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The pattern of gray matter atrophy in Parkinson's disease differs in cortical and subcortical regions

Mechelle M. Lewis, Ph.D.[#1,2], **Guangwei Du, M.D., Ph.D.**[#1], **Eun-Young Lee, Ph.D.**[1], **Zeinab Nasralah, M.S.**[1], **Nicholas W. Sterling, M.S.**[1], **Lijun Zhang, Ph.D.**[1], **Daymond Wagner, M.S.**[1], **Lan Kong, Ph.D.**[3], **Alexander I. Tröster, Ph.D.**[4], **Martin Styner, Ph.D.**[5,6], **Paul J. Eslinger, Ph.D.**[1], **Richard B. Mailman, Ph.D.**[1,2], and **Xuemei Huang, M.D., Ph.D.**[1,2]

[1]Department of Neurology, Pennsylvania State University, Hershey PA 17033

[2]Department of Pharmacology, Pennsylvania State University, Hershey PA 17033

[3]Department of Public Health Sciences, Pennsylvania State University, Hershey PA 17033

[4]Department of Clinical Neuropsychology, The Barrow Neurological Institute, Phoenix, AZ 85013

[5]Department of Psychiatry, UNC, Chapel Hill, NC 27599

[6]Department of Computer Science, UNC, Chapel Hill, NC 27599

[#] These authors contributed equally to this work.

Abstract

Background—Cortical and subcortical gray matter (GM) atrophy may progress differently during the course of Parkinson's disease (PD). We delineated and compared the longitudinal pattern of these PD-related changes.

Methods—Structural MRIs and clinical measures were obtained from 76 PD with different disease durations and 70 Controls at baseline, 18- and 36-months. Both cortical and subcortical (putamen, caudate, and globus pallidus) GM volumes were obtained, compared, and associated with PD clinical measures at baseline. Their volumes and rates of change also were compared among Controls, PDs, and PD subgroups based on duration of illness [≤1 year (PD_E), 1-5 years (PD_M), and >5 years (PD_L)].

Results—Compared to Controls, PD subjects displayed smaller cortical GM and striatal (putamen, caudate, ps≤0.001), volumes at baseline. Cortical GM volumes were negatively associated with disease duration at baseline, whereas striatal volumes were not. PD subjects demonstrated accelerated volume loss in cortical GM (p=0.006), putamen (p=0.034), and caudate (p=0.008) compared to Controls. Subgroup analyses demonstrated that accelerated cortical atrophy reached statistical significance in PD subjects with duration of illness 1-5 years (PD_M,

Corresponding Author: Xuemei Huang M.D., Ph.D., Departments of Neurology, Penn State University, H037, 500 University Drive, Hershey, PA 17033-0850, Phone: 717-531-0003, ext. 287082; Fax: 717-531-0266; ; Email: Xuemei@psu.edu.

Ethical Standards

The study was approved by the Penn State Hershey Institutional Review Board and conducted in accordance with the principles of the Declaration of Helsinki. All subjects gave their informed consent prior to their inclusion in the study.

Conflict of Interests

The authors declare that they have no conflict of interest.

ps<0.001) and the trend of accelerated atrophy seemed to persist until later stages, whereas striatal atrophy occurred in PD subjects with PD_E (p=0.021 for putamen, p=0.005 for caudate) and PD_M (p=0.002 for putamen, p=0.001 for caudate) that significantly slowed down in PD_L (ps for PD_L vs PD_E or PD_M: <0.01).

Conclusions—The pattern of GM loss in PD differs in cortical and subcortical regions, with striatal atrophy occurring earlier and extra-striatal cortical atrophy later.

Keywords

Parkinson's disease; brain atrophy; MRI; volume

Introduction

Parkinson's disease (PD) affects both motor and non-motor functions. Postmortem studies have shown focused pathology in the substantia nigra of the basal ganglia, as well as more diffuse Lewy pathology in extranigral brain regions.[1] Postmortem histologic studies are limited by the inability to capture dynamic changes as the disease unfolds in live patients. The exact pathoetiology and course of PD-related cell loss and its progression, however, remain unclear.

