Optic nerve disintegration as a visuospatial cognitive predictor of Parkinson's disease

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The Master's Thesis submitted to the Department of Medicine, the Graduate School of Yonsei University in partial fulfillment of the requirements for the degree of Master of Medical Science

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ABSTRACT

Optic nerve disintegration as a visuospatial cognitive predictor of Parkinson's disease

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Objective: To explore the microstructural integrity of the optic nerve and its role as a visuospatial cognitive predictor in patients with de novo Parkinson's disease (PD) using diffusion tensor image-based magnetic resonance scans.

Methods: We enrolled 82 patients with de novo PD; 36 patients had drug-induced parkinsonism (DIP), and 36 were normal controls. Fractional anisotropy (FA) and apparent diffusion coefficient (ADC) were measured on the mid-portion of the intraorbital optic nerve. A linear mixed-effects model was used to evaluate PD patients based on a

longitudinal change in cognitive subscore of a comprehensive neuropsychological test and optic nerve integrity.

Results: The mean FA value in PD was significantly lower (0.552 ± 0.103, $p < 0.001$) than that in DIP (0.645 ± 0.099) or the normal controls (0.689 ± 0.089), whereas the mean ADC value was significantly higher in the PD group compared to the DIP or control group ($p < 0.001$). Optic nerve integrity was not significantly related to parkinsonian motor severity, striatal dopamine transporter activity, or olfactory performance in PD patents. In a longitudinal assessment of cognition in PD patients, the lower FA group had a more rapid decline in Rey complex figure test performance (-4.26; 95% CI, -8.31 to -0.40; $p = 0.031$) and Clock drawing tests (-1.35; 95% CI, -2.59 to -0.11; $p = 0.034$) than the higher FA group.

Conclusion: This study demonstrated that microstructural integrity in the optic nerve was distorted in PD patients, and that this nerve integrity might act as a cognitive predictor of visuospatial dysfunction.

Key words : Parkinson's disease, optic nerve, diffusion tensor image, cognition

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I. INTRODUCTION

Parkinson's disease (PD) is a multi-system disorder that involves the nigrostriatal system as well as cognitive, behavioral, mood control, autonomic control, and sensory processing systems. Of these, visual processing-associated symptoms are common in patients with PD[1] and can range from primary visual dysfunction, such as decreased visual acuity,[2] contrast sensitivity,[1] color perception,[2] and ocular motor dysfunction[3] to higher-order dysfunctions including visual perception,[4] visual memory,[1] or even visual hallucinations.[5] Along with PD pathology-related neurochemical, structural, or functional alterations in the visual association cortex,[6, 7] accumulating evidence has suggested that the retina is an important contributor to visual dysfunction in PD. The principal dopaminergic actors in the retina are the A18 amacrine cells, which control dark adaptation, color vision, and spatial contrast sensitivity

through interactions between inner and outer plexiform layers.[8, 9] Pathological and in vivo studies have determined that PD patients exhibit retinal dopaminergic cell loss[10] and retinal nerve fiber layer (RNFL) thinning.[11] With regard to cognition, higher-order dysfunctions in visual processing are known to be an indicator of dementia in PD,[12] whereas the role of primary visual dysfunction in the cognitive prognosis is unknown.

Diffusion tensor imaging (DTI) has been developed to estimate microstructural integrity in white matter by measuring diffusion tensor, a three-dimensional unit of diffusion. This measure is mainly represented by indices such as fractional anisotropy (FA) and mean diffusivity or apparent diffusion coefficient (ADC), which reflect the directionality and magnitude of diffusion of water molecules, respectively. This technology has been widely used to evaluate white matter connectivity in PD and overall white matter involvement in nervous system disorders.[13] In the present study, we examined the microstructural integrity of the optic nerve in de novo PD patients using DTI-based imaging analysis. In addition, we analyzed the association between optic nerve integrity and nigrostriatal dopaminergic and cognitive status to determine whether optic nerve integrity acts as a clinically prognostic marker of PD.

II. MATERIALS AND METHODS

Subjects and clinical assessment

We retrospectively reviewed medical records from 82 consecutive PD patients that attended the Movement Disorders Clinic at Yonsei University Severance Hospital from January 2009 to June 2013. PD diagnosis was determined based on the clinical criteria of the United Kingdom's PD Society Brain Bank,[14] and all patients with PD were determined to have a drug-naïve de novo status. A total of 36 control subjects that did not exhibit any symptoms of neurologic deficits and did not have any other symptom profiles of abnormal movements or gait problems were recruited during the same period. The patients with drug-induced parkinsonism (DIP) were determined by the criteria in a previously published study,[15] and 36 eligible patients were finally included. All subjects involved in the present study underwent conventional brain magnetic resonance imaging (MRI) including DTI, and a [^{18}F] N-(3-fluoropropyl)-2β-carbon ethoxy-3β-(4-iodophenyl) nortropane (^{18}F-FP-CIT) positron emission tomography (PET) scan were performed to all PD or DIP participants at their initial evaluation. Subjects that suffered from any neurodegenerative or known ophthalmologic disorders, which were identified by medical records, an ophthalmologist, or a self-report of miscellaneous ocular problems (such as visual blurring, ocular pain, visuospatial dysfunction, or visual hallucinations), were excluded from this study. The Unified PD Rating Scale (UPDRS) part III (during the off status) and the Cross Cultural Smell Identification Test (CCSIT) were completed at initial diagnosis in all patients with PD. We received

approval from the Institutional Review Board at Yonsei University Severance Hospital, and written consent was obtained from all participants.

