Brain Morphological Alterations Are Detected in Early-Stage Parkinson’s Disease with MRI Morphometry

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ABSTRACT

BACKGROUND AND PURPOSE: To detect brain morphological alterations in patients with early Parkinson’s disease (PD) by using magnetic resonance imaging (MRI) morphometry under radiological diagnostic conditions.

METHODS: T1-weighted brain images of 18 early PD patients and 18 age-sex-matched healthy controls (HCs) were analyzed with free software Computational Anatomy Toolbox (CAT12). Regional cortical thickness (rCTh) in 68 atlas-defined regions-of-interest (ROIs) and subcortical gray matter volume (SGMV) in 14 atlas-defined ROIs were determined and compared between patients and HCs by paired comparison using both ROI-wise and voxel-wise analyses. False-discovery rate (FDR) was used multiple comparison correction. Possible correlations between brain morphological changes in patients and clinical observations were also analyzed.

RESULTS: Comparing to the HCs, the ROI-wise analysis revealed rCTh thinning significantly in left medial orbitofrontal (P = .001), by trend (P < .05 but not significant after FDR correction) in four other ROIs located in frontal and temporal lobes, and a volume decreasing trend in left pallidum of the PD patients, while the voxel-wise analysis revealed one cluster with rCTh thinning trend located between left insula and superior temporal region of the patients. In addition, the patients showed more distinct rCTh thinning in ipsilateral hemisphere and SGMV deceasing trends in contralateral hemisphere in respect of the symptom-onset body side.

CONCLUSION: Brain morphological alterations in early PD patients are evident despite of their inconspicuous findings in standard MRI. Quantitative morphological measurements with CAT12 may be an applicable add-on tool for clinical diagnosis of early PD. These results have to be verified in future studies with larger patient samples.

Keywords: Parkinson’s disease, MRI morphometry, early diagnosis, CAT12.

Introduction

Early diagnosis of Parkinson’s disease (PD) is important because it allows patients to receive adequate medical treatment in time to improve quality of life. However, up to date the diagnosis of PD is based on clinical symptomatic findings showing unsatisfied accuracy for PD in early stage. Standard magnetic resonance imaging (MRI) is mainly used for exclusion of other symptomatic reasons in diagnosis of PD due to lack of specific findings. Sophisticated MR methods enabling us to identify brain changes in early-stage PD are needed for improvement of early clinical diagnosis and for better understanding of the underlying pathological mechanisms. Numerous MR studies have thus been carried out by using quantitative estimation of morphological brain changes associated with early PD, eg, the alterations of cortical gray matter volume (CGMV), subcortical gray matter volume (SGMV), or brain cortical thickness (CTh). Moreover, it has been reported that changes in CTh in PD patients appeared to be more sensitive to disease progression than changes of CGMV. However, up to date, the reported findings are controversial concerning involved brain structures showing distinct cortical atrophy in early-stage PD patients. More data from carefully characterized patients are necessary to elucidate PD-related early brain morphological alterations. Therefore, we carried out the present study to estimate changes of brain regional CTh and SGMV in PD patients classified at Hoehn and Yahr stage I or II. For this purpose, the free software Computational Anatomy Toolbox (CAT12) (http://www.neuro.uni-jena.de/cat/) was used. Further we want to evaluate the applicability of quantitative measurements of brain morphology by using MRI protocols typical in clinical routine.
Methods

Subjects

The study was approved by the local medical ethics committee, and written informed consent was obtained from each participant. Patients were recruited from neurological wards and a movement disorders outpatient clinic. PD was diagnosed according to Movement Disorder Society clinical diagnostic criteria. The Hoehn and Yahr (H&Y) scale was used to classify the disease phase, and PD at H&Y stage I or II were considered as early PD. Only patients at early-stage PD (H&Y stage I or II) were included in this study. Patients with atypical Parkinsonism or PD at H&Y stage higher than II, additional neurological disease other than PD, severe head injury, drug abuse, other major medical illness, brain vascular disease, or hydrocephalus were excluded from the study. Eighteen patients (48-72 years old, mean = 60.39 ± 7.46 years old, 7 males) with PD at H&Y stage I or II were finally enrolled. The Dementia Detection Test (DemTect) was used to estimate cognitive ability. The Movement Disorder Society sponsored revision of Unified Parkinson’s Disease Rating Scale (MDS-UPDRS scores) was used to rate PD symptoms of the patient. All the estimations were performed at the best medical “on-state” of the individual patient. Clinical information including disease duration (years), disease onset body side, and medication calculated as levodopa equivalent daily dosages (LED) were also collected.