MR volumetric imaging can gauge *in vivo* macroscopic atrophy and assess both nigrostriatal and extranigral changes longitudinally. Extensive studies have demonstrated both cortical and subcortical gray matter (GM) atrophy in PD with both cross-sectional [2-4] and longitudinal designs [5-7] although some studies report no significant longitudinal volume changes in PD [8,9].

It is well-known that PD progression is not uniform over the disease course. Converging anatomical,[10] biochemical,[11] and clinical[12] evidence suggest the rate of motor and nigrostriatal pathological progression in PD is most rapid within the first five years of the diagnosis and then slows down or even plateaus, whereas extra-nigrostriatal and non-motor symptoms continue to progress during the remaining course of the disease [13]. Thus, GM changes in nigrostriatal and extra-nigrostriatal brain regions may evolve differently during the course of PD. This study investigated simultaneously cortical and subcortical GM changes and compared their atrophic patterns during the course of PD.

Methods

Subjects

A total of 76 PD and 70 matched control subjects (Controls; Table 1) were included in the study. PD subjects were recruited from a tertiary movement disorders clinic and Controls were recruited from the spouse population of the clinic or via IRB-approved recruitment materials posted in the local community. All subjects gave informed consent and were free of major/unstable medical issues such as liver, kidney, or thyroid abnormality, and deficiency of vitamin B_{12}, or any cerebrovascular disease or neurological condition (other than PD). PD diagnosis was confirmed according to published criteria [14]. Disease duration was obtained from subject history with onset defined as the first diagnosis by a medical

professional. The study was conducted in accordance with the principles of the Declaration of Helsinki and reviewed and approved by the Penn State Hershey Institutional Review Board.

At baseline, subjects were screened using the Mini Mental Status Exam (MMSE) and only those with MMSE≥24 were enrolled. Olfactory function was evaluated using the University of Pennsylvania Smell Identification Test (UPSIT) [15] and depression assessed using the Hamilton depression scale [16]. Imaging and clinical data were captured at baseline, 18-, and 36-month follow-up visits, with 18- and 36-month follow-up visits occurring on average 19.3±3.1 and 39.3±4.8 months after the baseline visit, respectively.

Motor function assessments

Unified PD Rating Scale part III-motor scores (UPDRS-III) [17] and Hoehn & Yahr (HY) stages were obtained for each PD subject in a practically defined “off” state after withholding PD medications overnight (~12 hr; [18]). The levodopa-equivalent daily dose (LEDD) was calculated according to published criteria [19].

MRI data acquisition

All subjects were scanned using a 3.0 Tesla MR Scanner (Trio, Siemens Magnetom, Erlangen, Germany, with an 8-channel phased array head coil) at baseline, 18-, and 36-months. To avoid systematic bias, PD and Controls were scanned in an intermixed fashion throughout the longitudinal study. A magnetization-prepared rapid acquisition gradient echo sequence was used to obtain T1-weighted images with TR/TE=1540/2.34, FOV=256 mm × 256 mm, matrix=256 × 256, slice thickness=1 mm (with no gap), slice number=176. Each MRI was inspected and deemed free of any significant structural abnormalities (tumor or vascular malformations).

Image processing and analysis

T1-weighted images were processed automatically using the longitudinal stream of FreeSurfer (version 5.1.0). This processing pipeline utilizes longitudinal image data from each time point to create an unbiased, within-subject template via a nonlinear surface-based registration procedure. Within-subject templates were used to initialize image processing (skull stripping, Talairach transforms, atlas registration, spherical surface maps, and parcellation) for subject scans at each visit. The final volumes of putamen, caudate, and globus pallidus are the sum of the left and right sides since there were no significant differences between sides (data not shown). The FreeSurfer longitudinal pipeline generated an average total intracranial volume (TIV, i.e., the sum of GM, WM, and CSF) across visits for each subject. Each region for individual subjects then was normalized by this TIV to calculate a percentage of TIV measurement that was included in the statistical analysis and presented in the results.