Cognitive assessment

To determine cognitive status in PD, a comprehensive neuropsychological test was performed by an experienced neuropsychologist in all 82 patients with PD. This assessment was performed at baseline evaluation using the Seoul Neuropsychological Screening Battery (SNSB)[16, 17] and a Korean version of the Mini Mental State Examination (K-MMSE).[18, 19] The SNSB is composed of various task subsets in five cognitive domains, and we selected representative tasks for each domain as follows: Attention (digit span forward and backward), Language function (Korean version of the Boston Naming Test), Visuospatial function (Rey Complex Figure Test (RCFT) copying, 10-point clock drawing,[20] six-point drawing interlocking pentagon[21]), Memory (verbal memory, 20-minute delayed recall using the Seoul Verbal Learning Test; visual memory, 20-minute delayed recall using the RCFT), and Frontal executive function (semantic and phonemic fluency using the Controlled Oral Word Association Test; Stroop color reading test). Additionally, we performed a subanalysis of longitudinal changes in cognitive function according to optic nerve integrity in 45 of 82 PD patients that had available neuropsychological test follow-up data.

MRI acquisition

All scans were performed with a 3T MR imaging (Achieva; Philips Medical Systems, Best, the Netherlands) using a 32-channel sensitivity-encoding head coil. DTI was performed using a single-shot spin-echo EPI. The axial images were obtained parallel to the anterior/posterior commissure line. The parameters for DTI were as follows: FOV = 220 mm, voxel size = 1.72 x 1.72 x 2 mm^3, TE = ~70 ms, TR = ~8000 ms, FA = 90°, slice gap = 0 mm, NEX = 1, b-factor = 600 s/mm^2, non-cardiac gating, and 70 axial slices. We acquired diffusion-weighted images from 32 non-collinear, non-coplanar directions, with a baseline image without diffusion weighting. Total acquisition time was 5 min 45 s. Isotropic fractional anisotropy (FA), trace, and apparent diffusion coefficient (ADC) maps were immediately generated on the console by the chosen software (Packman Tools; Philips Medical Systems).

Diffusion tensor image analysis

To obtain cross-sectional area measurements of the optic nerves, we made coronal reformatted FA and ADC maps using Aquarius iNtuition software (TeraRecon, Foster City, CA, USA) (Figure e-1). Circular regions of interest (ROIs) with a mean diameter of 7.6 mm^2 (range, 5.8 – 8.2 mm^2) were manually drawn on the mid-portion of the intraorbital optic nerve on FA and ADC maps. All ROIs were placed strictly within the optic nerve boundary to avoid contamination from adjacent fat or cerebrospinal fluid. FA and ADC values were measured in each optic nerve of all patients. For each patient, the mean FA and ADC values were calculated by averaging the values measured in bilateral optic nerves. To confirm the estimate consensus, two

board-certified neurologists (J.J.L. and Y.J.L.) separately conducted measurements of FA and ADC values and were blinded to patient information. The internal consistency (Cronbach's alpha) was demonstrated by inter-rater values of 0.804 for FA and 0.826 for ADC and intra-rater values of 0.886 for FA and 0.878 for ADC.

^{18}F-FP-CIT PET acquisition

A ^{18}F-FP-CIT PET scan was performed using a GE Discovery STe (DSTE) PET-CT scanner (GE Healthcare Technologies, Milwaukee, WI), which obtained images with a three-dimensional resolution of 2.3 mm at full-width at half-maximum. A 5mCi (185 MBq) of ^{18}F-FP-CIT was injected intravenously, and images were acquired in three-dimensional mode at 120 KVp and 380 mAs during a 20-minute session that occurred 90 minutes after contrast injection.

Quantitative analyses of the ^{18}F-FP-CIT image data

The quantitative analyses of the ^{18}F-FP-CIT PET images were carried out according to a previously published procedure.[22] Image processing was performed using SPM8 (Wellcome Department of Imaging Neuroscience, Institute of Neurology, UCL, London, UK) in MATLAB 2013a for Windows (MathWorks, Natick, MA). Quantitative analyses were based on volumes of interests (VOIs), which were defined based on a template in standard space. All reconstructed PET images were spatially normalized to the Montreal Neurology Institute template space using a standard