Eighteen healthy subjects were also studied as controls (HCs) (46-70 years old, mean = 59.78 ± 7.14 years old, 7 males), who matched to patients on a one-to-one basis with respect to age and sex. The HCs were recruited from the local population, who had no neurological disorder or other systemic diseases according to a self-report, and did not reveal potential cognitive or psychiatric impairments by presenting scales in normal range in two screening tests using Beck Depression Inventory (BDI-II) and the Dementia Detection test (DemTect). PD patients and HCs were all right handers according to self-report.

MRI Examination and Data Processing

MR examinations were conducted at a 3.0 Tesla MRI scanner (Verio, Siemens, Erlangen, Germany). All subjects were scanned with a protocol that contained among others an axial T1-weighted 3-dimensional magnetization prepared rapid gradient echo (3D MPRA G) sequence (160 contiguous axial slices with an in-plane field of view 256 × 224 mm² and a 1 mm isotropic voxel resolution TR/TE/TI = 1,900/2.93/900 ms, flip angle 9°, acceleration factor = 2), a T2-weighted transverse turbo spin echo sequence, and a fluid-attenuated inversion recovery (FLAIR) sequence. The 3D MPRA G data were processed by using free software Computational Anatomy Toolbox (CAT12) (http://www.neuro.uni-jena.de/cat/), within SPM12 (http://www.fil.ion.ucl.ac.uk/spm/software/spm12) on Matlab R2017a platform (MathWorks, Natick, MA). CAT12 was chosen for present study due to the advantages that it provides more advanced and computationally efficient brain segmentation with more accurate volumetric analysis in comparison to other available tools. The details of the calculation procedures contained in CAT12 have been described in http://www.neuro.uni-jena.de/cat12/CAT12-Manual.pdf. Briefly, after transformation of the 3D MPRA G images from DICOM to NIFTI format via SPM12, the data processing was performed by running the default processing pipelines within CAT12 as used by Seiger et al., in which voxel-based morphometry (VBM), surface-based morphometry (SBM), as well as region-based morphometry (RBM) (http://www.neuro.uni-jena.de/hbm2016/GaserHBM2016.pdf) were applied. Procedures of spatial normalization, brain extraction, segmentation of brain gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF), and alignment of brain images (from native space to Montreal Neurological Institute standard space MNI-152 template) were carried out. With the "surface and thickness estimation" function integrated in the pipelines a central surface between the GM/CSF boundary and the GM/WM boundary was established and the CTh was defined as the distance between the GM/WM boundary and GM/CSF boundary. The segmented GM images were smoothed with an 8-mm full-width-at-half-maximum (FWHM) isotropic Gaussian kernel via SPM 12 and the established central surfaces were smoothed with 15-mm FWHM Gaussian kernel via CAT12. The smoothed GM images and the smoothed central surfaces were used for statistical voxel-wise comparison between patients and controls for SGMV and CTh, respectively. After the automatically running procedures, following parameters were defined or estimated: (1) The values of regional CTh (rCTh) from 34 regions of interest (ROIs) in each hemisphere that were obtained by ROI extraction procedure from defined CTh (http://www.neuro.uni-jena.de/hbm2016/GaserHBM2016.pdf) where the ROIs were defined according to Desikan-Killiany atlas, with 13 ROIs being located in frontal lobe, 4 ROIs in occipital lobe, 7 ROIs in parietal lobe, and 10 ROIs in temporal lobe; (2) the values of SGMV from seven ROIs in each hemisphere defined according to Neuromorphometrics atlas (accumbens area, amygdala, caudate, pallidum, putamen, hippocampus, and thalamus proper); and (3) the estimated total intracranial volume (eITV).