Statistical analysis

Gender, age, and education were compared using Fisher's exact test or two-tailed Student's t-test as appropriate. Raw UPSIT scores were compared between groups using analysis of covariance (ANCOVA) with adjustment for age and gender. Clinical measures were

compared using two-sample t-tests (Controls and PDs) or analysis of variance (Controls and PD subgroups). The association between baseline volumes and clinical measures was assessed in PD subjects using Pearson's correlation.

For group and subgroup comparisons, baseline, 18-, and 36-month volumes were entered into a linear mixed-effects model to estimate baseline volume differences and the rate of GM atrophy for each region of interest (ROI). Age and gender also were entered as predictors in the mixed-effect models because of their known effects on brain volume and rate of brain atrophy [20]. Volume (normalized by TIV) at each visit was entered as the dependent variable and time elapsed since baseline visit was entered as the time variable. We assumed that the mean volume change was a linear function of time with intercept depending on linear and quadratic terms of baseline age (centered at 60 years), gender, and group (PD vs. Controls), and slope depending on the linear terms of age, gender, and group. A random intercept was included in the mixed-effects models to account for within-subject correlations of observations.

In order to evaluate the pattern of GM atrophy during the course of PD, the annual rate of change in both cortical and striatal regions was graphed (Figure S1) based on disease duration. In an effort to understand the stage-dependent volume changes in PD, PD subjects were sub-divided into three subgroups based upon the number of years since diagnosis [PD_E (≤1yr), PD_M (1-5yr), PD_L (>5yr)], as we have done previously [21]. All statistical analyses were performed using SAS 9.3 (SAS Institute Inc., Cary, NC, USA).

Results

Demographic and study characteristics

PD and Control subjects did not differ significantly in gender or education at any visit (Table 1). Overall, PD subjects showed significantly higher depression and lower UPSIT scores compared to Controls. PD subjects also were older than Controls at each time point.

At baseline, PD subjects displayed smaller total GM ($p<0.001$), cortical GM ($p<0.001$), putamen ($p=0.001$), and caudate ($p=0.001$) volumes compared to Controls (Table 2), with no significant difference observed in the globus pallidus. All three PD subgroups (PD_E, PD_M, and PD_L subjects) had decreased total GM, cortical GM, and putamen volumes compared to Controls. PD_M and PD_L subgroups demonstrated decreased caudate, with PD_E showing a trend ($p=0.058$). Within PD subgroups, there were no significant baseline volume differences.

From baseline, the dropout rate at 18-months was 18.5% for PD and 12.9% for Controls, respectively. Between the 18- and 36-month visits, the dropout rate for PDs and Controls was 19.4% and 7.2%, respectively. There were no significant differences between subjects remaining in the study and those who dropped out (data not shown).

Relationship of baseline volume and clinical measures in PD

Total and cortical GM volumes, but not striatum (caudate and putamen), were associated negatively with disease duration in PD subjects (Table 3). Cortical GM volume also was

correlated with UPDRS-III, UPSIT and MoCA scores, whereas caudate volume was correlated only with LEDD.

Longitudinal volume changes in PD and PD subgroups

Compared to Controls, PD subjects overall demonstrated significantly faster volume loss in total GM (p=0.002), cortical GM (p=0.006), putamen (p=0.034), and caudate (p=0.008; Table 4).

Visual inspection of Figure S1 indicates that whereas the most dynamic changes occurred within five years of diagnosis, the annual rate of volume loss remained at the rate of ~1% in total and cortical GM, even 15+ years following diagnosis. Statistically, cortical GM annual volume changes were significantly accelerated only in PD_M subjects (p=0.001), and there were no significant differences between PD_M and the other subgroups.

Conversely, annual volume changes in striatum (putamen and caudate) were accelerated only in PD_E and PD_M subjects compared to Controls (Table 4) but not in PD_L. Indeed, annual volume changes appeared to plateau in these regions (hover ~0) 5-10 years after diagnosis (Figure S1), with significant differences comparing PD_E and PD_M to PD_L subjects.

