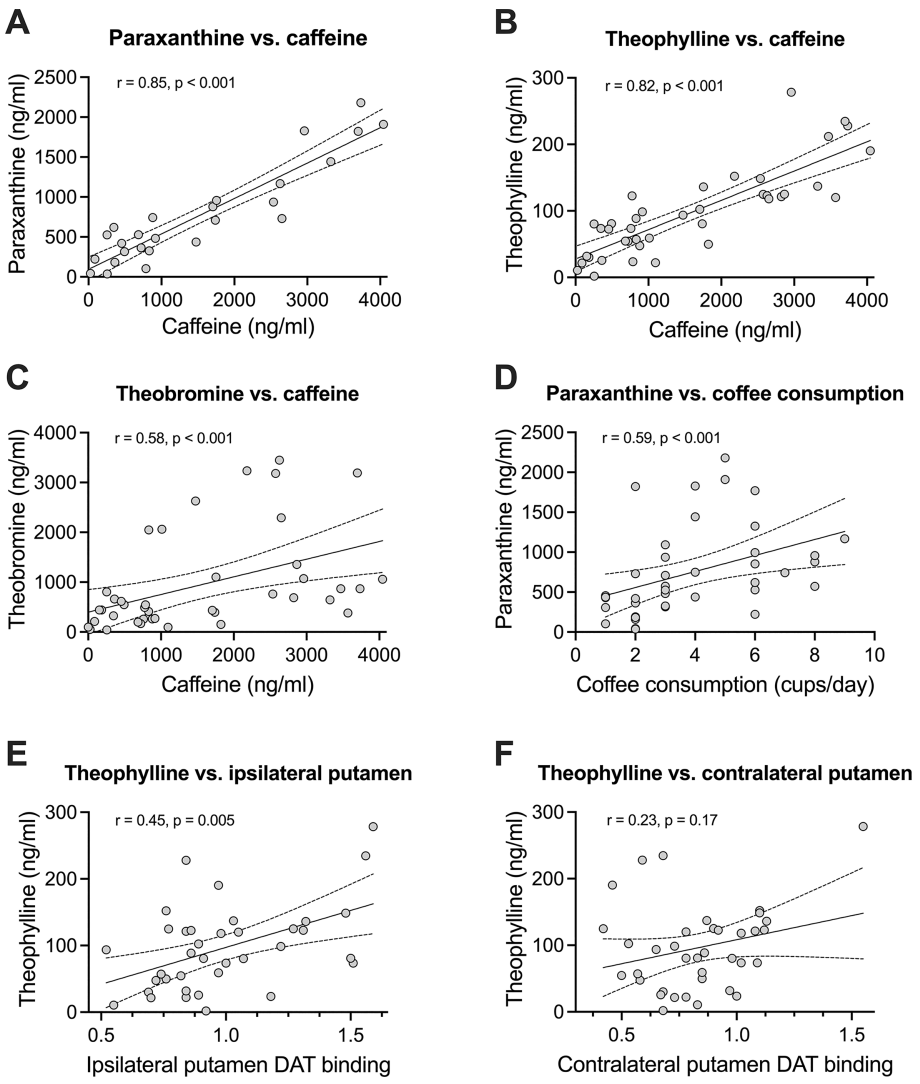

FIGURE 4: Concentrations of caffeine and its metabolites in relation to coffee consumption and dopamine transporter binding. (A) Positive correlation between blood paraxanthine and caffeine concentrations ($p < 0.001$, n = 40). (B) Positive correlation between theophylline and caffeine concentrations ($p < 0.001$, n = 40). (C) Positive correlation between theobromine and caffeine concentrations ($p < 0.001$, n = 41). (D) Positive correlation between blood paraxanthine concentration and daily coffee consumption ($p < 0.001$, n = 40). (E) Positive correlation between blood theophylline concentration and ipsilateral putamen ($p = 0.005$, n = 37). (F) Correlation between theophylline and contralateral putamen ($p = 0.17$, n = 37). Dashed lines delineate 95% confidence intervals; r = Spearman rank correlation coefficient.

leads to a restoration of DAT function, and postmortem examinations do not indicate any loss of dopaminergic neurons.[39] Therefore, although neuropathological evidence is needed, our findings suggest that long-term caffeine consumption in PD patients reduces DAT binding without causing neuronal loss. However, uncertainty persists regarding the functional integrity of dopaminergic neurons. There are considerable compensatory mechanisms at play in the dopaminergic system in PD that complicate the interpretation.[43] Therefore, the observed changes are probably not solely explained by downregulation of the system, but rather represent a mixture of neuromodulatory effects within dopaminergic neurotransmission.

