MORPHOLOGIC ANALYSIS OF THE STRIATUM IN PARKINSON'S DISEASE

A Thesis in
Public Health Sciences
by
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of the Requirements
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Abstract

**Background:** Parkinson’s disease (PD) is marked pathologically by progressive nigrostriatal dopaminergic terminal loss. Histopathological and *in vivo* labeling studies suggest that this loss occurs most extensively in the caudal part of the putamen and head of the caudate, although the caudate generally is less affected than the putamen. Previous studies have demonstrated reduced striatal (caudate and putamen) volume in PD subjects, yet the exact spatial pattern of striatal atrophy remains unknown.

**Objective:** To use shape analysis to delineate the spatial locations of striatal atrophy in relation to the known pattern of dopaminergic terminal loss in PD.

**Methods:** High resolution T1- and T2-weighted brain MR (3T) images were obtained from 40 PD and 40 controls matched for age distribution and gender. Striatal regions of interest (ROIs) were obtained using an atlas-based automatic segmentation algorithm, followed by manual correction of original and left-right mirrored images. Averaged ROIs were used in order to control rater left-right asymmetric bias. Shape analyses then were conducted using spherical harmonic shape descriptions and point distribution models. The associations between the clinical data and the striatal volumes/shapes also were determined, and adjustments were made for multiple comparisons.

**Results:** Compared to controls, PD subjects had lower putamen (p<0.001) and caudate (p=0.006) volumes. The greatest magnitudes of surface contractions in the PD striatum were located at the caudal putamen (p<0.005) and on the head and dorsal body of the caudate (p<0.005). Differences were detected even in relatively newly diagnosed patients (p<0.005). Contractions on the dorsolateral and rostral ventrolateral surfaces of the putamen were correlated with lower Montreal Cognitive Assessment (MoCA) scores (p<0.005).

**Conclusions:** The spatial distribution of striatal atrophy is consistent with the known pattern of nigrostriatal dopaminergic terminal losses in PD, and the shape differences between PD and controls are apparent even in early stages of the disease. Thus, shape characteristics may be useful for reflecting striatal pathological changes and thus for monitoring PD progression *in vivo*. To our knowledge, the current study is the first to report shape differences between the putamen of PD and control subjects.
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Preface

This thesis approximates the format of a scientific manuscript intended for peer review. The following authors also have contributed to the research contained in this thesis manuscript...

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Introduction

Parkinson’s disease (PD) is the second most common age-related neurodegenerative disorder and is characterized clinically by tremor at rest, bradykinesia, and rigidity (de Lau and Breteler, 2006). Pathologically, PD is marked by loss of dopaminergic neurons in the substantia nigra pars compacta of the midbrain (Braak et al., 2003; Jellinger, 2012). Dopamine depletion of the striatum (putamen and caudate), resulting from the loss of nigrostriatal terminals, reaches 60-80% before the onset of classic motor symptoms, most severely affecting the caudal portion of the putamen and head of the caudate (Kish et al., 1988; Lang and Obeso, 2004; Otsuka et al., 1996; Rodriguez-Oroz et al., 2009).

Previous studies have suggested that the striatum undergoes substantial cellular remodeling throughout the course of PD (for review, see Pitcher et al., 2012). Dopamine-depleted animal and post-mortem studies of PD subjects, for example, have demonstrated reduced dendritic length and spine density of the medium spiny neurons within the striatum (Ingham et al., 1993; McNeill et al., 1988; Stephens et al., 2005). In humans, spine density is reduced particularly in the caudal part of the putamen, where dopaminergic deficits are known to be most severe (Zaja-Milatovic et al., 2005). Moreover, dopamine is known to play an important role in maintaining striatal spine integrity (Villalba et al., 2009).