^{18}F-FP-CIT PET template, which was created using the ^{18}F-FP-CIT PET and T1 MRI scans of 13 normal controls to remove inter-subject anatomical variability. Twelve VOIs of bilateral striatal subregions and one occipital VOI were drawn on a coregistered spatially-normalized single T1 MRI and ^{18}F-FP-CIT PET template image on MRIcro version 1.37 (Chris Rorden, Columbia, SC), based on a previous study.[22] These VOIs were adjusted through a minor translation in our in-house VOI editing software called ANTIQUE.[23] Each unilateral striatum was divided into six subregions, consisting of two caudate nucleus subregions (anterior and posterior), the ventral striatum, and three putaminal subregions (anterior, posterior, and ventral). Then, using the DAT activity concentration in each VOI, we estimated the surrogate of non-displaceable binding potential (BPnd), defined as [(mean standardized uptake value (SUV) of the striatal subregion VOI - mean SUV of the occipital VOI)/mean SUV of the occipital VOI].[24] Finally, the mean BPnd values of each pairwise striatal subregion were used for analyses.

Statistical analysis

To assess the demographic characteristics of the patients, an analysis of variance followed by multiple comparisons was used to compare group differences of continuous variables. The normality of the continuous variables was evaluated using the Kolmogorov–Smirnov test. The χ^2 test was used for categorical variables. The group differences in mean FA and mean ADC were analyzed using analysis of covariance with adjustment for age, gender, and disease duration. To determine the

associations of mean FA or mean ADC with DAT activities of striatal subregions, UPDRS III, CCSIT, and K-MMSE in PD, the partial correlation coefficients controlled for onset age, gender, and disease duration were calculated. A linear mixed-effects model was adopted to determine associations between either FA or ADC and changes in cognitive performance as assessed by repetitive comprehensive neuropsychological tests. In this analysis, the PD group was dichotomized into lower or higher groups by the median value of FA or ADC, respectively. These models included random effects for intercept and subject, which accounted for the repeated measures among subjects. The interactions between time and dichotomized subgroup of FA or ADC represented the effects of FA or ADC on the change in the score of SNSB subsets over time. The independent variables of onset age, gender, and disease duration were used as adjustments. A two-tailed level of $p < 0.05$ was considered to be statistically significant, and all statistical analyses were performed using SPSS for Windows 20.0(SPSS, Inc., Chicago, IL).

III. RESULTS

Demographics and comparisons of optic nerve integrity among groups

Baseline demographic characteristics among the groups are summarized in Table 1. There were no significant differences in age, gender, K-MMSE score, or duration of education among the groups. The mean disease duration and UPDRS-III score were 1.3 ± 1.0 (range, 0.1 – 4.3) years and 22.0 ± 11.4 (range, 11 – 51) in patients with PD and 1.1 ± 0.8 (range, 0.4 – 2.8) years and 19.2 ± 9.7 (range, 6 – 48) in patients with DIP, which did not differ significantly. The drugs associated with decreased integrity in patients with DIP were gastrointestinal prokinetics (21), antipsychotics (15), antidepressants (11), antiarrhythmic agents (6), and anti-epileptics (3). The FA value was significantly lower in patients with PD (0.552 ± 0.103; interquartile range (IQR), 0.462 – 0.639; $p < 0.001$) compared with patients with DIP (0.645 ± 0.099; IQR, 0.586 – 0.703) or controls (0.689 ± 0.089; IQR, 0.639 – 0.741; table 2). Additionally, PD patients had a significantly higher ADC score (1334.7 ± 261.7 mm^2/s; IQR, 1146.6 – 1514.7; $p < 0.001$) compared with patients with DIP (1050.5 ± 252.9; IQR, 951.5 – 1079.6) or controls (1071.6 ± 203.9; IQR, 931.1 – 1185.7; table 2 and figure 1). No significant differences were found between the control and DIP groups in FA value (0.689 ± 0.089 vs. 0.645 ± 0.099, p = 0.999) or ADC value (1071.6 ± 203.9 vs. 1050.5 ± 252.9, p = 0.999).

Table 1. Demographic characteristics among controls, drug-induced parkinsonism patient, and Parkinson's disease patients.

Characteristics	Control (n=36)	DIP (n=36)	PD (n=82)	*p*
Age (years)	67.1 ± 7.7	68.4 ± 8.5	68.5 ± 8.1	NS
Gender (Male / Female)	20 / 16	15 / 21	42 / 40	NS
K-MMSE (30)	27.9 ± 1.5	26.7 ± 2.5	26.9 ± 2.9	NS
Education (years)	10.8 ± 5.7	9.3 ± 4.3	9.9 ± 4.9	NS
Age of onset (years)		67.2 ± 8.4	67.1 ± 8.1	NS
Disease duration (years)		1.1 ± 0.8	1.3 ± 1.0	NS
UPDRS III		19.2 ± 9.7	22.0 ± 11.4	NS

Data are expressed as mean ± SD or number.

DIP, drug-induced parkinsonism; PD, Parkinson's disease; K-MMSE, Korean-Mini Mental Status Examination; UPDRS, Unified Parkinson's disease rating scale; NS, no significance.

Table 2. Comparison of optic nerve integrity among control, drug-induced parkinsonism patients, and Parkinson's disease patients.