Altogether, the numeric values of rCTh and SGMV were derived by use of ROI measurements on each subject prior to statistical ROI-wise analysis. To avoid the influence of varied individual head size on brain tissue volume, the SGMV values of each subject were normalized to the individual eITV value and presented as a ratio amplified with a factor of 1,000.

Statistical Analysis

To estimate PD-related brain alterations, the regional CThs and SGMVs derived from ROI measurements of the PD patients were compared to those of paired-matched HCs (ROI-wise analysis). Doing this, normality of the numeric data distribution was first checked with Shapiro-Wilk tests and quantile-quantile plots. Paired t-test was used for normal distributed data, and Wilcoxon signed rank test (Wilcoxon test) for nonnormal distributed data. False-discovery rate (FDR) with a desired FDR to .05 was used for multiple comparison correction, with a corresponding FDR-corrected significance threshold $p_i = 0.05/\alpha$. The details of the calculation procedures contained in CAT12 have been described in http://www.neuro.uni-jena.de/cat12/CAT12-Manual.pdf. Briefly, after transformation of the 3D MPRA G images from DICOM to NIFTI format via SPM12, the data processing was performed by running the default processing pipelines within
by using nonparametric Spearman’s correlation test. Additionally, effect size\(^2\) (Cohen’s \(d = (\text{mean 1} − \text{mean 2})/\text{standard deviation}\)\(^2\) for paired \(t\)-test and \(γ = Z/\sqrt{N^2}\) for Wilcoxon test) were calculated. By grouping two brain hemispheres into contralateral or ipsilateral hemispheres in respect of symptom-onset body side of the PD patients, paired testing for rCTh values and for SGMV values was also made between the patients and the HCs, as well as between contralateral hemisphere and ipsilateral hemisphere within the patients, to search for possible effect of symptom lateralization to the brain morphological alteration. One patient with bilateral disease onset was excluded from this analysis. All statistical analyses of ROI measurements were carried out with SPSS software (Version 25, IBM, Armonk, New York, NY).

In voxel-wise analysis, comparison of CTh and SGMV between PD patients and paired-matched HCs were directly analyzed using a voxel-specific general linear model (GLM) for paired comparison. A raw statistical comparison map of smoothed central surface as well as smoothed GM images were generated at first by computing a GLM of the effects of each variable on thickness as well as on SGMV at each voxel. Based on the raw statistical images, a threshold-free cluster enhancement (TFCE) method was used to produce an output image (TFCE-map, without threshold), in which the voxel-wise values represent the amount of cluster-like local spatial support.\(^{28}\) After a permutation testing (5,000 iterations), voxel-wise statistical \(p\)-values (\(p\)-map, with threshold) was derived from the TFCE map, which indicated the significant level of corresponding changes in patients.\(^{28}\) With a threshold of \(P < .05\) and a confirmation by FDR correction, the cluster results were considered significant. If it failed to show any significant cluster results, a relaxed threshold \(P\) value (\(P_{\text{unc}} < .01\), without FDR correction) was used to estimate clusters with a size of continued 50 voxels \((k > 50)\), where the cluster results with \(P_{\text{unc}} < .01\) were considered as not significant but showing a trend of change. Possible correlations between altered rCTh or SGMV values and clinical observations were analyzed by using one sample \(t\)-test in GLM. The calculations were carried out with the procedures integrated in the software CAT\(12\) (http://www.neuro.uni-jena.de/cat12/CAT12-Manual.pdf).