Several structural studies have suggested that the putamen and caudate undergo atrophy in PD (for review, see Pitcher et al., 2012). The spatial distribution of atrophic areas, however, remains unknown. Information regarding the pattern of striatal atrophy is important because it may yield insight into the structural consequences of striatal cellular
remodeling and also may provide region-specific biomarkers that mirror PD disease progression. In this study, we aimed to characterize these atrophic sites using a state-of-the-art protocol for segmentation and shape analysis. Semi-automated segmentation was used to define regions of interest (ROIs), with left-right mirrored averaging to control for left-right rater bias. Shape analysis was performed on the average ROIs, subsequently, using spherical harmonic point distribution models (SPHARM-PDM). We hypothesized that striatal shape differences would be greatest in areas that are known to be affected most severely by dopamine depletion and consequent striatal spine pathology in PD, namely, the caudal portion of the putamen.

**Methods**

**Subjects**

Forty PD subjects (20 female, 20 male) and 40 healthy control subjects (20 female, 20 male) with matched age distributions were recruited from a tertiary movement disorders clinic. PD diagnosis was confirmed by a movement disorders specialist using published criteria (Hughes et al., 1992). All subjects were confirmed for absence of other major and acute neurological and psychological disorders, hypothyroidism, vitamin B₁₂ and folate deficiency, and kidney and liver disease. Unified Parkinson’s Disease Rating Scale section III-motor scores (UPDRS-III) were obtained for each subject, with PD subjects assessed after withholding PD medications overnight (>12 hours) as a practically-defined off-drug state (Langston et al., 1992). Duration of illness (DOI) was calculated based on date of clinical diagnosis. Levodopa equivalent daily dose (LEDd) was calculated using published criteria (Tomlinson et al., 2010). Written informed consent was obtained for each subject, in accordance with the Declaration of Helsinki.
The research protocol was reviewed and approved by the Penn State Hershey Medical Center Institutional Review Board (Protocol ID #28989).

**Neuropsychological assessment**

All subjects completed a basic neuropsychological battery to assess orientation, memory, and signs of dementia. The Mini Mental Status Exam (MMSE) is a brief (5-minute) 30-point test that assesses orientation memory and the ability to follow commands. The Montreal Cognitive Assessment (MoCA) was developed to address the limitations of the MMSE in detecting mild cognitive impairment (Hoops et al., 2009). Subjects also completed the Dementia Rating Scale-2 (DRS2) that is used in order to assess for dementia and determine its severity (Monsch et al., 1995). Subjects were included only if they had an MMSE score >24 and a DRS2 score > 5th scaled percentile.

**Image 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) and high-resolution T1- and T2-weighted images were acquired. A magnetization-prepared rapid acquisition gradient echo sequence was used to obtain T1-weighted images with TR=1540 ms, TE=2.34 ms, field of view=256 mm, matrix=256x256, slice thickness=1 mm (with no gap), and slice number=176. T2-weighted images were collected using a fast-spin-echo sequence with TR=2500, TE=316, and the same resolution configuration as that for T1-weighted images.
**Semi-automatic segmentation**

Putamen and caudate structures were obtained using a semiautomatic region of interest (ROI)-based approach. Probabilistic atlas-based automatic segmentation first was performed using AutoSeg (Neuro Image Research and Analysis Laboratories, University of North Carolina at Chapel Hill, NC, USA). This software features N4 bias field correction, expectation-maximization tissue segmentation, skull striping, and probabilistic atlas-based segmentation of subcortical structures (Lewis et al., 2009; Vachet et al., 2001; Van Leemput et al., 1999; Van et al., 1999). The resulting ROIs then were manually corrected by an investigator (NWS) blinded to subject diagnosis and symptoms using ITK-SNAP 2.2.0 (www.itksnap.org; Figure 1) (Yushkevich et al., 2006). This semi-automated process was repeated after a four week delay using a mirrored version of the original image set (in which left and right sides were inverted), in order to correct for potential left-right bias (Maltbie et al., 2012).