Characteristics	Control (n=36)	DIP (n=36)	PD (n=82)	*P**
FA	0.689 ± 0.089	0.645 ± 0.099	0.552 ± 0.103	< 0.001
ADC (mm^2/s)	1071.6 ± 203.9	1050.5 ± 252.9	1334.7 ± 261.7	< 0.001

*Analysis of covariance adjusting for age, gender, and disease duration.

Data are expressed as mean ± SD.

DIP, drug-induced parkinsonism; PD, Parkinson's disease; FA, fractional anisotropy; ADC, apparent diffusion coefficient.

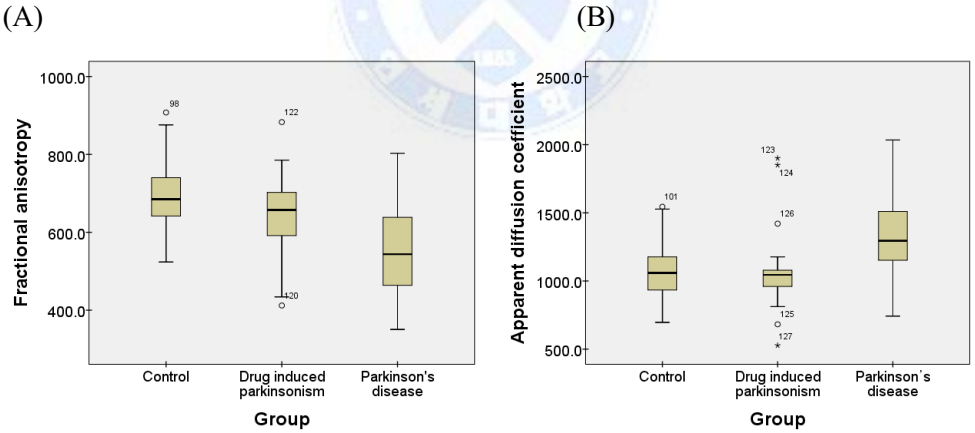


Figure 1. Boxplot of fractional anisotropy and apparent diffusion coefficient in controls, drug-induced parkinsonism patient, and Parkinson's disease patients. (A) Fractional anisotropy, (B) Apparent diffusion coefficient.

Correlation analyses of optic nerve integrity in PD with motor, premotor, and cognitive status surrogates

The age of disease onset in patients with PD was negatively correlated with BPnd in the anterior putamen (r = - 0.136, p = 0.024) and caudate nucleus (r = - 0.315, p < 0.001). As expected, the UPDRS-III was negatively correlated with BPnd in the anterior putamen (r = - 0.278, p = 0.012) and caudate nucleus (r = - 347, p = 0.006). After adjusting for onset age, gender, and disease duration, the correlation analysis of optic nerve integrity and parkinsonian motor severity indicated that the values of FA and ADC were not associated with UPDRS III score or BPnd in any striatal subregions (Table 3). Additionally, neither the FA nor ADC value was significantly correlated with CCSI or K-MMSE score.

Table 3. Relationships between optic nerve integrity and clinical markers of parkinsonian motor severity, olfaction, general cognition, and dopamine transporter activities in patients with Parkinson's disease.

	FA		ADC	
	*r**	*p*	*r**	*p*
UPDRS III	-0.202	0.125	-0.164	0.218
CCSIT	0.119	0.300	0.007	0.950
K-MMSE	-0.049	0.683	0.036	0.768
BPnd of striatal subregions				
Anterior caudate	-0.126	0.273	0.090	0.437
Posterior caudate	-0.124	0.278	0.173	0.136
Ventral striatum	-0.072	0.530	0.035	0.767
Anterior putamen	-0.093	0.417	0.076	0.516
Posterior putamen	-0.007	0.953	0.085	0.468
Ventral putamen	-0.035	0.763	0.136	0.241

*Partial correlation adjusting for age of onset, gender, and disease duration.

FA, fractional anisotropy; ADC, afferent diffusion coefficient; UPDRS, Unified Parkinson's disease rating scale; CCSIT, Cross Cultural Smell Identification Test; K-MMSE, Korean-Mini Mental Status Examination; BPnd, non-displaceable binding potential.

Association between optic nerve integrity and cognitive performance

Multivariate linear regression analysis showed that neither FA nor ADC value was significantly associated with any cognitive subsets (Table e-1 in supplementary data). Forty-five patients with PD completed a follow-up neuropsychological test with a mean interval of 2.5 years. The mean FA and ADC values in this subpopulation of PD were 0.451 ± 0.042 (IQR, 0.422 – 0.475) and 1406.6 ± 212.1 mm^2/s (IQR, 1258.5 – 1519.7), respectively, in the dichotomized lower FA group and 0.540 ± 0.107 (IQR, 0.432 – 0.653) and 1559.9 ± 162.3 mm^2/s (IQR, 1408.0 – 1721.1) in the dichotomized higher ADC group. Table 4 shows changes in cognitive subscores of each PD patient between baseline and follow-up neuropsychological tests, according to optic nerve integrity. The lower FA group was strongly associated with a greater decline in RCFT drawing (β = -4.26 (1.91), p = 0.031) and clock drawing test (CDT) (β = -1.35 (0.61), p = 0.034) compared to the higher FA group. No significant differences in interval changes in the remaining cognitive subsets were found between the lower and higher FA groups. However, a distinct pattern of changes in RCFT and CDT performance is demonstrated in Figure 2. Compared to the higher FA group, the lower FA group showed a steeper estimated slope (ES) of RCFT performance decline (ES [SD], -4.86 (1.47) vs. -0.59 (1.23); 95% CI, -8.31 to -0.40; p = 0.031) and CDT performance (-0.96 (0.47) vs. 0.43 (0.38); 95% CI, -2.59 to -0.11; p = 0.034; table 5).