**Results**

**Demographic and Clinical Characteristics of the Subjects**

The demographic and clinical characteristics of the PD patients and the HCs are summarized in Table 1. The PD group had a slightly lower mean DemTect score than that of the HCs (15.39 ± 3.07 vs. 17.33 ± 1.46) but still in normal range \([≥ 13]\),\(^{13}\) indicating an age-appropriate cognitive performance in most of our patients. The mean MDS-UPDRS total score (30.39 ± 11.37) of the patients pointed to a mild disease severity,\(^{29}\) showing that the studied patients were at early stage of PD (8 patients at H&Y stage I and 10 at H&Y stage II). All the patients demonstrated inconspicuous brain MRI findings based on visual inspections on T1-weighted, T2-weighted, and FLAIR images.

**Brain Morphological Measurements**

**ROI-Wise Analysis**

Paired \(t\)-tests and Wilcoxon tests of ROI measurements-derived numeric data revealed significant or tended changes in several brain areas between PD patients and HCs, as shown in Table 2. In comparison to HCs, the PD patients exhibited a significant decrease of rCTh in left medial orbitofrontal cortex \(−6.37\%\), \(P = .001\), effect size = −.955\), and a decreasing tendency of rCTh in four ROIs, ie, in right lateral orbitofrontal cortex \(−3.23\%\), \(P = .015\), effect size = −.635\), left superior temporal cortex \(−3.81\%\), \(P = .029\), effect size = −.561\), right bankssts located in temporal cortex \(−5.97\%\), \(P = .007\), effect size = −.717\), and left insula \(−4.61\%\), \(P = .025\), effect size = −.578\).

Concerning SGMV, the PD patients showed only a trend of decreasing volume in left pallidum \(−18.75\%\), \(P = .030\), effect size = −.381\).

In concern of symptom lateralization, the paired comparison between PD patients and matched HCs revealed a significant decrease of rCTh in ipsilateral medial orbitofrontal cortex \(2.38 ± .12\ mm\ vs. 2.49 ± .12\ mm, \(P = .003\), effect size = −.843\), Table 3\), while the rCTh in contralateral medial orbitofrontal cortex seemed to change in the same direction but without reaching the significance level \(2.37 ± .15\ mm\ vs. 2.49 ± .16\ mm, \(P = .053\), not shown\) in our PD patients group. In addition, a decreasing trend of volume was observed in contralateral pallidum of the PD patients \(1.2 ± .03\ vs. 1.6 ± .07, \(P = .023\), effect size = −.386\, Table 3\). The paired comparison between contralateral and ipsilateral hemispheres within the PD patients did not reveal significant results, but some changing trends: the volume of the contralateral putamen was smaller than that of ipsilateral putamen \(2.19 ± .25\ vs. 2.25 ± .27, \(P = .043\), effect size = −.534\); while the rCTh in ipsilateral precuneus was thinner than that in contralateral precuneus \(2.38 ± .15\ vs. 2.43 ± .14, \(P = .025\), effect size = .600, Table 3\).

Spearman’s correlation test did not reveal correlations between observed brain morphological changes and the clinical characteristics (disease duration, MDS-UPDRS scores).

**Table 1. Demographic and Clinical Characteristics of Early-Stage PD Patients and Age-Sex-Matched Healthy Controls**

| Number | PD Patients | Controls | \(P\) |
|--------|-------------|----------|------|
| Sex (female/male) | 11/7 | 11/7 | |
| Age (years) | 60.39 ± 7.46 | 59.78 ± 7.14 | .803 |
| DemTect | 15.39 ± 3.07 | 17.33 ± 1.46 | .021 |
| Handedness (left/right) | 0/18 | 0/18 | |
| Disease duration (year) | 6.00 ± 3.90 | NA | |
| Onset body side | 7/10 | NA | |
| MDS-UPDRS I | 7.44 ± 4.58 | NA | |
| MDS-UPDRS II | 6.83 ± 4.12 | NA | |
| MDS-UPDRS III | 15.72 ± 7.58 | NA | |
| MDS-UPDRS IV | .39 ± 1.04 | NA | |
| MDS-UPDRS total | 30.39 ± 11.37 | NA | |
| Subtype (Tremor/Bradykinesia-Rigidity/Mixed) | 8/4/6 | NA | |
| Levodopa Equivalent Daily Dose (mg) | 785.30 ± 545.82 | NA | |
| H&Y stage (I/II) | 8/10 | NA | |

All the data represent mean ± standard deviation unless otherwise indicated. All clinical characteristics of the PD patients were collected in the best medical “ON-state.” \(* P < .05\) is considered statistically significant difference of two-sided \(t\)-test.

