Contents lists available at SciVerse ScienceDirect

Neurobiology of Aging

journal homepage: www.elsevier.com/locate/neuaging

Striatal shape in Parkinson's disease

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ARTICLE INFO

ABSTRACT

Parkinson's disease (PD) is marked pathologically by nigrostriatal dopaminergic terminal loss. Histopathological and in vivo labeling studies demonstrate that this loss occurs most extensively in the caudal putamen and caudate head. Previous structural studies have suggested reduced striatal volume and atrophy of the caudate head in PD subjects. The spatial distribution of atrophy in the putamen, however, has not been characterized. We aimed to delineate the specific locations of atrophy in both of these striatal structures. T1- and T2-weighted brain MR (3T) images were obtained from 40 PD and 40 control subjects having no dementia and similar age and gender distributions. Shape analysis was performed using doubly segmented regions of interest. Compared to controls, PD subjects had lower putamen ($p = 0.0003$) and caudate ($p = 0.0003$) volumes. Surface contraction magnitudes were greatest on the caudal putamen ($p \leq 0.005$) and head and dorsal body of the caudate ($p \leq 0.005$). This spatial distribution of striatal atrophy is consistent with the known pattern of dopamine depletion in PD and may reflect global consequences of known cellular remodeling phenomena.

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1. 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% to 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 progression. 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). One previous study by Apostolova et al. (2010) demonstrated trend-level shape differences in the caudate between non-demented PD and control subjects. The spatial distribution of atrophic areas of the putamen, however, remains uncharacterized. 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 reflect PD disease progression. In this study, we aimed to characterize these atrophic sites using a state-of-the-art protocol for segmentation followed by shape analysis using spherical harmonic point distribution models (SPHARM-PDM) (Styner et al., 2005). The present study included only non-demented subjects to avoid potentially confounding influences of dementia-related neuropathology. 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.

2. Method

2.1. Subjects

A total of 40 subjects with PD (20 female, 20 male) and 40 healthy control subjects (20 female, 20 male) having similar age distributions (61.3 ± 7.8 years for PD subjects, 59.4 ± 7.8 years for control subjects) 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 B_{12} 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). Contralateral and ipsilateral sides were defined, respectively, as opposite to the body sides having the greater and lesser UPDRS-III motor scores. Duration of illness was determined 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.

2.2. Neuropsychological assessment

All subjects completed a basic neuropsychological battery to assess orientation, memory, and symptoms of dementia. The Mini Mental State Exam (MMSE) is a brief (5-minute) 30-point test that assesses orientation, memory, and the ability to follow commands (Folstein et al., 1975). The MMSE has been shown to have 98% sensitivity and 77% specificity in detecting dementia among PD subjects using a cutoff score of 23 (Hobson and Meara, 1999). The Montreal Cognitive Assessment (MoCA) was developed to address the limitations of the MMSE in detecting mild cognitive impairment (MCI) (Hoops et al., 2009) and has been shown to have higher sensitivity for detecting PD-MCI than the MMSE (Marras et al., 2013). The Dementia Rating Scale-2 (DRS2) examines a broader range of cognitive functions (attention, initiation and perseveration, conceptualization, construction, and memory) and has been demonstrated to be sensitive for detecting cognitive impairments in PD (Brown et al., 1999). In this study, the cutoff for dementia was set at the fifth percentile (i.e., 1.67 standard deviations below the mean), in line with recommended guidelines (Jurica et al., 2004; Monsch et al., 1995). Subjects were included in this study only if they had both an MMSE score >24 and a DRS2 score greater than the fifth percentile to ensure that they were not demented.

2.3. 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 = 256 × 256, 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.

2.4. Semi-automatic segmentation

Putamen and caudate structures were obtained using a semi-automatic 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, 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 et al., 1999; Van Leemput et al., 1999). The resulting ROIs then were manually corrected by an investigator (N.W.S.), who was blinded to subject diagnosis and symptoms, using ITK-SNAP 2.2.0 (www.itksnap.org) (Yushkevich et al., 2006). To establish consistent boundaries of the caudate and putamen, and to exclude the nucleus accumbens, manual corrections were performed following the anatomical guidelines available in the UNC NeuroImage Analysis Lab Manual (2007). In addition to the use of these guidelines for manual correction of the striatal structures, the lateral ventricles also were segmented using the level-set region-growing tool in ITK-SNAP, to maximize the accuracy of the caudate–ventricle borders. To avoid potential left–right rater bias and to increase the consistency of the final ROIs, this semi-automated process was repeated after a delay of 4 weeks using a mirrored version of the original image set [in which left and right sides were inverted (Maltbie et al., 2012)].

2.5. Volume extraction and average ROIs

Volumes for each ROI were extracted from mirrored and original image sets, and then were averaged together, maintaining original left and right designations. Average ROIs from the original and mirrored ROI sets also were generated for subsequent shape analysis using a Gaussian averaging process. Mirrored ROIs first were reverted to their original orientations. Subsequently, 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 summed at each corresponding voxel and then scaled so that the maximum and minimum intensities per combined ROI were 1 and 0, respectively. To yield average ROIs having solid borders and fill, the combined ROIs then were binarized using an intensity threshold of 0.8. This process of averaging the original and reverted mirrored ROIs was performed to increase the accuracy of each shape and to correct for the known phenomenon of asymmetric (right–left) rater bias (Maltbie et al., 2012).

2.6. 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) (Styner et al., 2003, 2005, 2006b). The ROIs first were processed to fill any internal holes and were adapted to guarantee spherical topology. Surface meshes and corresponding spherical parameterizations then were computed using area-preserving, distortion-minimizing spherical mapping. The