Notably, this caffeine-induced neuromodulation appears to be prominent in PD patients who already have a degeneration of nigrostriatal neurons and a 52 to 64% reduction in putaminal DAT binding,[44] suggesting that these patients have a reduced threshold for the effects of caffeine. Previous research utilizing a sample from the Parkinson's Progression Markers Initiative project reported lower caudate DAT binding in current coffee consumers than in former consumers in both the healthy control and PD patient groups, but the effect was more pronounced in PD patients, similar to the findings of our study.[24] Together, these findings suggest that chronic caffeine intake might induce DAT downregulation in both healthy individuals and PD patients but that the effect is more

prominent in those with compromised dopaminergic neurotransmission. In our study, the difference in sample sizes between the medicated and unmedicated groups, as well as between PD patients and healthy controls, poses a challenge in definitely establishing the exclusivity of the effect in unmedicated patients or individuals with PD. The smaller number of medicated individuals and controls precludes conclusive interpretations, underscoring the need for additional investigations in advanced medicated PD patients and healthy individuals.

Although we observed clear differences in DAT binding between PD patients with high and low caffeine consumption, we observed no significant differences in clinical symptoms, including motor symptom severity, disease duration, and the presence of nonmotor symptoms in the cross-sectional analysis at approximately 1.5 years after the onset of motor symptoms. This aligns with previous research indicating minimal detectable clinical changes after 6–18 months of caffeine treatment in PD patients.[14] However, clinically meaningful differences could emerge over a longer follow-up period. Moreover, our investigations into the raphe nucleus suggested that the influence of caffeine on tracer binding might extend beyond DAT to include serotonin transporter. Nevertheless, this effect seemed less prominent when compared to the impact on DAT in striatal regions and was not observed in the longitudinal analysis (Part II). Consequently, this finding should be interpreted cautiously, as it remains preliminary and warrants additional validation.

High Levels of Caffeine Consumption Are Associated with Progressive DAT Downregulation

In the longitudinal part, higher caffeine intake was associated with a greater annual decline in striatal DAT binding in PD patients. This finding aligns with the results from the cross-sectional analysis, where high coffee consumption was linked to lower DAT binding. There are no previous longitudinal neuroimaging studies of caffeine consumption in patients with PD. Taken together, these findings demonstrate that in PD patients, the downregulation of DAT induced by caffeine is cumulative, progressing as the disease advances and as neuronal loss becomes more severe.

Moreover, we observed clinical changes that coincided with DAT binding alterations in the longitudinal analysis. Initially unmedicated patients exhibited improved MDS-UPDRS motor scores upon the introduction of dopaminergic medication, but their PD-related quality of life (PDQ-8) deteriorated. Medicated patients showed a modest decline in cognition during the follow-up period. Importantly, these longitudinal clinical changes did not correlate with caffeine consumption.

Subacute Caffeine Intake Is Associated with a Transient Increase in DAT Binding

Blood sample analysis revealed a significant increase in DAT binding among PD patients following recent caffeine consumption, as evidenced by the positive correlation between caffeine's primary metabolite, paraxanthine (1,7-dimethylxanthine), and DAT binding. This effect persisted after a minimum of 7.5 hours of caffeine abstinence before DAT imaging. The subacute increase in tracer binding induced by caffeine can be attributed to temporary dopaminergic activation, possibly facilitated by paraxanthine's dopaminergic effects in the dorsal striatum.[45] This effect was specifically observed in the ipsilateral putamen or the putamen with higher DAT binding, suggesting that the disease process masks the effect in the more severely affected contralateral hemisphere.

