RESEARCH ARTICLE

Apathy in Parkinson's Disease Is Associated With Nucleus Accumbens Atrophy: A Magnetic Resonance Imaging Shape Analysis

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ABSTRACT: Apathy is characterized by lack of interest, loss of initiative, and flattening of affect. It is a frequent, very disabling nonmotor complication of Parkinson's disease (PD). The condition may notably occur when dopaminergic medications are tapered after the initiation of subthalamic stimulation and thus can be referred to as "dopaminergic apathy." Even in the absence of tapering, some patients may develop a form of apathy as PD progresses. This form is often related to cognitive decline and does not respond to dopaminergic medications (dopa-resistant apathy). We aimed at determining whether dopa-resistant apathy in PD is related to striatofrontal morphological changes. We compared the shape of the striatum (using spherical harmonic parameterization and sampling in a three-dimensional point distribution model [SPHARM-PDM]), cortical thickness, and fractional anisotropy (using tract-based spatial statistics) in 10 consecutive patients with dopamine-refractory apathy, 10 matched nonapathetic PD patients and 10 healthy controls. Apathy in PD was associated with atrophy of the left nucleus accumbens. The SPHARM-PDM analysis highlighted (1) a positive correlation between the severity of apathy and atrophy of the left nucleus accumbens, (2) greater atrophy of the dorsolateral head of the left caudate in apathetic patients than in nonapathetic patients, and (3) greater atrophy in the bilateral nucleus accumbens in apathetic patients than in controls. There were no significant intergroup differences in cortical thickness or fractional anisotropy. Dopa-resistant apathy in PD was associated with atrophy of the left nucleus accumbens and the dorsolateral head of the left caudate.

Key Words: Parkinson's disease; apathy; MRI

Apathy is characterized by lack of interest, loss of initiative, indifference, and flattening of affect. As noted by Marin, apathy is not just a symptom of depression or dementia, but can also exist as a syndrome per se.[1] Apathy is frequent in Parkinson's disease (PD), with a point prevalence ranging between 17% and 50%.[2] Moreover, apathy in nondepressed, nondemented patients may precede occurrence of dementia.[3]

The mechanisms underlying apathy in PD remain largely unknown and have mainly been investigated using functional imaging in patients with STN-DBS. In this population, apathy is presumably related to the tapering of dopaminergic treatments after initiation of STN-DBS and improves after increasing the dopamine agonist dosage.[4] Several studies have demonstrated the presence of dopaminergic limbic cortex denervation[5] and cortical hypometabolism[6] in stimulated, apathetic PD patients. These results suggest that apathy in PD may be related to insufficient doses of dopaminergic medication—leading to a "hypodopaminergic state" in the limbic circuit.

Additional Supporting Information may be found in the online version of this article.

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However, in non-STN-DBS patients, apathy has been correlated with (1) hypometabolism in the left insula and right frontal and occipital regions, (2) cerebellar hypermetabolism,[7] and (3) low gray matter density in cortical associative and limbic regions.[8] These results prompted the hypothesis whereby mechanisms other than dopaminergic mesolimbic denervation could lead to apathy in PD. Moreover, in the absence of treatment tapering, patients (with or without STN-DBS) frequently develop apathy as PD progresses; if the apathy is related to cognitive decline, it does not usually respond to dopaminergic medications.[3]

We hypothesized that degeneration of the deep brain nuclei (which are significantly involved in the disease mechanism of PD) may contribute to the occurrence of dopa-resistant apathy. Indeed, deep brain nuclei damage and/or atrophy appear to be involved in apathy in patients with stroke and those with Alzheimer's disease.[9,10] We therefore sought to establish whether patients suffering from "dopa-resistant" apathy displayed morphological changes (e.g., local atrophy) in the deep brain nuclei. The morphological analysis used here enables the detection of focal changes in the shapes of complex structures. Dopa-resistant apathy might also be related to either cortical atrophy (especially in associative and limbic regions) or corticosubcortical disconnection. These two alternative hypotheses were tested by analyzing cortical thickness and tract-based spatial parameters.