Table 4. Linear mixed-effects model of repetitive comprehensive neuropsychological tests in patients with Parkinson's disease.

	Lower FA group		Higher ADC group	
	β† (SE)	*p*	*β*† (SE)	*p*
Attention				
Digit span forward	-0.18 (0.47)	0.704	-0.54 (0.46)	0.254
Digit span backward	-0.06 (0.25)	0.810	-0.03 (0.25)	0.903
Language				
K-BNT	-1.41 (2.57)	0.585	-0.65 (2.59)	0.802
Visuospatial function				
RCFT	-4.26 (1.91)	0.031	-0.74 (2.02)	0.717
CDT	-1.35 (0.61)	0.034	-0.77 (0.63)	0.235
Interlocking Pentagon	-0.28 (0.53)	0.608	-0.04 (0.46)	0.930
Verbal memory (SVLT)				
Delayed recall	-2.01 (2.30)	0.387	-2.59 (2.29)	0.266
Visual memory (RCFT)				
Delayed recall	1.87 (1.82)	0.309	-1.53 (1.83)	0.407
Frontal executive function				
COWAT, animal	-2.39 (1.35)	0.082	-0.48 (1.40)	0.731
COWAT, supermarket	0.04 (2.16)	0.985	1.79 (2.14)	0.408
COWAT, phonemic	-1.22 (3.26)	0.711	2.35 (3.26)	0.474
Stroop color test	-4.42 (8.55)	0.608	-6.55 (8.25)	0.152

Data are adjusted for age of onset, gender, and disease duration.

†Regression coefficients represent the difference in rate of change in each cognition

task between dichotomized groups.

FA, fractional anisotropy; ADC, afferent diffusion coefficient; K-BNT, Korean version of the Boston naming test; RCFT, Rey complex figure test; CDT, clock drawing test; SVLT, Seoul verbal learning test; COWAT, Controlled oral word association test

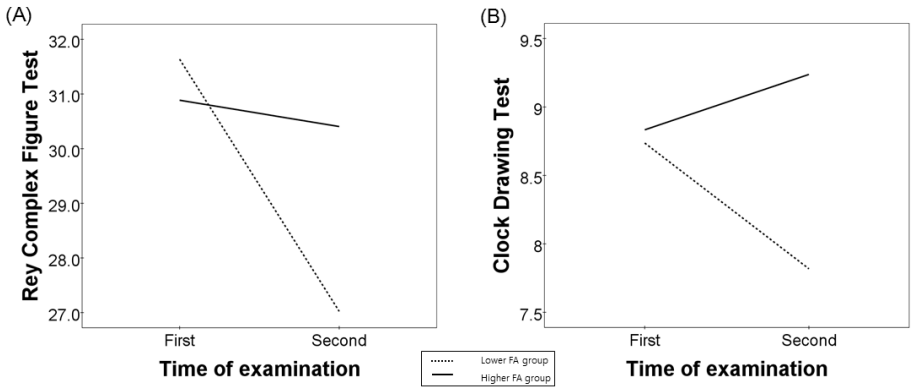


Figure 2. Alterations in longitudinal visual cognitive function depending on level of fractional anisotropy in 45 patients with PD. (A) Rey complex figure test, (B) Clock drawing test.

Table 5. Rate of visual cognitive decline in respective lower FA and higher ADC group in Parkinson's disease.

	Estimated slope*		95% CI	*p*
	Lower FA group	Higher FA group		
RCFT	-4.86 (1.47)	-0.59 (1.23)	-8.31 to -0.40	0.031
CDT	-0.96 (0.47)	0.43 (0.38)	-2.59 to -0.11	0.034

* Adjustment for onset age, gender, and disease duration.

FA, fractional anisotropy; RCFT, Rey-Osterrieth complex figure test; CDT, clock drawing test.

Supplementary data

Table e-1. The relationships between optic nerve integrity and baseline cognitive subscores in patients with Parkinson's disease.