Discussion

The current study replicated past results indicating that GM atrophy occurs in PD. Most importantly, the current study provides the first *in vivo* evidence that cortical and subcortical GM have a different pattern and rate of atrophy during the course of PD. The results may reconcile past controversial findings relating GM changes associated with PD and guide the choice of more sensitive stage-dependent biomarkers for PD progression.

Cortical gray matter loss and its clinical and pathological implications

Previous imaging studies have reported mixed results in overall GM volumes in PD [2,8,9]. Several recent studies demonstrated [7,22,23], yet others failed to find [24,25], reduced cortical volume in PD. The exact reason for these discrepancies is not known but different methodologies (region of interest vs. voxel-based) may be one possible contributory factor. The current study employed a ROI-based and longitudinal design that allowed us to perform focused hypothesis testing. The finding of significant differences in both atrophy at baseline and rates of change longitudinally strengthens the argument for accelerated atrophy occurring in PD.

In our study, cortical GM volume was associated with MoCA and UPSIT scores. These results suggest that GM volume may reflect extra-nigral changes associated with PD. The findings are consistent with a recent report indicating that GM atrophy is associated with cognitive impairment and decline in PD [26] and with other studies linking GM changes to cognitive performance [3,4]. Moreover, they are congruent with reduced olfactory function in PD being related to reduced volume in piriform and orbitofrontal cortices [27].

It is well established that the striatum makes significant connections with cortical areas through striato-thalamo-cortical pathways and reciprocal, topographic projections via

cortico-striatal circuits [28]. Our finding of a significant association between cortical GM changes and UPDRS-III scores is supportive of the hypothesis that cortical GM changes also may capture at least part of nigrostriatal pathologies. Future studies interrogating the relationship between detailed motor/non-motor dysfunctions and refined cortical regions of interest in PD are warranted, and may yield knowledge on the neuropathological underpinning of different PD-related symptomologies.

As expected, cortical GM volumes were related to disease duration. Visual inspection of the time course of GM volume changes and PD subgroup analyses suggested that the accelerated cortical GM seems to be most significant one year after PD diagnosis, and the accelerated rate seems to maintain thereafter at 1% per year (Figure S1). This finding is consistent with Braak staging, which demonstrated that diffuse cortical involvement of PD pathology probably does not occur until later disease stages [1]. Cortical GM changes may be useful to gauge pathological changes in later-stage patients.

Striatal volume loss and its clinical and pathological implications

The striatum (caudate and putamen) composes the primary input stage of the basal ganglia and receives direct projections from dopamine neurons of the substantia nigra, whereas the globus pallidus is regulated indirectly by the substantia nigra pars compacta via the striatum [28]. Basal ganglia structures may undergo structural changes due to nigrostriatal denervation. In this study, PD subjects (and subgroups) displayed putamen and caudate atrophy, with no significant change in the globus pallidus, compared to Controls. These results are consistent with several prior studies [26,29] but in contrast to a recent study that reported no change in basal ganglia volumes in cognitively-intact PD subjects [7]. The current data, however, support the hypothesis that nigral denervation affects the structure of immediate downstream targets. Consistent with this, the current study also found that caudate volume is significantly associated with LEDD, a measurement reflecting striatal dopamine deficits. In addition, positive correlations also were found between putamen volume and MoCA scores. These results underscore the function of striatal structures in cognition [30].

Interestingly, striatal atrophy was not correlated with duration of illness. These results are consistent with previous clinical and radioligand studies that have shown dopamine cell loss in PD may not be linear throughout PD progression [31,32]. In order to understand the potential stage dependent GM changes, we subdivided PD group to three subgroups based on the following rationale: 1) The upper limit of disease duration of one year was chosen to define a group of PD_E subjects that had not received extended treatment. 2) PD_L was defined as those PD subjects having at least five years of disease duration because nigrostriatal terminal labeling is known to reach a floor after approximately five years [33], although there are some data suggesting that nigral cell death may continue [34]. 3) Clinically, dyskinesias, cognitive decline, and dopamine-non-responsive symptoms tend to be more prominent after the first five years (“honeymoon” phase) [35]. 4) Lastly, these subgroup categorizations also happen to yield relatively balanced subgroup sample sizes, which is powerful for equivalence testing [33,36,37]. Consistent with our expectations, the highest rates of striatal atrophy were observed in patients during the first five years of disease (PD_E