**Average regions of interest**

Volumes for each ROI were extracted from mirrored and original image sets and then were averaged together, maintaining original left and right designations. After mirrored ROIs were reverted to their original orientations, a Gaussian smoothing process (standard deviation=0.3 mm) was applied to the original and reverted mirrored ROIs. Intensity values of original and mirrored ROIs were added and normalized so that the maximum and minimum intensities were 1 and 0, respectively. The smoothed ROI borders then were binarized using an intensity threshold of 0.8 to yield the average ROIs for further analysis.
Mesh generation, spherical parameterization, and alignment

Shape analysis was performed on the averaged ROIs using the SPHARM-PDM (Spherical Harmonics Point Distribution Models) toolbox (Neuro Image Research and Analysis Laboratories, University of North Carolina at Chapel Hill, NC, USA) (Styner et al., 2003; Styner et al., 2005; Styner et al., 2006b). The ROIs first were processed in order to fill any internal holes and adapted to guarantee spherical topology. Surface meshes and corresponding spherical parameterizations then were computed using area-preserving, distortion minimizing spherical mapping. The SPHARM descriptions were generated from surface meshes and their spherical parameterizations. The first order ellipsoid from the spherical harmonic coefficients was used to establish initial correspondence between the spherical parameterizations and each model was coregistered via generalized rigid Procrustes alignment. The SPHARM descriptions then were sampled into surface meshes with each of the 1442 surface points by icosahedron subdivision. All models were scaled to normalize for intracranial cavity volume differences. Models were inspected visually by an independent investigator (ZN) for anatomical accuracy and proper alignment.

Statistical analyses

Demographic and clinical parameters were compared using Student’s t-tests (Table 1). Group comparisons of volume were performed by analysis of covariance with adjustment for intracranial volume (ICV). Partial correlation analyses between clinical measurements and striatal volumes were corrected for ICV and/or age, as appropriate. All volume analyses were performed using SAS 9.3.
Group shape differences were analyzed using the multivariate analysis of variance (MANOVA) tool that is part of the SPHARM-PDM toolkit (Paniagua et al., 2009; Styner et al., 2006a). Specifically, shape statistics were calculated by treating the three-dimensional spatial coordinates as multivariate response variables at each surface point, and by general linear modeling and permutation based testing of the local Hotelling trace (Paniagua et al., 2009). Pearson correlation analysis between MoCA scores (adjusted for age) and distance from average surface was performed using generalized linear modeling. Topographical statistical significance maps for each surface coordinate were generated after correction for multiple comparisons using false-discovery rate (FDR). Reported p-values for shape analyses were adjusted via the Benjamini-Hochberg step-up procedure (FDR) using an expected proportion of incorrectly rejected null hypotheses of 5%.

Results

Study subjects

Detailed subject characteristics and clinical parameters are summarized in Table 1. There were no significant differences in age or cognitive assessment scores between PD and control groups. In PD subjects, the mean time since diagnosis was 4.1 years with a range of 0.1-15.8 years. LEDD varied widely in PD subjects, ranging from 0-1,975 mg.

Volume comparisons between PDs and controls

To account for possible effects of disease-related asymmetry, contralateral and ipsilateral striatal structures were first compared. For both PD and control subjects, no statistical differences were found between left and right or contralateral and ipsilateral
putamen or caudate volumes. Thus, bilateral striatal volumes were averaged for each subject and the mean volume was used in subsequent analyses.

PD subjects had significantly lower mean striatal volumes (Table 2). Average putamen volumes in PD subjects were 6.8% lower (p<0.001) than controls and caudate volumes were 5.7% lower (p=0.006). Subgroup analysis of PD subjects with shorter duration of illness (lowest 50% and lowest 25%) compared to controls showed similar results (Table 2).

**Striatal volume and clinical correlations with PD subjects**

In PD subjects, mean putamen and caudate volumes correlated positively with MoCA scores (Table 3). This relationship remained significant after correction for multiple comparisons (p=0.012). Caudate volume also correlated negatively with LEDD, but this correlation was not significant after correction for multiple comparisons. MMSE and DRS2 scores did not correlate with striatal volumes.