Patients and Methods

Patients

Ten consecutive apathetic patients fulfilling the Queen Square Brain Bank Criteria for PD[11] were enrolled in the study. They met apathy criteria published by Robert et al.[12] and had a score greater than −16 on the Lille Apathy Rating Scale (LARS).[13] Ten matched, nonapathetic PD patients and 10 healthy controls were included as PD and healthy control groups, respectively. None of the patients met the diagnostic criteria for PD dementia[14] or depression according to the *Diagnostic and Statistical Manual of Mental Disroders, Fourth Edition, Text Revision*. Dopa-resistant apathy was defined as apathy that occurred or persisted despite the administration of high and/or increased doses of dopaminergic medications (i.e., dopaminergic agonists and levodopa). To determine whether the level of dopaminergic medication was sufficient, apathetic patients were prescribed, for least 3 months, (1) an increase in the dose of dopaminergic agonist up to the maximum recommended level (if dopaminergic agonists were allowed) and (2) a 25% to 50% increase in the dose of L-dopa or until dyskinesia appeared. Patients in whom troublesome dyskinesia prevented an increase in the dopaminergic dose had to have been on a stable course of dopaminergic medication for at least 3 months. All patients were included between March 2011 and January 2012.

Severity of PD was assessed using the H & Y score.[15] Motor disability was rated using the motor part of the UPDRS (UPDRS-III).[16] Overall cognitive efficiency was assessed with the Mattis Dementia Rating Scale (DRS).[17] Depressive symptoms were assessed with the Montgomery-Åsberg Depression Rating Scale (MADRS).[18]

All participants gave their informed consent to participation in the study. The protocol was approved by the local independent ethics committee (Protocol ID: 2008-002578-36).

MRI Acquisition

MRI was performed on a 3T scanner (Achieva; Philips Medical Imaging, Best, the Netherlands) with an eight-channel head coil. Volumic T1-weighted images were acquired using a magnetization prepared gradient-echo sequence (voxel size: 0.750 x 0.727 x 0.727 mm; repetition time [TR]: 10.4 ms; echo time [TE]: 4.76 ms; matrix size: 214 x 352 x 352 voxels). Diffusion tensor imaging (DTI) was performed using an echo-planar technique (TR, 12,000 ms; TE, 55 ms; matrix size: 128 x 128 x 60; voxel size: 2 x 2 x 2 mm) repeated in 15 independent directions ($b = 1{,}000$ s/mm^2) and with the acquisition of a reference image without diffusion weighting.

Data Processing

Volumetric segmentation was performed with the FreeSurfer image analysis suite (http://surfer.nmr.mgh.harvard.edu/). The technical details for volumetric segmentation have been described by Fischl et al.[19] The following subcortical regions of interest (ROIs) were extracted from the FreeSurfer brain segmentation: the nucleus accumbens, caudate, and putamen in both hemispheres. All segmented volumes were visually inspected and manually corrected (four right caudates and five left caudates, but none of the nuclei accumbens or putamens) to rule out segmentation errors. Cortical thickness was measured along the entire cortical ribbon and blurred at 20 mm full width at half maximum.[20]

Shape analysis using spherical parameterization was performed using spherical harmonic parameterization and sampling in a three-dimensional (3D) point distribution model (SPHARM-PDM).[21] The SPHARM-PDM analysis pipeline is presented in Supporting Figure 1. Briefly, the shape of the deep brain nuclei is modelled as 3D spherical harmonic functions; the greater the number of harmonics used, the more precise the model. Shape approximation using the first-order spherical harmonic aligns subjects according to

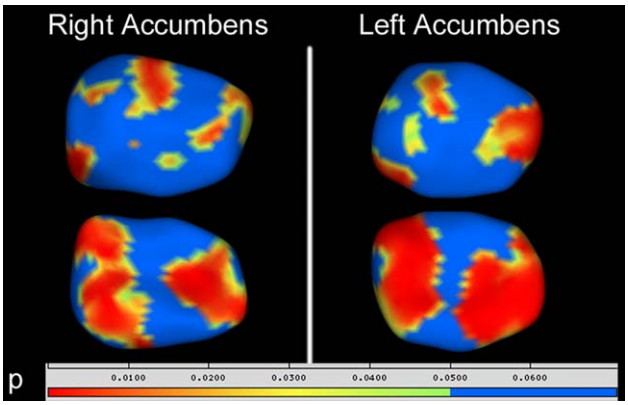

FIG. 1. Shape differences between controls and apathetic PD patients. Statistically significant regions of inward deformation (when comparing apathetic patients to healthy controls) appear in yellow/red superimposed on the mean shape of the nucleus from all subjects. Upper view: anteroventral; lower view: posterodorsal. FDR-corrected threshold for $P = 0.05$. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

the structure's main axes, whereas higher-order spherical harmonics refine the surface modeling. This ensures vertex-to-vertex correspondence from one subject to another and enables intergroup shape comparisons. Each striatal ROI was resampled to an isotropic resolution of 0.5 mm, closed and then smoothed with a 2 mm closing operator. The ROIs were then binarized and converted into surface meshes. The latter were mapped to a sphere and spherical harmonic coefficients were computed.[22] Twelve harmonics were computed to achieve the best compromise between mesh smoothness and precision. The spatial location of each vertex was then directly compared from one group to another or correlated with the variable of interest.