and PD_M) and then plateaued thereafter (Figure S1). These temporal relations of our study lend further support to the hypothesis that basal ganglia atrophy may be the consequence of nigrostriatal dopamine denervation, rather than an independent pathology (such as new spreading Lewy pathology). We recognize that despite our rationale, the selection of subgroups based upon disease duration might seem arbitrary, so we repeated our analyses using HY stage, yielding similar results (data not presented). Together, our results support the notion that cortical and subcortical GM atrophy have different patterns and are stage-dependent.

Limitations

Despite a number of strengths, the study has several limitations. The number of subjects included in the study was moderately large for a longitudinal imaging study, but small compared to PD-related epidemiological studies. Moreover, because most PD subjects included in the study were within ~10 years of diagnosis, we may not have captured disease changes that may arise in very late stages of disease. The subcortical volume analysis was focused on striatal and pallidal regions, and thus may have missed important changes associated with PD in other brain areas. In addition, cortical GM was not parcellated into refined regions of interests to interrogate their individual trajectories or clinical implications.

Summary

In summary, the current study not only confirmed GM atrophy in PD, but demonstrated different patterns of cortical and subcortical atrophy during PD. Further studies are warranted to investigate the potential of using striatal atrophy to gauge early nigrostriatal denervation-related changes and cortical GM volumes to monitor later, global pathological processes and their clinical implications in PD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Demographic and clinical characteristics of participants at baseline, 18 months, and 36 months.

	Control	PD	PD_E	PD_M	PD_L	P-values[1]	P-values[2]
Baseline							
N Subjects (F,M)	70 (36, 34)	76 (29, 47)	22 (11, 11)	27 (10, 17)	27 (8, 19)	0.134*	0.207*
Age (y)	59.8 ± 7.7	63.3 ± 8.4	61.5 ± 9.8	61.4 ± 6.9	66.6 ± 7.8	***0.011***	***0.008***
Education (y)	16.6 ± 2.8	15.9 ± 2.7	16.1 ± 2.4	15.8 ± 2.4	15.9 ± 3.3	0.135	0.163
MMSE	29.5 ± 0.9	29.1 ± 1.1	29.3 ± 1.2	29.1 ± 1.3	29.0 ± 0.9	0.121	0.124
HAM-D	3.8 ± 2.5	7.7 ± 4.5	7.3 ± 4.4	7.2 ± 3.7	8.4 ± 5.3	***<0.0001***	***<0.0001***
UPSIT	34.1 ± 5.3	21.3 ± 7.4	23.9 ± 7.6	20.6 ± 8.3	20.1 ± 5.5	***<0.0001***	***<0.0001***
Clinical Measures							
Disease duration (y)	na	4.9 ± 5.5	0.4 ± 0.3	2.5 ± 1.2	11.0 ± 5.0	-	***0.0001***
LEDD (mg)	na	557 ± 458	247 ± 203	474 ± 361	893 ± 484	-	***<0.0001***
UPDRS-III	na	22.5 ± 14.3	13.1 ± 7.2	22.6 ± 11.1	31.2 ± 17.3	-	***0.002***
HY Stage	na	1.8 ± 0.7	1.4 ± 0.6	1.7 ± 0.7	2.2 ± 0.6	-	***<0.0001***
18 months							
N Subjects (F,M)	61 (31, 30)	62 (27, 35)	18 (10, 8)	21 (10, 11)	23 (7, 16)	0.472*	0.329*
Age (y)	61.3 ± 7.8	64.9 ± 8.4	62.7 ± 9.4	63.2 ± 7.1	68.1 ± 8.0	***0.017***	***0.002***
Education (y)	16.5 ± 2.9	15.8 ± 2.7	16.2 ± 2.4	15.6 ± 2.3	15.7 ± 3.4	0.140	0.112
Clinical Measures							
Disease duration (y)	na	6.6 ± 5.5	2.1 ± 0.4	4.1 ± 1.2	12.3 ± 5.1	-	***<0.0001***
LEDD (mg)	na	767 ± 491	444 ± 223	709 ± 438	1043 ± 528	-	***0.0001***
UPDRS-III	na	26.3 ± 19.7	14.8 ± 7.1	26.4 ± 21.3	37.8 ± 20.6	-	***<0.0001***
HY Stage	na	2.2 ± 1.0	1.6 ± 0.7	2.2 ± 0.9	2.6 ± 1.1	-	***<0.0001***
36 months							
N Subjects (F,M)	56 (30, 26)	50 (24, 26)	16 (8, 8)	18 (9, 9)	16 (7, 9)	0.697*	0.956*
Age (y)	63.0 ± 7.8	66.4 ± 7.9	66.7 ± 9.5	64.3 ± 6.2	68.6 ± 7.6	***0.027***	***0.024***
Education (y)	16.4 ± 2.8	15.7 ± 2.7	16.3 ± 2.5	15.3 ± 2.3	15.5 ± 3.3	0.206	0.139
Clinical Measures							
Disease duration (y)	na	7.8 ± 5.3	3.7 ± 0.4	5.6 ± 1.2	14.5 ± 4.1	-	***0.008***
LEDD (mg)	na	911 ± 604	685 ± 250	745 ± 509	1304 ± 738	-	***0.009***
UPDRS-III	na	32.7 ± 18.6	22.0 ± 9.0	33.6 ± 19.9	46.8 ± 18.1	-	***<0.0001***
HY Stage	na	1.9 ± 0.6	1.7 ± 0.7	2.0 ± 0.5	2.1 ± 0.8	-	***<0.0001***