The underlying pathophysiological mechanism explaining the differential impact of subacute and chronic caffeine consumption on DAT binding remains unclear. For chronic effects of caffeine, changes in neuronal plasticity could be one of the explaining factors, although it is not currently clear whether caffeine-induced plasticity changes are beneficial or detrimental.[46] The subacute effect could be driven by direct influences of paraxanthine on the striatal system.[45] Larger scale studies on temporal dynamics of caffeine are required to explore the acute and subacute effects of caffeine on DAT in other patient groups and healthy individuals.

Implications for Clinical Practice

The finding of caffeine's subacute effects on dopamine function has significant implications for clinical DAT imaging in patients with parkinsonism. Notably, caffeine, unlike several other psychostimulants, is not currently included in the list of substances to avoid when undergoing routine clinical DAT imaging.[47] However, the transient increase in striatal DAT binding induced by recent caffeine consumption could complicate clinical decision-making in cases with borderline or unclear DAT results. It may be necessary to refrain from caffeine-containing products for at least 24 hours before DAT imaging (equivalent to 5 times the half-life observed with other psychostimulants[47]).

Considering the observed initial (Part I) and progressive (Part II) loss of DAT binding in PD patients, a crucial question arises regarding the role of caffeine-containing products in the management of PD. Although our findings strongly suggest reduced DAT binding in PD patients with high caffeine intake, the loss of DAT

binding itself may not be harmful. Studies on other psychostimulants indicate that decreases in DAT binding following chronic exposure are transient and do not imply permanent neuronal loss. However, these transient changes in DAT have been observed primarily in healthy individuals or those without specific functional loss in the dopaminergic system. Considering the progressive decline in DAT binding in our study, along with the lack of beneficial clinical symptomatic effect or potential exacerbation of dyskinesia associated with caffeine consumption,[14] our results do not support advocating caffeine treatment or increased coffee intake for newly diagnosed PD patients. Instead, a cautious approach to caffeine-based treatment may be warranted due to the progressive deficit in DAT, regardless of the possible underlying downregulatory mechanisms.

Limitations

Study limitations include the relatively small sample size in the longitudinal analysis, despite the exceptionally long follow-up duration (median = 6.1 years). Importantly, the demonstrated subacute effect of caffeine on DAT does not compromise the validity of our findings overall. The observed chronic downregulation of DAT could have been more pronounced with prolonged abstinence from caffeine. Additionally, clinical evaluations were performed when medicated patients were at on-stage, whereas for possible disease modification, off-stage would be more relevant. Furthermore, detailed caffeine consumption data and blood analyses were available only at the follow-up visit. Despite the validity of the CCQ-R questionnaire, reliance on self-reported caffeine consumption and possible recall bias can introduce measurement inaccuracies. Nevertheless, this study offers valuable long-term insights into the interplay between caffeine and brain dopamine function in the context of PD.

Conclusions

These insights have implications for clinical practice and future research. In particular, the findings do not support the use of caffeine to treat newly diagnosed PD patients, but clinicians should consider caffeine's potential influence on DAT imaging results and incorporate appropriate guidelines for caffeine abstinence prior to imaging. In future studies, it is also necessary to directly assess the relative change in DAT binding following acute caffeine consumption. This will provide a precise and quantified insight into the acute effects of caffeine from a diagnostic perspective, assessing the extent to which it might complicate the interpretation of DAT imaging results. Additionally, further research encompassing longitudinal studies of the acute and long-term effects of caffeine consumption on dopamine-adenosine receptor interactions in healthy subjects and individuals at risk for PD is warranted.

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Author Contributions

V.K. and F.S. contributed to the conception and design of the study. All authors contributed to the acquisition and analysis of data; E.K.S., T.K., K.N., E.H., T.N., M.S., T.I., K.M., T.M., E.J., E.M., M.E., S.N., K.R.C., A.A., T.V., M.L., J.J., F.S., and V.K. contributed to drafting the text or preparing the figures.

Potential Conflicts of Interest

Nothing to report.

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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