DemTect = Dementia Detection test; H&Y stage = Hoehn & Yahr stage; MDS-UPDRS = Movement Disorder Society sponsored revision of Unified Parkinson’s Disease Rating Scale; NA = not available; PD = Parkinson’s disease.

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\(\text{Cohen’s } d = (\text{mean 1} − \text{mean 2})/\text{standard deviation}\)\(^2\)

\(\gamma = Z/\sqrt{N^2}\)
Voxel-Wise Analysis

The results of voxel-wise comparison of CTh (p-maps derived from TFCE-test) between PD patients and matched HCs are illustrated in Figure 1. With the relaxed threshold, the p-map revealed one cluster with cortical thinning trend (with cluster size of 656 voxels and $P_{unc} = .0028$) located between left insula (57%) and left superior temporal cortex (43%) in PD patients (Figure 1, indicated by red color). No significant or tended difference of SGMV between early-stage PD patients and matched HCs was found. Also, no correlation between observed cortical thinning trend and the clinical data was found by use of one sample t-test in GLM.

Discussion

In this cross-sectional study, based on MRI data of brain, rCTh and SGMV values of the patients suffering from early-stage PD (H&Y ≤ II) and the age- and sex-matched healthy subjects were obtained by using free software CAT12, enabling an estimation of PD-related alterations of rCTh and SGMV. By focusing on evaluating its clinical applicability of the quantitative measurements of brain morphology with CAT12, all the MR images were scanned under clinical routine conditions and the T1-weighted image data were analyzed straightforward by running the default processing pipeline, without considering computationally expensive options provided in CAT12. We found in our early PD patients a significant cortical thinning in the left medial orbitofrontal cortex, as well as in the ipsilateral medial orbitofrontal cortex when grouping two brain hemispheres in respect of the symptom-onset body side of the PD patients. In addition, a trend of rCTh thinning or SGMV decreasing was observed in several other brain regions of the PD patients. These results demonstrated that brain morphological alterations in early PD patients were evident and detectable, indicating the potential of brain morphological measurements with CAT12 as an add-on tool for clinical diagnosis of early PD.

We found that, in early-stage PD patients, the regional cortical thinning occurred in frontal and temporal lobes (Fig 1, Table 2), which is consistent with those reported by previous studies. Tinaz et al found focal cortical thinning in orbitofrontal and parietal cortices in 15 early-stage PD patients. Similarly, Jubault et al also reported focal cortical thinning trend in left medial supplementary motor area (SMA) and in the right dorsal pre-SMA in 49 nondemented PD patients with H&Y ≤ 2.5. According to Danti et al, cortical thinning was found in frontal, temporal, and parietal lobes of early-stage PD patients with mild cognitive impairment (MCI). The brain regions showing cortical thinning reported in present study and in previous imaging studies have been linked to certain dysfunctions in PD patients, eg, the orbitofrontal (bilaterial medial orbitofrontal) thinning was associated with olfactory impairments thus considered as marker for early-phase PD; the temporal thinning (left superior temporal and right banks sts) was associated with decline in sensory function in the PD patients; and thinning of the insula (left insula) was associated with executive dysfunction in PD patients. Of note, we only found a significant decrease of the left medial orbitofrontal cortex in early PD patients. Reasons for the lesser amount of significant cortical thinning found in our study may be attributed to the fact that most of our PD patients were in a rather early disease stage with less brain changes, besides the possible potentiation-like plasticity effect of levodopa medication.

