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Alterations of mean diffusivity in brain white matter and deep gray matter in Parkinson's disease

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HIGHLIGHTS

- We investigated brain MD changes in Parkinson's disease patients.
- MD changes in corticofugal tract, cingulum and other white matter tracts in PD.
- MD changes in left putamen, caudate, pallidum and thalamus in PD

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ABSTRACT

Although Parkinson's disease is a neurodegenerative disease primarily involving basal ganglia and midbrain, the deficit of white matter is also involved during the disease progression. As the diffusion tensor imaging method is sensitive to the microstructural changes, we investigated the microstructural alterations in white matter and deep gray matter in patients with Parkinson's disease.

Brain images of 64 patients and sex- and age-matched 64 healthy controls were obtained from a 3T MRI scanner. Tract-based spatial statistics were used to compare the mean diffusivity of the white matter tract between the groups. Voxel-based analysis was used to compare the mean diffusivity of the subcortical gray matter between the groups.

There were white matter deficits in the corticofugal tract, cingulum, uncinate fasciculus, crus of fornix or stria terminalis, corpus callosum, external capsule, superior longitudinal fasciculus, posterior thalamic radiation including optic radiation, and the tracts adjacent to the precuneus and supramarginal gyrus, as indicated by higher mean diffusivity in Parkinson's disease patients than in controls. There were also deficits in the left putamen, pallidum, thalamus, and caudate as indicated by higher mean diffusivity in Parkinson's disease patients than in controls.

Using diffusion tensor imaging and multi-methods of image analysis, we successfully characterized and visualized brain white matter and deep gray matter areas with microstructural deficits in Parkinson's disease patients.

1. Introduction

Parkinson's disease (PD) is characterized by motor symptoms, such as bradykinesia, muscular rigidity, resting tremor, and postural instability [14]. These cardinal motor signs are known to be related to dopamine depletion caused by the degeneration of dopaminergic neurons in the substantia nigra [21]. Therefore, the nigrostriatal dopaminergic system has been a main target for treatments. However, there are also a variety of non-motor symptoms of PD that can affect a patient's quality of life [5,8]. Among these symptoms, early features are olfactory dysfunction and rapid-eye-movement sleep behavior disorder [8]. Cognitive impairments, depression, and autonomic dysfunction, including abnormal thermoregulation and urinary tract dysfunction, also commonly accompany PD [14,16].

Diffusion tensor imaging (DTI) is a more sensitive method than conventional volumetric MRI for detecting the neurobiological

Abbreviations: DTI, diffusion tensor imaging; DWI, diffusion-weighted image; FA, fractional anisotropy; FSL, FMRIB software library; FWE, family-wise error; MD, mean diffusivity; PD, Parkinson's disease; ROI, region-of-interest; TBSS, tract-based spatial statistics.

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Table 1
Demographic and clinical data of PD patients and controls.

Group (n)	Sex (M/F)	Age[a]	Disease duration	Age at onset	Hoehn and Yahr
PD patients (n = 64)	22/42	62.9 (9.0)	5.3 (5.4)	57.6 (11.1)	2 (1–4)
Controls (n = 64)	22/42	63.0 (8.9)	–	–	–

Note: Age, disease duration, and age at onset are presented as mean (SD) year, and the Hoehn and Yahr scale is expressed as the median (range).
[a] $p = 0.93$ (t-test)

features of PD [4]. It can be used for detecting axon and myelin injury in white matter [34] and for measuring the microstructural integrity of nuclei in the subcortical gray matter and the midbrain [22,28]. A number of DTI studies have been conducted to detect the microstructural changes in substantia nigra, which found lower fractional anisotropy (FA) in PD patients using region-of-interest (ROI) analysis [7]. ROI analyses also have revealed the deficits in the striatum, thalamus, internal capsule, cingulum, and superior longitudinal fasciculus [13,28]. Although the ROI analysis is a widely-used approach, it has some drawbacks. First, ROI selection mainly depends on the hypothesis and subjective expectations of researchers. Second, manual segmentation of ROI often had the intra- or inter-rater variability [25]. In order to reduce this type of variability, automatic segmentation method can be applied to ROI analysis. To overcome these drawbacks, whole brain-wise analysis was adopted and found the microstructural alterations in frontal lobe, orbitofrontal cortex, corpus callosum, and cingulum in PD patients [1,18,30].

