Parkinsonism and Related Disorders xxx (2018) 1–6

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

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

Neurite orientation dispersion and density imaging of the nigrostriatal pathway in Parkinson's disease: Retrograde degeneration observed by tract-profile analysis

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ARTICLE INFO

Article history:
Received 29 May 2017
Received in revised form
21 February 2018
Accepted 27 February 2018

Keywords:
Diffusion tensor imaging
Neurite orientation dispersion and density imaging
Parkinson's disease
Nigrostriatal pathway
Retrograde degeneration
Tract-profile analysis

ABSTRACT

Introduction: Parkinson's disease (PD) is marked by the degeneration of dopaminergic neurons in the nigrostriatal pathway (NSP). We aimed to identify the microstructural changes in the NSP of PD patients using neurite orientation dispersion and density imaging (NODDI).
Methods: NSPs of 29 PD patients, who were retrospectively selected from patients previously admitted to our institution, and 29 age- and gender-matched healthy controls were isolated via deterministic tractography. The NODDI indices, intracellular volume fraction (Vic), orientation dispersion index (OD), and isotropic volume fraction (Viso) were compared between the two groups. The significant results were assessed with a tract-profile analysis. The correlation between indices and disease duration or motor symptom severity was evaluated with the Pearson's correlation test.
Results: The contralateral distal Vic ($p = 0.00028$) of the nigrostriatal pathway was significantly lower in PD patients than in healthy controls. No correlations were detected between any of the indices and disease duration or motor symptom severity.
Conclusions: NODDI can be used to identify retrograde degeneration of the NSP in PD patients and might be useful for monitoring the disease progression of PD.

1. Introduction

Parkinson's disease (PD) is a neurodegenerative movement disorder characterized by the degeneration of dopaminergic neurons projecting from the substantia nigra pars compacta (SNpc) to the corpus striatum, which is known as the nigrostriatal pathway (NSP) [1,2]. The loss of nigrostriatal projections is presumed to be the cause of the motor symptoms observed in PD [1]. Altered protein handling plays a key role in the etiopathogenesis of PD. The aggregation of presynaptic protein α-Synuclein was shown to be the major component in the accumulation of Lewy bodies and neurites, which are pathological hallmarks of neuronal degeneration in PD [3–5]. Lewy neurites are found more abundantly and earlier in the distal axons and may impair retrograde axonal transport, leading to neuronal loss [5,6]. Based on these findings, it was assumed that the progression of PD involves a dying back process that begins in the distal axons [2,4].

Diffusion tensor imaging (DTI) has been used to examine nigrostriatal degeneration; however, previous studies [7,8] have failed to demonstrate sufficient clinical diagnostic accuracy and reliability, likely due to the limitations of DTI, which include 1) the diffusion of water molecules in living tissue exhibits a non-Gaussian distribution; and 2) despite its sensitivity, fractional anisotropy (FA) cannot be used to determine the specific pathological changes of the NSP in PD [7,8]. Decreased FA can be caused by a reduction in neurite density, an increase in the dispersion of

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https://doi.org/10.1016/j.parkreldis.2018.02.046

neurite orientation distribution, as well as demyelination [7,8].

In this study, neurite orientation dispersion and density imaging (NODDI) was applied to examine the NSP. NODDI enables the quantification of neurite density and orientation dispersion with an orientation-dispersed cylinder model and Watson distribution [8,9]. NODDI indices, the intracellular volume fraction (Vic) and the orientation dispersion index (OD), are assumed to describe more specific microstructural changes and represent changes in FA [7–9].

We hypothesized that NODDI could be used to identify the retrograde degeneration of the NSP in PD as a useful marker of disease progression. To test this hypothesis, the usefulness of NODDI analysis to examine the NSP was compared between PD patients and healthy controls.

2. Materials and methods

2.1. Subjects

This study was a retrospective case-control study included 58 subjects (29 PD patients and 29 healthy controls). The characteristics of all study participants are listed in Table 1. PD patients were previously admitted to our institution and diagnosed by movement disorders specialists based on the UK Parkinson's Disease Society Brain Bank criteria [10] and had stage I, II, or III PD according to the Hoehn and Yahr scale [11]. All PD patients remained free from atypical parkinsonism and exhibited a good response to anti-parkinsonian therapy for ≥18 months after diagnosis. All patients were taking levodopa in combination with a dopamine decarboxylase inhibitor (benserazide or carbidopa) at the time of magnetic resonance imaging (MRI) and clinical examination. Age- and gender-matched healthy subjects with no history of neurologic or psychiatric disorders and having no abnormal signals on structural MRI were recruited as a control group. Although some of the healthy volunteers had normal age-related brain atrophy, none had pathological atrophy indicative of other neurodegenerative diseases, such as Alzheimer's disease or frontotemporal lobar degeneration. The study protocol was approved by the institutional review boards and informed consent was obtained from all participants before evaluation.