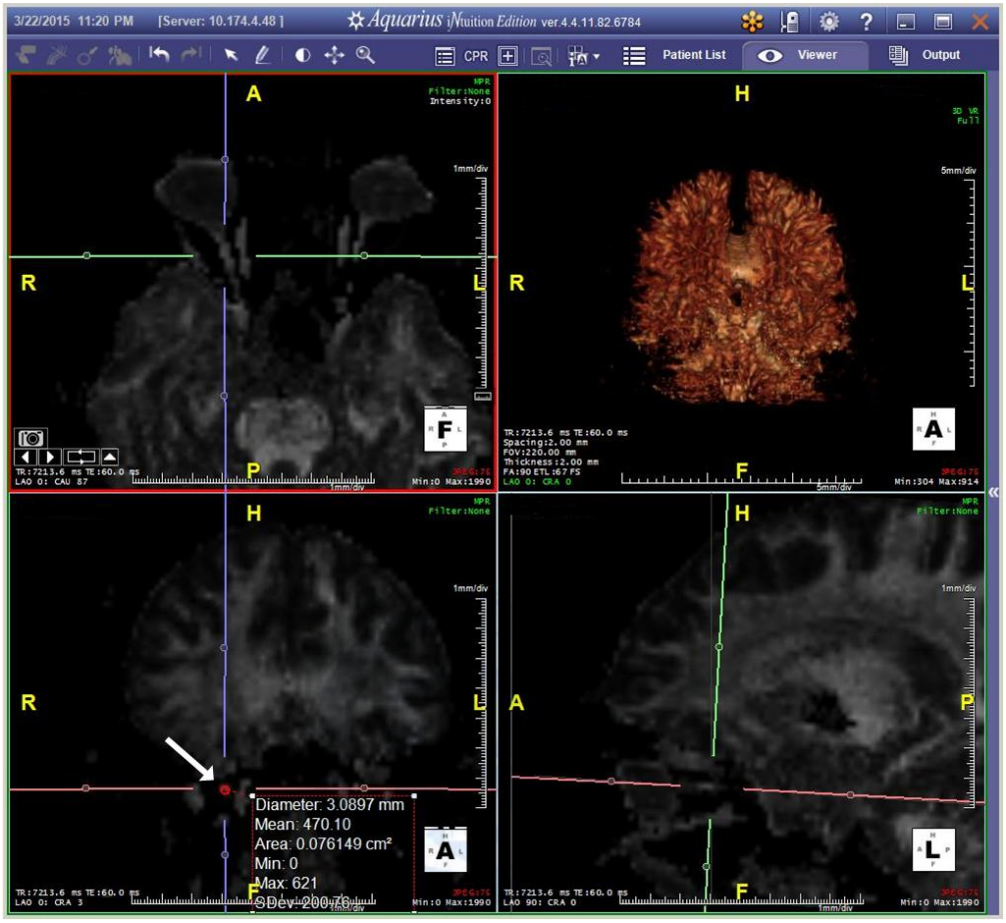
	FA		ADC	
	ß (SE)	*P**	*ß* (SE)	*P**
RCFT	-0.012 (0.008)	0.120	0.001 (0.003)	0.811
CDT	-0.001 (0.002)	0.824	0.001 (0.001)	0.537
Interlocking pentagon	-0.003 (0.002)	0.143	0.001 (0.001)	0.414
Digit span test, forward	-0.003 (0.002)	0.121	0.001 (0.001)	0.893
Digit span test, backward	-0.001 (0.002)	0.645	0.001 (0.001)	0.471
K-BNT	-0.019 (0.011)	0.077	0.003 (0.004)	0.535
SVLT delayed recall	-0.002 (0.003)	0.393	-0.001 (0.001)	0.369
RCFT delayed recall	0.002 (0.007)	0.768	0.001 (0.003)	0.649
COWAT, animal	-0.011 (0.005)	0.063	0.001 (0.002)	0.803
COWAT, supermarket	-0.008 (0.006)	0.205	0.001 (0.002)	0.884
COWAT phonemic	-0.008 (0.012)	0.482	-0.009 (0.004)	0.054
Stroop test color reading	-0.001 (0.003)	0.975	-0.011 (0.013)	0.423

*Multiple linear regression analysis adjusting for age at onset, gender, and disease duration.

FA, fractional anisotropy; ADC, afferent diffusion coefficient; K-BNT, Korean version of the Boston naming test; RCFT, Rey complex figure test; CDT, clock drawing test; SVLT, Seoul verbal learning test; COWAT, Controlled oral word

association test

Figure e-1. Diffusion tensor imaging of fractional anisotropy and apparent diffusion coefficient measurements in PD patients' optic nerves. The horizontal sections of the images were converted and reformatted to the coronal plane using Aquarius iNtuition software (TeraRecon, Foster City, CA, USA) to draw the circular region of interest on the mid-portion of the intraorbital optic nerve. This was performed because the horizontal section of the diffusion tensor image was identified in our routine magnetic resonance process. The sectioning produced: a 1) mean value of fractional anisotropy or apparent diffusion coefficient, 2) diameter and area of the region of interest, which are indicated by a white arrow and red dotted boxes, respectively, in the bottom left corner. Top left, horizontal section; top right, 3D reconstructed image of maximum intensity projection; bottom left, coronal section; bottom right, sagittal section. A, anterior; P, posterior; L, left; R, right; H, head; F, foot.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[Server: 10.174.4.48]
Aquarius iNtuition Edition ver.4.4.11.82.6784
CPR
Patient List
Viewer
Output
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Mean: 470.10
Area: 0.076149 cm²
Min: 0
Max: 621