Diffusion-Weighted MRI Processing and Tract-Based Spatial Statistics

All DTI images were visually inspected to ensure that there were no obvious abnormalities. Voxel-wise statistical analysis of the fractional anisotropy (FA) data was carried out with the Tract-Based Spatial Statistics (TBSS)[23] module of FMRIB Software Library software (http://fsl.fmrib.ox.ac.uk/fsl/). First, FA images were created by fitting a tensor model to the raw diffusion data (using the FMRIB diffusion toolbox [https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FDT]) and then brain-extracted using the brain extraction toolbox. For all subjects, whole-brain FA data were then aligned into a common space using the FNIRT nonlinear registration tool. Next, the mean FA image was created and thinned to create a mean FA skeleton, which represents the centers of the tracts common to all members of the group. The aligned FA data from each subject were then projected onto this skeleton. Last, the resulting data were fed into a cross-subject voxel-wise statistical analysis.

Statistical Analysis

Demographic, clinical data and basal ganglia volume data were compared using nonparametric tests (Kruskal-Wallis' and Mann-Whitney's test for intergroup comparisons). Effect sizes were computed using Cohen's d.

Intergroup comparisons of cortical thickness were performed using a vertex-wise general linear model running in SurfStat software.

Between-group striatal shape variations were assessed using a multiple analysis of covariance (MANCOVA), as described by Panaguia et al.[24] Briefly, a general linear model is fitted to the raw coordinates of each vertex. The model includes the group and (for PD patients) the L-dopa-equivalent daily dose (LEDD) and disease duration. Given that the nuclei were aligned by rigid Procrustes transformation (which corrects for overall volume differences), there was no need to correct for intracranial volume, gender, or age.[21] Metrics were computed in a MANCOVA, and the local P values were computed in a Roy λ_{max} permutation test. The false discovery rate (FDR) method was used to control for multiple comparisons of the different vertexes, and the t-map threshold was set to $P < 0.05$. Whenever an intergroup shape difference was detected, Spearman's coefficient for the correlation between striatal shape and the LARS score was computed using the same method (i.e., controlling for disease duration and LEDD and with FDR correction).

To assess group-related differences, voxel-wise tract-based spatial statistics were performed by using a permutation-based inference method for nonparametric thresholding. Results were corrected for multiple comparisons by using threshold-free cluster enhancement, and the t-map threshold was set to $P < 0.05$.

Results

Demographic and Clinical Characteristics

Demographic and clinical data are summarized in Table 1. The three groups did not differ in terms of age or Mattis DRS score. Apathetic and nonapathetic PD patients did not differ in terms of disease duration, LEDD, and UPDRS-III score. As expected, apathetic patients had significantly higher LARS and MADRS scores than the other two groups.

Basal Ganglia Analyses

Basal Ganglia Volume

Apathetic PD patients had a smaller left nucleus accumbens than the two other groups did. No other differences in striatum volume were noted (Table 2).

TABLE 1. Mean (SD) demographic and clinical characteristics in the three participant groups

Characteristics	Apathetic PD Patients	Nonapathetic PD Patients	Healthy Controls	*P* Value	Effect Size
Age, years	67.2 (8.4)	60.7 (11.1)	66.8 (6.8)	0.34	
n, M/F	10 (6/4)	10 (6/4)	10 (4/6)		
Educational level (years in full-time education)	10 (3.5)	12.5 (2.5)	10.8 (2.7)	0.21	
Time since PD onset, years	11.9 (6.5)	11.9 (3.2)		0.85	0.22[a]
UPDRS-III score (of 108)	28.1 (10.8)	28.7 (11.2)		0.91	−0.01[a]
LEDD, mg	857.2 (301.4)	1,072.1 (379.4)		0.29	−0.69[a]
Mattis DRS score (of 136)	136.2 (4.6)	137.2 (4.9)	138 (1.73)	0.49	0.31[a]−0.80[b]
MADRS score (of 60)	8.3 (3.7)	2.7 (3.2)	0 (0)	0.005	1.38[a]2.02[b]
LARS score (from −36 to 36)	−10.8 (4.9)	−26.6 (5.0)	−29.3 (4.6)	<0.001	2.84[a]3.70[b]