In the current study, with a moderate number of sex- and age-matched subjects, we aimed to detect brain region deficits and compared the microstructural integrity of the white matter and subcortical gray matter between patients with PD and controls using DTI. For the evaluation of the white matter, we adopted tract-based spatial statistics (TBSS, skeleton-based analysis) as this method has a high sensitivity for identifying white matter deficits using nonlinear registration and tract projection [11,30,33]. For the evaluation of the subcortical gray matter, we performed voxel-based analysis because deficits in these areas cannot be assessed by TBSS. In the voxel-based analysis, we focused on basal and central part of brain gray matter for accurate alignment. Finally, for confirming our findings, we conducted ROI analysis to evaluate the microstructural changes in the subcortical gray matter and motor-related white matter tract. Using three image analysis methods, we attempted to detect brain region deficits in PD.

2. Materials and methods

2.1. Participants

Seventy-one patients with PD consecutively recruited from the Movement Disorders Clinic at our institution between October 2009 and September 2010. Sixty-four healthy controls were selected from spouses, relatives or neighbors of patients (both PD cases and non-PD cases). These age- and sex- matched control subjects had no history of neurologic or psychiatric diseases. PD was diagnosed by a movement disorder specialist (C.S.L.) according to the United Kingdom Parkinson's Disease Society Brain Bank criteria [15]. The severity of the symptoms was assessed off medication, according to the Hoehn and Yahr stage [17]. The number of patients in each stage was: stage I, 9; stage II, 39; stage III, 15; stage IV, 1. Of the 9 patients in stage I, the number of right side affected patients was 3. The number of left side affected patients was 6. Patients with suspected PD but significant cognitive impairment (mini mental state examination score < 24) were excluded [12]. Clinical follow-up of 12 months or more after MR imaging further confirmed the absence of symptoms of atypical Parkinsonism or PD with dementia. Participants were excluded if they had a history of traumatic brain injury, stroke or any other neurological disorders. Experienced neuroradiologists who were blinded to the patients' diagnoses, examined all brain images. Four patients with brain abnormalities such as chronic infarction or confluent white matter hyperintensity seen on T2-weighted image were excluded. Diffusion-weighted images (DWI) of three patients were excluded due to the presence of motion artifact in the cerebellum. A total of 64 patients and sex- and age-matched 64 controls were included in the final analyses. The demographic and clinical characteristics of the two groups are presented in Table 1. The Institutional Review Board approved the study protocol and each subject provided written, informed consent.

2.2. MRI acquisition

Brain MRI scans were obtained using a 3T whole-body imaging system (Achieva, Philips Healthcare, Best, The Netherlands). Diffusion-weighted images were obtained using a single-shot spin-echo echo-planar imaging (EPI) sequence. The diffusion-sensitizing gradients with a b-value of 800 s/mm^2 were applied to the 15 non-collinear directions, and a non-diffusion weighted image with $b = 0$ s/mm^2 was also acquired. Seventy contiguous axial slices were obtained with the following parameters: echo time (TE) = 80 ms; repetition time (TR) = 8346 ms; number of excitation (NEX) = 2; matrix = 112 × 112; field of view (FOV) = 224 × 224 mm; and 2 mm slice thickness with no gap. T1-weighted images with 3D magnetization-prepared rapid gradient echo (MPRAGE) sequence, T2-weighted images and fluid-attenuated inversion recovery (FLAIR) images were also acquired.

2.3. Image processing

DWIs were aligned to the b0 image using affine registration, which serves to correct for distortion due to eddy currents. After removal of non-brain tissue, maps of FA and mean diffusivity (MD) were computed from the diffusion-weighted images using FMRIB's Diffusion Toolbox (FDT), which fits a diffusion tensor model to each voxel.

TBSS were used to compare FA and MD in white matter between groups [33]. All FA maps were aligned to the FMRIB58_FA template using FMRIB's Nonlinear Registration Tool (FNIRT) and an FA threshold of 0.2 was used to include the major white matter pathways but exclude peripheral tracts where there was significant inter-subject variability and/or partial volume effects with gray matter. A mean FA map was then created from all the aligned FA maps and was thinned to generate a mean FA skeleton, which represents the centers of all tracts common to the group. Aligned FA maps were projected onto this skeleton, and the resulting data was fed into voxel-wise, cross-subject statistics. For MD maps, the exact transformations derived for the FA maps were applied.

A voxel-based analysis was performed to compare FA and MD in the subcortical gray matter between groups. For accurate alignment of deep gray matter, two-step registration using T1-weighted image, DWI and the reference-weighing mask including subcortical gray matter and brainstem was used. For the