IV. DISCUSSION

Based on comparative analyses of optic nerve integrity using DTI scanning, the present study demonstrated that microstructural integrity in the optic nerve was distorted in patients with PD compared to normal controls. Optic nerve disintegration was not significantly correlated with baseline parkinsonian severity, nigrostriatal dopaminergic depletion, olfactory performance, or cognitive performance. However, PD patients in the lower FA group showed more profound longitudinal decline in visuospatial cognitive performance relative to those in the higher FA group, which might suggest that optic nerve integrity is an important factor in predicting visuospatial cognitive decline in PD.

Because neurons in the retina project axons toward the optic nerve head and then eventually form an optic nerve bundle, optic nerve integrity might be influenced by pathological alterations in the retina. For example, retina thickness in patients with optic neuritis was well-correlated with optic nerve atrophy, which was quantified by MRI scans.[25] In addition, ganglion cell layer thickness was a significant predictor of axonal damage around the optic disc in patients with PD.[26] DTI can be used as a parameter and has been recognized as a valuable marker for determining axonal or myelin injury in the optic nerve.[27] Therefore, a DTI analysis method has been widely used to assess several ophthalmological diseases, such as glaucoma,[28] optic neuritis,[29] and multiple

sclerosis,[30] and microstructural changes in the optic nerve showed a close relationship with structural retinal changes.[28] Accordingly, DTI analysis is adequate for assessing the integrity of the optic nerve due to the basic nature of the optic nerve with axonal organization and architecture.

Along with a pathological report that dopaminergic neurons in the retina were decreased in PD patients, in vivo evidence has demonstrated that retina or macular thickness, determined by optical coherence tomography, was reduced in patients with PD. This structural change in the retina appears to be inversely correlated with disease duration or parkinsonian motor severity.[26, 31] Additionally, several studies have indicated that patients with PD showed lower amplitudes and delayed latencies on visual evoked potential[32, 33] and reduced amplitude on multifocal electroretinogram,[33] suggesting functional alteration in the retina. In the present study, microstructural white matter integrity assessed by DTI was significantly altered in patients with PD compared with controls or DIP patients, which provides further in vivo evidence of optic nerve disintegration in PD. Even though the precise mechanism of optic nerve disintegration in PD has not yet been determined, the data from this study suggest that white matter disintegration is not ascribed to functional dopamine deficiency but to PD-related pathological changes.

Interestingly, we found that optic nerve disintegration in patients with PD is a

remarkable factor for predicting the decreased visuospatial cognitive performance. In PD patients, visuospatial function deteriorated as the disease progressed,[34] and visuospatial memory impairment was greater in severely disabled PD patients.[35] Visual dysfunction is a strong predictor of dementia in PD.[36] Accordingly, overall visual dysfunction is critical for PD patients and can influence everyday functioning, including activities of daily living,[1] gait,[37] and problems in driving,[38] which lead to a lower quality of life and social isolation. However, there were no correlations between optic nerve disintegration and baseline MMSE scores or specific cognitive domains on comprehensive neuropsychological tests. As the subjects included in this study were in the early stage of PD without dementia, it was inferred that optic nerve disintegration has little influence on cognitive status in the early stages of PD. Rather, our data suggest that optic nerve integrity plays a putative role in cognitive decline when optic nerve disintegration is combined with extensive PD pathologies that involve visual cortical areas as the disease progresses.

The correlation analysis indicated that optic nerve integrity in patients with PD was not significantly related to parkinsonian motor severity, striatal DAT activity, or olfactory performance. However, this data indicated that the optic nerve disintegration process might be independent of nigrostriatal dopaminergic degeneration in PD. According to pathological staging, the retina and optic nerve are positioned at a similar longitudinal level with the olfactory bulb in the anatomic structure of a bottom-up alpha synuclein deposition.[39] Thus,

pathological changes in the retina and optic nerve might precede alpha synuclein deposition in the substantia nigra, suggesting a non-tangible relationship between optic nerve integrity and nigrostriatal system-dependent motor system in PD.

Optic nerve integrity in this study was not closely related to olfactory performance. A previous study indicated a close association between olfactory performance and cardiac sympathetic denervation;[40] however, we suggest that the non-motor systems, as the main induction sites of alpha-synuclein accumulation, are closely involved in the development and progression of PD regardless of involvement of the nigral dopaminergic system. If this is true, the visual system might not serve as the main induction site of synuclein accumulation compared with olfactory and cardiac sympathetic systems.