Concerning SGMV, we did not find significant changes in our PD patients in comparison to HCs, but a trend of volume decreasing was found in left pallidum (Table 2). Previous reports on changes of SGMV in PD were heterogeneous. Tinaz et al and Lewis et al reported decreased putamen volume in early-stage PD. Jia et al reported decreased volume of caudate body in early-stage PD. Although the observed decreasing trend of pallidal volume may correspond to the pathological degeneration of substantia nigra pars compacta in PD pathology, the effect size ($\delta = .359$, Table 2) is at a moderate level ($\delta = .3-.5$), indicating that caution is necessary by the interpretation. The fact that no significant SGMV shrinkage found in this study might be corresponding to nearly unimpaired cognitive performance of our PD patients, who revealed a mean DemTect score though slightly lower than that of matched HCs ($15.39 \pm 3.07$ vs. $17.33 \pm 1.46$) but still within the normal range ($> 13$) [Table 1], while an atrophy of SGMV has been linked to cognitive impairment. This detail indicated

| Regions of Interest | PD Patients$^a$ | Controls$^a$ | $P$ (Paired t-Test) | $P$ (Wilcoxon Test) | Effect Size | Deviation (%)$^b$ |
|---------------------|----------------|-------------|---------------------|---------------------|-------------|------------------|
| rCTh                |                |             |                     |                     |             |                  |
| Left medial orbitofrontal (mm) | 18 | 2.35 .12 | 2.51 .13 | .001$^*$ | −.955$^b$ | −6.37 |
| Right lateral orbitofrontal (mm) | 18 | 2.70 .11 | 2.79 .12 | .015 | −.635$^b$ | −3.23 |
| Left superior temporal (mm) | 18 | 2.78 .16 | 2.89 .15 | .029 | −.561$^b$ | −3.81 |
| Right banks sts (mm) | 18 | 2.52 .19 | 2.68 .15 | .007 $^*$ | −.717 | −5.97 |
| Left insula (mm) | 18 | 3.31 .21 | 3.47 .19 | .025 | −.578 | −4.61 |
| SGMV                |                |             |                     |                     |             |                  |
| Left pallidum$^g$ | 18 | .13 .03 | .16 .05 | .030 $^*$ | −.381$^b$ | −18.75 |

$^a$Mean and standard deviation (SD) of regional cortical thickness and subcortical gray matter volume (in ratio to estimated total intracranial volume timed with 1,000) are presented for patients and controls; $N$ is the number of paired patients and controls.

$^b$These data are not in normal distribution.

$^g$Cohens' $d$ was calculated for effect size of paired $t$ test or Wilcoxon test.

$^*$Deviation of the patients’ mean value from that of the healthy controls was calculated in ratio to the mean value of the healthy controls.

$^\dagger$Significant results after multiple comparison correction with false-discovery rate at desired ratio of .05.

$^\ddagger$Results showing tended changes.

mm = millimeter; rCTh = regional cortical thickness; SGMV = subcortical gray matter volume; PD = Parkinson’s disease.

Table 2. Significant or Tended Changes of Regional Cortical Thickness and Subcortical Gray Matter Volume in PD Patients Derived from ROI-Wise Analysis
In concern of symptom lateralization, we found no significant changes of SGMV in our cohort. However, the PD patients showed SGMV decreasing trends in contralateral hemisphere, that is, the contralateral putamen (in comparison to ipsilateral putamen in patients) as well as the contralateral pallidum (in comparison to that of the HCs) showed both a trend of decreasing volume (Table 3), indicating a preference of the contralateral basal ganglia being involved into PD pathological changes. This finding is in line with the observation of basal ganglia degeneration being more severe in the hemisphere contralateral to the symptom-onset side reported by a previous study.40

In this study, PD-related morphological changes have also been estimated by using voxel-wise analysis, which provided an opportunity to compare the usage of the two different methods of data analysis. With voxel-wise analysis, one cluster showed a cortical thinning trend located between insula and superior temporal cortex of left hemisphere. Further, the ROI-wise analysis found a significant rCTh thinning in left medial orbitofrontal cortex, and a trend of rCTh thinning in four further brain regions located in frontotemporal cortex, as well as a trend of decreasing volume in left pallidum. These results derived with both analyses confirmed each other showing that early PD patients display decreased brain CTh in the frontotemporal region. However, there were differences concerning involved fine brain structures, which could be deduced mainly to the methodological differences between voxel-wise analysis and ROI-wise analysis, as was also reported by Tinaz et al.4 With the possibility to quantify the sizes of specific and standardized brain structures, the ROI-wise analysis could be used to estimate brain morphological changes individually and thus may be more applicable for clinical diagnostic use on individual patients, while the voxel-wise analysis allowed an unbiased overall assessment of anatomical differences throughout the whole brain and thus could provide a supplemental overview (as shown in Fig 1).41