[a]Effect size when comparing apathetic PD patients to nonapathetic PD patients.
[b]Effect size when comparing nonapathetic PD patients to controls. Effect sizes (Cohen's d) of 0.2, 0.5, and 0.8 are considered to be small, average, and high, respectively.[31]
Abbreviations: SD, standard deviation; M, male; F, female.

Shape differences between the three groups and shape correlations with the LARS score are depicted in Figures 1, 2, and 3.

Apathetic PD Patients Versus Healthy Controls

Compared to healthy controls, apathetic patients had significant atrophy in (1) the anterior, posterior, medial, and lateral part of the left nucleus accumbens and (2) the anterior, medial, and lateral parts of the right nucleus accumbens. There were no differences between the two groups in terms of the shape of the caudate and putamen.

Nonapathetic PD Patients Versus Healthy Controls

There was no difference between these two groups in the shape of the basal ganglia.

Apathetic Versus Nonapathetic PD Patients

Apathetic patients showed a significant atrophy in the dorsolateral part of the head of the left caudate. There were no other significant intergroup differences in the shape of the basal ganglia. There was a nonsignificant trend toward localized atrophy of the dorsolateral part of the left nucleus accumbens in apathetic patients ($P < 0.1$, FDR-corrected; Fig. 2).

Clinical Correlations

Apathy severity (according to the LARS) was correlated with atrophy in the left nucleus accumbens (Fig. 3), but not with the shape of the left caudate nucleus or the right nucleus accumbens.

Cortical Structures

We did not observe any intergroup differences in cortical thickness (Supporting Fig. 3).

Tract-Based Spatial Statistics

We did not observe any intergroup differences when applying TBSS.

Discussion

Our results show that dopa-resistant apathy in nondemented, nondepressed PD patients was associated with atrophy in the left nucleus accumbens. Moreover, severity of apathy was correlated with morphological changes in this region; localized atrophy in the dorsolateral part of the left caudate was greater in apathetic PD patients than in nonapathetic PD patients. Despite these morphological changes, we did not observe any clear alterations in FA values (using TBSS) or cortical

TABLE 2. Mean (SD) volume of the striatal nuclei in the three groups

Volume	Apathetic PD Patients	Nonapathetic PD Patients	Controls	*P* Value	Effect Size
Right accumbens, mm^3	488 (127)	599 (127)	614 (171)	0.15	−0.73[b]−0.89[c]
Left accumbens, mm^3	396 (139)	605 (148)	587 (220)	0.03[a]	−1.19[b]−1.18[c]
Right caudate, mm^3	3,588 (370)	3,884 (692)	4,068 (670)	0.28	−0.58[b]−0.85[c]
Left caudate, mm^3	3,861 (447)	4,179 (939)	4,019 (642)	0.90	−0.55[b]−0.25[c]
Right putamen, mm^3	4,574 (346)	4,886 (733)	5,043 (769)	0.12	−0.48[b]−0.74[c]
Left putamen, mm^3	4,622 (468)	4,927 (749)	5,112 (939)	0.17	−0.35[b]−0.67[c]

[a]Post-hoc analysis: $P = 0.019$, when comparing apathetic PD patients to nonapathetic PD patients; $P = 0.035$, when comparing apathetic PD patients to controls; $P = 0.529$, when comparing nonapathetic PD patients to controls.
[b]Effect size when comparing apathetic PD patients to nonapathetic PD patients.
[c]Effect size when comparing nonapathetic PD patients to controls. Effect sizes (Cohen's d) of 0.2, 0.5, and 0.8 are considered to be small, average, and high, respectively.[31]
Abbreviation: SD, standard deviation.