Measurements presented as mean ± SD unless otherwise indicated.

Abbreviations: HY: Hoehn-Yahr; HAM-D: Hamilton Depression score; MMSE: Mini-Mental Status Exam; LEDD: levodopa daily equivalent dosage; UPDRS: Unified Parkinson's Disease Rating Scale; UPSIT: University of Pittsburgh Smell Identification Test.

[1] P-values for comparisons between all PD and Control subjects using two-sample t-tests.

[2] P-values of ANOVA across PD subgroups (and Controls as appropriate).

* P-values obtained using Fisher's exact test.

Table 2

Baseline volume estimate data of Controls, PDs, and PD subgroups.

	Total GM	Cortical GM	Putamen	Caudate	GP
Baseline Volumes of PD and its subgroups (mean ±SE)					
Control, N=70	414.8±2.6	305.3±2.1	3.254±0.044	2.370±0.030	0.890±0.019
PD, N=76	402.5±2.8	294.5±2.2	3.029±0.047	2.248±0.032	0.908±0.020
PD_E, N=22	400.6±4.5	292.6±3.6	2.978±0.076	2.268±0.030	0.930±0.033
PD_M, N=27	405.1±3.8	296.8±3.0	3.068±0.064	2.257±0.043	0.900±0.027
PD_L, N=27	400.3±4.4	292.6±3.5	3.020±0.074	2.214±0.050	0.899±0.032
P-values for group comparisons					
Control vs. PD	**<0.001**	**<0.001**	**0.001**	**0.001**	0.450
Control vs. PD_E	**0.004**	**0.001**	**0.001**	0.058	0.245
Control vs. PD_M	**0.032**	**0.018**	**0.014**	**0.024**	0.781
Control vs. PD_L	**0.002**	**0.001**	**0.004**	**0.003**	0.809
PD_E vs. PD_M	0.409	0.349	0.340	0.868	0.443
PD_E vs. PD_L	0.959	0.999	0.656	0.394	0.433
PD_M vs. PD_L	0.364	0.332	0.596	0.477	0.986

The volume estimate for each subject was expressed relative to baseline total intracranial volume (TIV) for that subject, with units per mille. Baseline volumes were compared among groups using longitudinal mixed-effects analysis (see Methods for details). P values are bolded for those reaching statistical significance.