In our early-stage PD patients, no correlations between observed brain morphological alterations and the disease duration or MDS-UPDRS scores were found, which is in line with those observed by others. For example, Danti et al reported that there was no significant association of alternated rCTh or SGMV with disease duration or UPDRS II-III, and no contribution of motor laterality to the correlations between changes of rCTh or SGMV and the disease duration or MDS-UPDRS II-III scores.3 Lee et al also did not find correlations of changes in cortical or SGMV to disease duration or to UPDRS motor subscale score in early-stage PD patients.10 Similarly, Lewis et al reported that the changes of SGMV did not correlate to disease duration or to UPDRS III in early-stage nondemented PD patients (with Mini-Mental State Exam scores ≥24).11 A possible reason for it could be that the brain morphological changes in our early PD patients might be too subtle for the correlation analyses.

The major limitation of present study is the rather small sample size of our early-stage PD patients so that caution against over interpretation should be given, especially by

Table 3. Significant or Tended Changes of Regional Cortical Thickness and Subcortical Gray Matter Volume in Hemispheres Contralateral and Ipsilateral to Symptom-Onset Body Side of PD Patients-Derived ROIs

| Regions of Interest        | Mean (SD) Control | Mean (SD) PD | P (Paired T-Test) | Effect Size | Deviation (%)* |
|----------------------------|------------------|--------------|-------------------|-------------|---------------|
| Contralateral Hemisphere   |                  |              |                   |             |               |
| Pallidum                   | 1.70 (.12)       | 1.29 (.12)   | .03               | .07         | -.36          |
| Ipsilateral Hemisphere     | 2.38 (.14)       | 2.49 (.12)   | .003              | .07         | -.84          |
| Medial orbitofrontal (mm)  | 2.38 (.14)       | 2.49 (.12)   | .003              | .07         | -.84          |
| Precuneus (mm)             | 2.43 (.14)       | 2.38 (.14)   | .025              | .07         | -.50          |
| Putamen                    | 2.19 (.25)       | 2.25 (.27)   | .043              | .07         | -.50          |
| ROI-Wise Analysis          |                  |              |                   |             |               |
| Controls, Mean and SD      |                  |              |                   |             |               |
| N                          | 17               | 17           |                   |             |               |
| Mean                       | 1.70 (.12)       | 1.29 (.12)   | .03               | .07         | -.36          |
| SD                         | 1.27 (.12)       | 1.27 (.12)   | .03               | .07         | -.36          |
| P (Paired T-Test)          |                  |              |                   |             |               |
| Effect Size                |                  |              |                   |             |               |
| Deviation (%)              |                  |              |                   |             |               |

*Mean and standard deviation (SD) of regional cortical thicknesses and subcortical gray matter volumes (in ratio to estimated total intracranial volume timed with 1,000) are presented for patients and controls; N is the number of paired patients and controls.

**Significant results after correction with false-discovery rate at desired ratio of .05.

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interpretation of results observed on pallidum with a small effective size (Cohens’ d ≈ −.38). Also, most of our PD patients were under levodopa therapy and the levodopa medication may have some impact on our measurements of rCTh or SGMV. Further studies with larger sample size of early PD subjects are needed to validate these findings.

In conclusion, present work confirmed altered rCTh and SGMV in patients with early-stage PD, and demonstrated that the early PD-related brain morphological changes could be detected under clinical routine conditions, indicating the potential use of brain morphological measurements with CAT 12 as an add-on tool for clinical diagnosis of early PD.

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