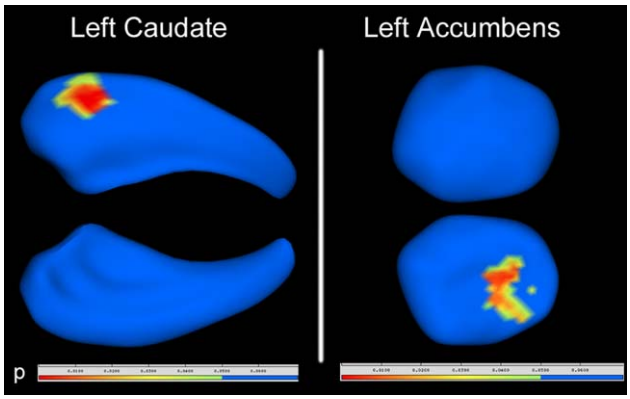

FIG. 2. Shape differences between apathetic and nonapathetic PD patients. Statistically significant regions of inward deformation (when comparing apathetic patients to healthy controls) appear in yellow/red superimposed on the mean shape of the nucleus from all subjects. Caudate: upper view: lateral; lower view: medial. Accumbens: upper view: anteroventral; lower view: posterodorsal. FDR-corrected threshold for $P = 0.05$ (caudate) or 0.1 (left accumbens). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

thickness; this suggests that the alterations were related more to the basal ganglia than to putative secondary degeneration of striatofrontal projections. Nevertheless, alterations in cortical structures and white matter tract cannot be completely ruled out because of the study's limited power. Moreover, we did not perform tractography and thus cannot be sure that frontostriatal tracts were intact. Despite the exploratory nature of the study and the small sample size, the significant degree of specific atrophy of the nucleus accumbens and the caudate suggests that these parameters may have value as a biomarker if our findings are replicated in larger studies. The sample size was limited by the very specific patient profile, which prevented us from recruiting a large sample for our single-center study.

The nucleus accumbens has a central role in the limbic pathway, which also includes the prefrontal cortex, hypothalamus, amygdala and ventral tegmental area (VTA) and subserves cognitive and emotional functions.[26] This network is involved in goal-directed behavior; dopaminergic inputs from the VTA presumably modulate nucleus accumbens cells to determine whether the benefit of reward outweighs the cost of the required behavior. The involvement of nucleus accumbens dysfunction in apathy has already been demonstrated in MPTP-lesioned monkeys; lesions in the VTA and dopaminergic denervation of the nucleus accumbens were more predictive of reductions in goal-directed behavior than were motor function and dysfunction of the nigrostriatal pathway.[27]

Nucleus accumbens atrophy has already been linked to severity of apathy in nondemented patients infected by human immunodeficiency virus.[28] Moreover, a left predominance of basal ganglia lesions in apathy has been noted in stroke patients.[29]

In the present study, we carefully selected PD patients whose apathy was not improved by dopaminergic medication. In fact, we hypothesize that apathy in PD can result from at least two different mechanisms. First, apathy may sometimes occur as a "hypodopaminergic" symptom that reflects dopaminergic denervation in the mesolimbic pathway—such as when dopaminergic medications are dramatically tapered after initiation of STN-DBS or when dopamine agonists are withdrawn in impulse control disorder patients.[5,6] Under these conditions, a moderate increase in LEDD (if possible) is likely to resolve the apathy. Second, when apathy is not improved by dopaminergic treatment, the condition may be related to the more extensive spreading of the disease associated with cognitive dysfunction and may precede dementia.[3] Elsewhere, bilateral atrophy in the precentral gyrus, the inferior parietal gyrus, the inferior frontal gyrus, and in the insula and atrophy in the right (posterior) cingulate gyrus and the right precuneus have been correlated with severity of apathy symptoms in PD patients.[8] However, in our study, we did not find any cortical atrophy in apathetic patients. This may be related to several factors. First of all, the two studies differed in terms of how atrophy was measured. Whereas Rejinders et al. [8] used voxel-based morphometry (VBM), we applied a cortical thickness analysis based on surface registration. Cortical thickness analysis is usually more sensitive than VBM; the latter technique's final output corresponds to a mixture of combines thickness, cortical folding, and changes in