**Shape comparisons of PDs and controls**

Contralateral and ipsilateral sides first were compared within the PD group. Similar to the volume analysis above, there were no differences in shape between contralateral and ipsilateral structures. Thus, striatal structures were sampled bilaterally. Group comparisons were performed without covariance for age and gender, since the PD and control groups were well matched for these distributions. Comparison of PD and control striatal shapes revealed significant differences. For the putamen, the most significant differences were localized to the caudal and ventrolateral areas (p<0.005; Figure 2). Inspection of the vector field map revealed that the magnitude of surface contraction was greatest in the caudal portion of the putamen (Figure 2). For the caudate,
the most significant shape differences were present on the head and dorsal body
(p<0.005; Figure 3). The most prominent areas of caudate surface contraction were
located at the anterior head (Figure 3). Subgroup analysis comparing all controls with PD
subjects having shorter duration of illness (lowest 50% and 25%) showed similar results.

**Shape and MoCA correlations in PD**

After the determination that MoCA was the only clinical measurement that was
significantly correlated with striatal volume, we focused our shape correlation analysis on
this measurement. Indeed, we found that MoCA scores correlated significantly with
shape on the dorsolateral and rostral ventrolateral surfaces of the putamen (p<0.005;
Figure 4). MoCA scores displayed only minor areas of correlation with caudate shape (on
the ventral body), having significance (p<0.005) in less than 1.3% of all surface points
after FDR correction. We also explored potential striatal shape correlations with other
clinical measurements. No significant correlations between striatal shape and clinical
parameters were found.

**Discussion**

The current data are consistent with previous reports of striatal atrophy in PD and
indicate that striatal shape differences between PD and control subjects are most robust in
the caudal part of the putamen and caudate head. These shape differences were present
even in recently diagnosed PD patients. To our knowledge, this is the first study
demonstrating PD-related shape differences in the putamen. Consistent with our
hypothesis, these region-specific shape differences are reflective of the known
differential pattern of striatal dopamine depletion and associated spine loss in PD (Kish et
al., 1988; Otsuka et al., 1996; Rodriguez-Oroz et al., 2009; Zaja-Milatovic et al., 2005). It is possible, therefore, that disruption of dopaminergic innervation may play a role in PD-related striatal atrophy. Furthermore, these results support the notion that striatal shape may be useful as a biomarker for monitoring disease progression.

**Technical innovations**

Apostolova et al. (2010) studied shape differences in PD subjects across various stages of cognitive decline and reported some differences in caudate shape between 35 PD subjects (12 with normal cognition, 8 with mild cognitive impairment, and 15 with dementia) and 20 healthy controls. The current study differed substantially from that of Apostolova et al. (2010) in terms of sample characteristics and methodologies. First, in order to evaluate processes occurring relatively early in PD progression, and in order to exclude any confounds related to dementia, we included only non-demented PD subjects. The average duration of disease among the present PD subjects (4.1 years) also was much shorter (> 10 years in the report of Apostolova et al. (2010)). Second, Apostolova et al. (2010) used a machine learning approach for segmentation, whereas we utilized a semi-automated ROI-based segmentation protocol that supplements the consistency of an atlas-based approach with the anatomic validity of manually defined ROIs. Third, we controlled for the known phenomenon of left-right rater segmentation bias by averaging original and left-right mirrored ROI sets (Maltbie et al., 2012). Fourth, the present study utilized SPHARM-PDM in order to quantify shape differences, whereas the aforementioned study used radial distance mapping (Styner et al., 2005) which, as employed by Apostolova et al. (2010), necessitates the computation of a single corresponding radial/medial axis that is not reliably possible for structures like the
putamen. Conversely, the SPHARM-PDM shape analysis technique provides an analysis that is independent of the co-alignment of the original MRI scans.