There were several strengths and limitations to this study. To the best of our knowledge, this is the first study to investigate and identify optic nerve disintegration in PD. A large number of drug-naïve de novo patients with PD and ^{18}F-FP-CIT PET-supported diagnoses of the disease strengthened this study. However, atypical parkinsonian disorders could not be completely excluded due to the recruitment of early-stage patients and relatively short follow-up periods. Second, we could not evaluate structural or functional changes in the retina, which would provide clues about the relationship between the integrity of the retina and the optic nerve in PD. Finally, the present study did not examine

optic nerve integrity in other parkinsonism plus syndromes, which might have extended clinical applications. Therefore, a large-scale multicenter trial could be instrumental for confirming optic nerve integrity as a valuable biomarker in PD. In summary, our data suggest that optic nerve integrity is a useful marker for distinguishing PD from normal controls, and a parameter of DTI of the optic nerve could be used as a valuable predictor of declining visuospatial function in PD.

V. CONCLUSION

In summary, our data suggest that being a useful marker for distinguishing PD from normal controls, a parameter of DTI on optic nerve might be regarded as a valuable predictor for decline of visuospatial function in PD.

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ABSTRACT(IN KOREAN)

파킨슨병 환자에서 시공간 인지 기능에 대한 시신경 손상의 예측성

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이재정

목적: 새로이 진단된 파킨슨병 환자에서 시신경의 구조적 손상이 존재하는지 확인하기 위해 확산텐서 자기공명영상을 이용한 연구를 계획하였다.

배경: 파킨슨병에서 시각 경로 전반에 걸친 시각 기능 장애에 대해서는 다양한 근거들이 제시되어 왔다. 특히 동물을 대상으로 하거나 파킨슨 환자를 대상으로 한 인체 연구 등 몇몇 연구들에서 망막에 존재하는 도파민 신경 세포의 변성이나 망막신경섬유층이 얇아져 있음을 밝혀 내었다. 시신경은 망막신경섬유층으로부터

유래하는 축삭 다발로서 아직까지 파킨슨병에서는 연구가 이루어진 바가 없었다.

방법: 파킨슨병 환자 82명 (남성 42명, 여성 40명), 약물 유발 파킨슨증 환자 36명, 정상군 36명으로부터 얻어진 확산텐서 자기공명영상을 이용하였다. 모든 파킨슨병 환자와 약물 유발 파킨슨증 환자에게 [^{18}F] N-(3-Fluoropropyl)-2β-carbon ethoxy-3β-(4-iodophenyl) nortropane (^{18}F-FP-CIT) 양전자방출단층촬영 검사를 각각 시행하였다. 시신경의 구조적 안정성을 확인하기 위해 확산텐서 분석을 통해 얻어진 분획비등방성(fractional anisotropy) 지도와 겉보기확산계수 (apparent diffusion coefficient) 지도 각각에서 양측 눈확 내에 위치한 시신경의 가운데 부위에서 원 모양의 관심영역(region of interest)을 그렸고 이로부터 얻어진 측정치들을 평균낸 값을 이용하였다. 추가적으로 파킨슨병 환자의 임상 양상을 대변할 수 있는 척도들을 다음과 같이 확인하였다. 환자의 운동 증상을 측정하기 위해 통합된 파킨슨병 척도 파트 III, 운동증상 전 시기를 대변하는 Cross cultural smell identification test (CCSIT), 인지 상태를 확인하기 위해 통합적 신경심리 검사를 각각 시행하였다.

결과: 분획``비등방성 측정치는 약물 유발 파킨슨증 환자 (0.645 ±

0.099) 나 정상군 (0.689 ± 0.089) 에 비해서 파킨슨병 환자 군 (0.552 ± 0.103, $p < 0.001$) 에서 의미 있게 낮았으며, 겉보기확산계수 측정치는 약물 유발 파킨슨증 환자 (1050.5 ± 252.9 mm^2/s) 나 정상군 (1071.6 ± 203.9 mm^2/s) 에 비해서 파킨슨병 환자 군 (1334.7 ± 261.7 mm^2/s, $p < 0.001$) 에서 의미 있게 높게 확인되었다. 파킨슨병 환자에서 분획비등방성 또는 겉보기확산계수 측정치와 ^{18}F-FP-CIT 양전자방출단층촬영에서 측정된 도파민운반활동 (dopamine transporter) 측정치, 통합된 파킨슨병 척도 파트 III, CCSIT 사이에 의미 있는 상관관계는 관찰되지 않았다. 신경심리 검사를 2회 이상 시행한 (평균 간격 2.5년) 파킨슨병 환자에서 분획비등방성이 낮은 군에서 높은 군에 비해 Rey-Osterrieth complex 그림 그리기 검사 (-4.26 ± 1.91; 95% CI, -8.31 to -0.40; $p = 0.031$) 와 시계 그리기 검사 (-1.35 ± 0.61; 95% CI, -2.59 to -0.11; $p = 0.034$) 에서 더 빠른 악화가 관찰되었다.

결론: 본 연구는 파킨슨병 환자의 시신경에서 미세한 구조적 손상이 존재함을 밝혀 내었으며, 이러한 손상은 파킨슨병 환자의 시각 인지 기능에 중요한 역할을 할 수 있음을 시사한다.

핵심되는 말 : 파킨슨병, 시신경, 확산텐서영상, 인지