2.2. MRI

A 3.0-T MR system (Achieva; Philips Healthcare, Best, The Netherlands) was used for all imaging. Diffusion-weighted images (DWIs) were obtained with a spin-echo echo planar imaging (EPI) sequence consisting of two b values (1000 and 2000 s/mm^2) acquired along 32 isotropic diffusion gradients in the anterior–posterior phase-encoding direction. Each DWI acquisition was complemented with a gradient-free image (b = 0). Standard and reverse phase-encoded blipped images with no diffusion weighting (Blip Up and Blip Down) were also acquired to correct magnetic susceptibility-induced distortions related to the EPI acquisitions [12,13]. The sequence parameters were as follows: repetition time, 9810 ms; echo time, 100 ms; diffusion gradient pulse duration (δ), 26.4 ms; diffusion gradient separation (Δ), 50.6 ms; field of view, 256 × 256 mm; matrix size, 128 × 128; slice thickness, 2 mm; and acquisition time, 13 min.

Table 1
Demographic characteristics of the subjects.

	Healthy controls	PD patients	*P* value
Number	29	29	
Sex (male/female)	14/15	14/15	1.000
Age (years)	65.52 ± 11.87	67.79 ± 10.00	0.483
Disease duration (years)	NA	6.24 ± 3.40	
UPDRS-III Motor Score	NA	15.93 ± 9.18	
Hoehn-Yahr stage	NA	1.97 ± 0.68	

PD, Parkinson disease; *NA*, not applicable; *UPDRS-III*, Unified Parkinson's Disease Rating Scale-III.

2.3. Diffusion MRI pre-processing

All original DWI datasets were checked visually for each direction from 32 different axial, sagittal, and coronal directions. No dataset had severe artifacts (e.g., gross geometric distortion, signal dropout, or bulk motion). All DWIs were corrected for susceptibility-induced geometric distortions, eddy current distortions, and inter-volume subject motion using the EDDY and TOPUP toolboxes [13]. Next, the resulting DWI data were fitted to the NODDI model [8] using the NODDI Matlab Toolbox5 (http://www.nitrc.org/projects/noddi_toolbox). Vic, OD, and isotropic volume fraction (Viso) maps were generated by Accelerated Microstructure Imaging via Convex Optimization (AMICO) [14]. Only DWIs with b = 0 and 1000 s/mm^2 were used for DTI fitting because DTI indices (FA, mean diffusivity [MD], axial diffusivity [AD], and radial diffusivity [RD]) can be estimated using a conventional mono-exponential model [15]. FA, MD, AD, and RD maps for all subjects were calculated using the tool DTIFIT implemented in FMRIB Software Library 5.0.9 (FSL, Oxford Centre for Functional MRI of the Brain, UK; www.fmrib.ox.ac.uk/fsl) to fit a tensor model to each voxel of the DWI data.

2.4. Tractography

Only the b = 0 and 1000 s/mm^2 datasets of the diffusion-weighted data were used to generate tractography. To achieve successful visualization of the small fibers, DWIs were subjected to up-sampling with trilinear interpolation to 1 mm^3 resolution in MATLAB (version 7.9.0; The Mathworks, Inc., Natick, MA, USA), based on a published protocol [16,17]. The nigrostriatal tract (as the tract of interest) and the corticospinal tract (CST) (as the control tract) were visualized and analyzed with TrackVis version 0.6.0.1 (http://www.trackvis.org/). Earlier, the Diffusion Toolkit version 0.6.3 was used to reconstruct DWIs and generate fiber track data for visualization by TrackVis. The modified fiber assignment by a continuous tracking algorithm was used to obtain optimal visualization of the tract, with an FA threshold of 0.2, angle threshold of 60° for nigrostriatal and of 35° for corticospinal tractography, and default step length of 0.1 mm [16,18]. Then, to isolate the tracts, regions of interest (ROIs) were applied in the designated areas by two authors (C.A. and M.N.), who were blinded to the disease status of the subjects. Finally, point-to-point profiles of the indices along the segmented tracts were extracted using MATLAB and FSL.

2.4.1. Nigrostriatal tractography

To isolate the nigrostriatal tract, ROIs were placed in the SN and globus pallidus (GP). A nigrofugal tracing study demonstrated that nigrostriatal projections traverse the GP to synapse directly in the striatum. Moreover, striatomesencephalic fibers from the posterior putamen have been found to form a discrete bundle coursing through the GP to converge at the SN [16].

At first, a 3–mm-diameter sphere seed ROI was placed on the ventral SN, which was identified on the anterior midbrain as a green structure on the color FA map from the axial view, inferior to the level of the red nucleus (Fig. 1a). Second, a 4–mm-diameter sphere target ROI was placed in the inferomedial GP, which was identified on the axial and coronal views of the B0 map (Fig. 1b–c). The seed ROI was moved marginally until the streamlines reached the designated target (Fig. 1d) [17].

Please cite this article in press as: C. Andica, et al., Neurite orientation dispersion and density imaging of the nigrostriatal pathway in Parkinson's disease: Retrograde degeneration observed by tract-profile analysis, Parkinsonism and Related Disorders (2018), https://doi.org/10.1016/j.parkreldis.2018.02.046