**Striatal shape characteristics and known cellular mechanisms**

The current study supports the findings of previous volume studies suggesting striatal atrophy in PD (for review, see Pitcher et al., 2012). While the exact mechanisms of volume and shape differences remain unknown, it is possible that striatal atrophy is linked to intrinsic biochemical changes within the striatum, in association with dopamine depletion. It is well known that the most extensive dopamine depletion in PD occurs in the caudal part of the putamen and head of the caudate (Geng et al., 2006; Krabbe et al., 2005; O'Neill et al., 2002; Pitcher et al., 2012; Smith and Villalba, 2008). The current shape analysis demonstrated that the striatal regions bearing the greatest magnitude of shape contractions in PD correspond with these areas, suggesting that dopaminergic dysfunction may contribute to the atrophic differences demonstrated herein. Indeed, striatal spine loss has been demonstrated to be highly dependent upon the degree of dopamine depletion in MPTP-treated monkeys, occurring even in the absence of overt motor symptoms (Villalba et al., 2009). Taken together, these early pathologic features coupled with PD-related striatal shape differences occurring in recently diagnosed individuals offer the tantalizing hypothesis that striatal shape characteristics may serve as biomarkers for early PD-related changes. The sensitivity and specificity of these measurements require further characterization in studies of PD and Parkinsonism subjects (Nandhagopal et al., 2011).

In addition to dopamine depletion, a number of other biochemical changes occur within the PD striatum. Several lines of evidence suggest that glutamatergic synaptic and
intraspine calcium channel dysregulation may play key roles in PD-related striatal spine pathology (Burguière et al., 2013; Tian et al., 2010; Villalba and Smith, 2010). Previous studies, for example, have shown that reducing glutamate release may prevent and/or reverse dopamine depletion-induced dendritic spine loss on medium spiny neurons (Garcia et al., 2010; Neely et al., 2007). These losses, furthermore, are known to be most severe in the caudal part of the putamen, bearing remarkable resemblance to the known gradient of dopamine depletion within the PD striatum (Zaja-Milatovic et al., 2005). The administration of an L-type calcium channel blocker in an animal model was shown to attenuate spine losses (Bezard, 2010; Schuster et al., 2009; Soderstrom et al., 2010). Thus, it is possible that dopamine depletion and glutamatergic dysregulation may be involved in the observed differences in striatal shape. The putative contribution of these cellular mechanisms to global striatal atrophy may be evaluated in future studies of targeted neuroprotective agents in PD.

*Striatal shape characteristics and clinical implications*

The MoCA is known to be a particularly sensitive instrument for detecting early cognitive decline in PD (Dalrymple-Alford et al., 2010). The finding that striatal volume and shape correlate significantly with MoCA scores is consistent with the notion that the striatum has a complex role in normal cognition as part of several large scale neural networks. The rostral portions of the putamen and caudate are known to receive projections from the dorsolateral, orbital, and medial prefrontal cortices (Haber, 2003). Similarly, limbic projections from the hippocampus and amygdala project to the ventral regions of the putamen. These striatal limbic, associative, and motor circuits are highly integrated and allow for a hierarchical flow of information through the striatal system
(Haber et al., 2000). In line with the cognitive correlations demonstrated herein, which are primarily localized to the rostral regions of the putamen, frontostriatal dysfunction is well documented in PD and may be responsible for some neuropsychological deficits that occur throughout disease progression (Brown et al., 1997; Lewis et al., 2003).