Abbreviations: GM = gray matter; GP = globus pallidus; PD = Parkinson's disease; PD_E = early stage Parkinson's disease; PD_M = middle stage Parkinson's disease; PD_L = late stage Parkinson's disease. Disease stage was defined based on disease duration (see Methods for details).

Table 3

Correlations between volume and clinical measures in PD subjects at baseline.

	Disease duration		UPDRS-III		LEDD		MoCA		HamD		UPSIT	
	r	*p-value*	*r*	*p-value*	*r*	*p-value*	*r*	*p-value*	*r*	*p-value*	*r*	*p-value*
Total GM	**−0.304**	**0.008**	−0.219	0.057	−0.193	0.095	**0.370**	**0.001**	−0.038	0.751	0.221	0.066
Cortical GM	**−0.316**	**0.005**	**−0.231**	**0.045**	−0.207	0.072	**0.384**	**<0.001**	−0.022	0.853	**0.242**	**0.044**
Putamen	−0.157	0.177	−0.074	0.550	−0.070	0.550	**0.280**	**0.016**	0.004	0.973	−0.134	0.267
Caudate	−0.156	0.177	−0.103	0.374	**−0.304**	**0.008**	0.213	0.069	−0.029	0.807	0.016	0.895
Globus pallidus	−0.001	0.993	−0.020	0.861	−0.053	0.648	0.004	0.976	−0.125	0.296	−0.081	0.503

Values represent the Pearson's correlation coefficient (r), with the associated p-value to the right.

Bold text represents significant correlations.

Abbreviations: GM = Gray matter, HamD = Hamilton Depression Scale, LEDD = Levodopa equivalent daily dosage, MoCA = Montreal Cognitive Assessment, UPDRS-III = Unified Parkinson's Disease Rating Scale – motor score, UPSIT = University of Pittsburgh Smell Identification score

Table 4

Annual rates of change estimate data over 36 months in Controls, PDs, and PD subgroups.

	Total GM	Cortical GM	Putamen	Caudate	GP
Estimates of annual rates of volume changes (mean±SE):					
Control, N=70	−2.26±0.35	−1.81±0.30	−0.015±0.004	−0.021±0.005	0.001±0.002
PD, N=76	−3.71±0.38	−2.86±0.32	−0.027±0.005	−0.037±0.005	0.002±0.002
PD_E, N=22	−3.12±0.61	−2.33±0.52	−0.032±0.007	−0.044±0.008	−0.003±0.003
PD_M, N=27	−4.55±0.53	−3.48±0.45	−0.037±0.006	−0.045±0.007	0.003±0.003
PD_L, N=27	−3.02±0.58	−2.44±0.50	−0.008±0.007	−0.019±0.007	0.004±0.003
P values of group comparisons:					
Control vs. PD	**0.002**	**0.006**	**0.034**	**0.008**	0.802
Control vs. PD_E	0.136	0.278	**0.021**	**0.005**	0.205
Control vs. PD_M	**<0.001**	**0.001**	**0.002**	**0.001**	0.434
Control vs. PD_L	0.166	0.186	0.443	0.852	0.374
PD_E vs. PD_M	0.064	0.081	0.618	0.864	0.097
PD_E vs. PD_L	0.896	0.870	**0.010**	**0.011**	0.074
PD_M vs. PD_L	**0.042**	0.101	**0.002**	**0.006**	0.918

Control, PD, and PD subgroup annual rates of change estimates for each group or subgroup. The annual volume change for each subject was expressed relative to total intracranial volume (TIV) for that subject, with units per mille. Annual rates of change were compared among groups using longitudinal mixed-effects analysis (see Methods for details), with decreasing numbers of subjects at the 18- and 36 month visits (see Table 1 for subject sample sizes at the different time points). P values are listed for the relevant comparisons, with those reaching statistical significance bolded.

Abbreviations: GM = gray matter; GP = globus pallidus; PD = Parkinson's disease; PD_E = early stage Parkinson's disease; PD_M = middle stage Parkinson's disease; PD_L = late stage Parkinson's disease. Disease stage was defined based on disease duration (see Methods for details).