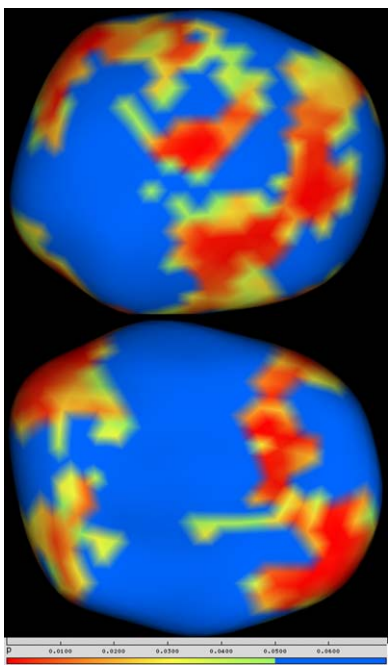

FIG. 3. p-map of the correlation between the LARS score and the nucleus accumbens shape. Upper view: posterodorsal aspect. Lower view: anteroventral aspect. P threshold = 0.05 (FDR corrected). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

signal intensity. Cortical thickness provides a more direct index of cortical morphology and is less susceptible to positional variance; indeed, the measurement of cortical thickness follows the surface of the gray matter and takes account of local variations in the latter's position. Second, we included apathetic patients on the basis of apathy criteria, whereas Rejinders et al.[8] searched for correlations with scores on an apathy scale without checking the patient's status (i.e., apathetic or not) beforehand. Correlations with severity scores and comparisons of clinically defined groups are likely to yield different results. Third and last, our sample size may have been too small to have identified cortical atrophy. Despite these limitations, we believe that our use of a sensitive technique in a small group of patients nevertheless shows that left nucleus accumbens alterations is likely to be a more sensitive marker for dopa-resistant apathy in PD than cortical atrophy. Indeed, left nucleus accumbens may possibly precede cortical atrophy.

Accumbens atrophy may thus prevent dopaminergic medications from restoring normal dopaminergic transmission in the limbic striatum and could thus explain the apathy's nonresponsiveness to treatment. We hypothesize that PD patients with dopaminergic apathy (related to dopaminergic limbic denervation) or dopa-resistant apathy (related to striatal limbic atrophy) might differ in terms of the striatum's shape, but further studies looking specifically at imaging correlates of dopa-resistant and dopaminergic apathy are needed.

The second interesting result is that the patients in the apathetic group displayed moderate, localized atrophy of the dorsolateral head of the caudate nucleus. This striatal region is known to be involved in the dorsolateral cognitive circuit, whereas the nucleus accumbens and putamen are parts of the limbic and motor corticostriatopallidothalamocortical loops.[30] This atrophy of the caudate is presumably related to either extension of the disease or dopaminergic denervation and supports the hypothesis whereby dopa-resistant apathy corresponds to a predementia state in PD. Indeed, as mentioned above, apathy in PD is predictive of the occurrence of dementia.[3]

To the best of our knowledge, this pilot study is the first to have assessed structural striatal changes in apathetic PD patients. Moreover, we are not aware of a published shape analysis of the striatum in PD. This is surprising for such a sensitive, widely availability technique, for which only a single, high-resolution morphological image per subject is required. Shape analysis is a sensitive method that can localize the region in which atrophy is greatest. We then refined the results of the volume comparison. Volume and shape comparisons gave similar results for small structures, such as nucleus accumbens; we interpreted these results in the same way (i.e., global atrophy of the nucleus accumbens in apathetic PD patients). The shape analysis also localized a small region of atrophy in the dorsolateral head of the left caudate in apathetic patients (when compared to nonapathetic PD patients). Although there was no significant difference between the three groups in terms of the volume of the caudate, the shape analysis evidenced a localized zone of atrophy in the head of the caudate.

A few study limitations must nevertheless be taken into account. First, there was a slight, nonsignificant difference in LEDD between the two patient groups, although they did not differ in terms of UPDRS-III scores and disease duration (see Table 1). However, LEDD and disease duration were used as covariates in our comparisons of apathetic and nonapathetic patients. Second, we noticed that apathetic patients had a higher MADRS score than did nonapathetic patients. This was mainly the result of items assessing apathy as a symptom of depression; however, according to established diagnostic criteria applied in the present study, none of our participants was depressed. Third, multiple comparisons were performed (with six regions for shape and two hemispheres for the cortical thickness), but (as a result of the small sample size) no correction for multiple comparisons was applied. Therefore, a type 1 error cannot strictly be ruled out.

To further understand striatal atrophy in PD, our present findings need to be confirmed in larger studies. We showed that shape analysis is a useful, sensitive technique for analyzing striatal atrophy and could be used to look for morphological correlates of other symptoms in PD, such as depression, dementia, and severity of motor disorders.

Dopa-resistant apathy in PD is associated with atrophy of the left nucleus accumbens and the head of the caudate. Additional studies are needed to compare imaging-based correlates of dopaminergic and dopa-resistant apathy in PD. ■

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