**Limitations and Conclusions**

The cross-sectional nature of the study design and individual variations in the rate of disease progression, coupled with the relatively broad ranges of disease duration and clinical staging, made impossible the assessment of time-related changes. Longitudinal follow-up of this cohort will be necessary to confirm volume and shape alterations as dynamic components of PD progression. Second, in order for shape analysis to be practical in future clinical trials and medical practice, reliable fully automatic processes are needed. Nevertheless, this study demonstrated region-specific shape differences, measured via MRI, within the putamen and caudate of PD patients that are consistent with the known differential pattern of dopamine depletion in the striatum. We propose that shape characteristics may be useful for reflecting early PD-related striatal changes, monitoring disease progression, and ultimately gauging the efficacy of neuroprotective therapies.
# Appendix A: Tables

## Table 1. Demographic and clinical information of PD and control subjects

<table>
<thead>
<tr>
<th></th>
<th>Control (SD)</th>
<th>PD (SD)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>59.4 (7.8)</td>
<td>61.3 (7.8)</td>
<td>0.270a</td>
</tr>
<tr>
<td>Years Since Diagnosis</td>
<td>NA</td>
<td>4.1 (4.2)</td>
<td>NA</td>
</tr>
</tbody>
</table>

### Motor Measurements

<table>
<thead>
<tr>
<th></th>
<th>Control (SD)</th>
<th>PD (SD)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hoehn-Yahr Stage</td>
<td>0 (0)</td>
<td>1.8 (0.6)</td>
<td>&lt; 0.001b</td>
</tr>
<tr>
<td>UPDRS-III</td>
<td>1.1 (1.26)</td>
<td>22.6 (14.7)</td>
<td>&lt; 0.001b</td>
</tr>
<tr>
<td>LEDD (mg)</td>
<td>NA</td>
<td>465.3 (376.8)</td>
<td>NA</td>
</tr>
</tbody>
</table>

### Cognitive Measurements

<table>
<thead>
<tr>
<th></th>
<th>Control (SD)</th>
<th>PD (SD)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DRS2</td>
<td>141.2 (2.3)</td>
<td>140.2 (3.6)</td>
<td>0.145a</td>
</tr>
<tr>
<td>MMSE</td>
<td>30.5 (0.8)</td>
<td>30.2 (1.2)</td>
<td>0.184b</td>
</tr>
<tr>
<td>MoCA</td>
<td>25.8 (2.4)</td>
<td>25.6 (2.9)</td>
<td>0.746b</td>
</tr>
</tbody>
</table>

All values are presented as group means and standard deviations (SD), except for the number and gender of subjects. Motor and cognitive measurements in PD subjects were obtained in the off-medication state (see Methods).

a P-values calculated using two-sample t-tests with pooled variance.

b P-values calculated using two-sample t-tests with non-pooled variance.

Abbreviations: DRS2 = Dementia Rating Scale-2; LEDD = levodopa equivalent daily dose; MMSE = Mini Mental State Examination; MoCA = Montreal Cognitive Assessment; UPDRS-III = Unified Parkinson’s Disease Rating Scale section III.
Table 2. Striatal volumes (voxels, mm$^3$) in PD and control subjects

<table>
<thead>
<tr>
<th></th>
<th>PD</th>
<th>Control</th>
<th>PD/Control (%)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Analysis of all subjects</strong>†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>40</td>
<td>40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Putamen</td>
<td>4168 (61.4)</td>
<td>4473 (61.4)</td>
<td>93.2</td>
<td>&lt; 0.001$^a$</td>
</tr>
<tr>
<td>Caudate</td>
<td>3118 (46.6)</td>
<td>3308 (46.6)</td>
<td>94.3</td>
<td>0.006$^a$</td>
</tr>
<tr>
<td><strong>Subgroup analysis</strong>‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PD subjects with diagnosis 0.1 - 2.3 years</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>20</td>
<td>40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Putamen</td>
<td>4117 (78.0)</td>
<td>4412 (78.9)</td>
<td>93.3</td>
<td>0.005$^b$</td>
</tr>
<tr>
<td>Caudate</td>
<td>3118 (68.6)</td>
<td>3280 (50.9)</td>
<td>95.0</td>
<td>0.011$^b$</td>
</tr>
<tr>
<td><strong>PD subjects with diagnosis 0.1 - 1.1 years</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>10</td>
<td>40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Putamen</td>
<td>3969 (70.9)</td>
<td>4412 (78.9)</td>
<td>90.0</td>
<td>0.005$^b$</td>
</tr>
<tr>
<td>Caudate</td>
<td>3075 (74.6)</td>
<td>3280 (50.9)</td>
<td>93.7</td>
<td>0.028$^b$</td>
</tr>
</tbody>
</table>

† Adjusted mean volumes and standard errors.

‡ Raw mean volumes and standard errors.

$^a$ Corrected for total intracranial volume.

$^b$ Corrected for total intracranial volume, age, and gender, due to unmatched distributions.
Table 3. Partial correlation coefficients and p-values between mean striatal volumes and clinical measurements in PD subjects

<table>
<thead>
<tr>
<th></th>
<th>Putamen</th>
<th>Caudate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hoehn-Yahr Stage</strong></td>
<td>-0.01(^a) (0.967)</td>
<td>-0.04(^a) (0.803)</td>
</tr>
<tr>
<td><strong>LEDD</strong></td>
<td>0.09(^b) (0.588)</td>
<td>-0.33(^b) (0.046)</td>
</tr>
<tr>
<td><strong>UPDRS-III</strong></td>
<td>0.03(^b) (0.875)</td>
<td>-0.21(^b) (0.207)</td>
</tr>
<tr>
<td><strong>DRS2</strong></td>
<td>0.04(^c) (0.800)</td>
<td>0.26(^c) (0.121)</td>
</tr>
<tr>
<td><strong>MMSE</strong></td>
<td>0.07(^c) (0.673)</td>
<td>0.23(^c) (0.171)</td>
</tr>
<tr>
<td><strong>MoCA</strong></td>
<td>0.52(^c) (0.001(^*))</td>
<td>0.38(^c) (0.017)</td>
</tr>
</tbody>
</table>

\(^a\) Spearman’s partial correlation coefficients (corrected for total ICV).

\(^b\) Spearman’s partial correlation coefficients (corrected for age and total ICV).

\(^c\) Pearson’s partial correlation coefficients after (corrected for age and total ICV).

\(^*\) Significant after Bonferroni correction for multiple comparisons (p=0.012).

Abbreviations: DRS2 = Dementia Rating Scale-2; LEDD = levodopa equivalent daily dose; MMSE = Mini Mental State Examination; MoCA = Montreal Cognitive Assessment; UPDRS-III = Unified Parkinson’s Disease Rating Scale section III.
Appendix B: Figures

Figure 1. Axial slice of average ROIs calculated from original and mirrored ROIs.

*Left and right putamen (P) and caudate nuclei (C) are depicted.*
Figure 2. Putamen shape differences between PD (n=40) and control (n=40) subjects

Distance maps represent vector magnitudes (M). FDR-corrected p-values are for comparisons between PD and control subjects, bilaterally sampled and scaled for ICV.
**Figure 3.** Caudate shape differences between PD (n=40) and control (n=40) subjects

Distance maps represent vector magnitudes (M). FDR-corrected p-values are for comparisons between PD and control subjects, bilaterally sampled and scaled for ICV.

Distance maps represent vector magnitudes (M). FDR-corrected p-values are for comparisons between PD and control subjects, bilaterally sampled and scaled for ICV.
**Figure 4.** Partial correlation of MoCA scores with putamen shape in PD subjects

<table>
<thead>
<tr>
<th>Distance map</th>
<th>P-value map</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anterior</strong></td>
<td><strong>Posterior</strong></td>
</tr>
<tr>
<td><strong>Lateral surface</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Superior</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Inferior</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Medial surface</strong></td>
<td></td>
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</tbody>
</table>

Distance maps represent Pearson’s partial correlation coefficients. FDR-corrected p-value maps represent the correlation between bilaterally sampled shape surface points and MoCA/age correlation residuals, scaled for ICV.
References


