RESEARCH ARTICLE

Retinal Nerve Fiber Layer Thickness and Visual Hallucinations in Parkinson's Disease

Jee-Young Lee, MD,[1,2,3*] Jae Min Kim, MD,[4] Jeeyun Ahn, MD,[4,5] Han-Joon Kim, MD,[2,3] Beom S. Jeon, MD, PhD,[2,3] and Tae Wan Kim, MD, PhD[4,5*]

[1]*Department of Neurology, Seoul National University-Seoul Metropolitan Government Boramae Medical Center, Seoul, Republic of Korea*
[2]*Department of Neurology, Seoul National University College of Medicine, Seoul, Republic of Korea*
[3]*Parkinson Disease Study Group, Movement Disorders Center, Seoul National University Hospital, Seoul, Republic of Korea*
[4]*Department of Ophthalmology, Seoul National University College of Medicine, Seoul, Korea, Seoul, Republic of Korea*
[5]*Department of Ophthalmology, Seoul National University-Seoul Metropolitan Government Boramae Medical Center, Seoul, Republic of Korea*

ABSTRACT: Defective visual information processing from both central and peripheral pathways is one of the suggested mechanisms of visual hallucination in Parkinson's disease (PD). To investigate the role of retinal thinning for visual hallucination in PD, we conducted a case-control study using spectral domain optical coherence tomography. We examined a representative sample of 61 patients with PD and 30 healthy controls who had no history of ophthalmic diseases. General ophthalmologic examinations and optical coherence tomography scans were performed in each participant. Total macular thickness and the thickness of each retinal layer on horizontal scans through the fovea were compared between the groups. In a comparison between patients with PD and healthy controls, there was significant parafoveal inner nuclear layer thinning, whereas other retinal layers, including the retinal nerve fiber layer, as well as total macular thicknesses were not different. In terms of visual hallucinations among the PD subgroups, only retinal nerve fiber layer thickness differed significantly, whereas total macular thickness and the thickness of other retinal layers did not differ. The retinal nerve fiber layer was thinnest in the group that had hallucinations without dementia, followed by the group that had hallucinations with dementia, and the group that had no hallucinations and no dementia. General ophthalmologic examinations did not reveal any significant correlation with hallucinations. There were no significant correlations between retinal thicknesses and duration or severity of PD and medication dosages. The results indicate that retinal nerve fiber layer thinning may be related to visual hallucination in nondemented patients with PD. Replication studies as well as further studies to elucidate the mechanism of thinning are warranted. © 2013 International Parkinson and Movement Disorder Society.

Key Words: retina thickness; visual hallucination; Parkinson's disease; optical computed tomography

Visual hallucination (VH) is a common symptom in both nondemented and demented patients[1] with Parkinson's disease (PD) and is reported in 22% of those with incident PD.[2] Cognitive dysfunction, long duration of PD, and sleep disturbance are risk factors for VH,[3,4] and its presence may predict nursing home placement and poor survival.[5]

VH in PD covers simple, minor hallucinations, such as sensation of passage, sensation of presence, or simple illusions (misinterpretation of images with overlap of humanoid or animal tracts on animated objects, etc), as well as complex, formed VHs.[6,7] In studies addressing the poor prognostic value of VH, complex, formed VH was the major focus, and there was no concern for patients who had having only minor VHs. However, in 1 study that included a considerable number of patients who had with minor VHs, ocular

*Correspondence to: Dr. Tae Wan Kim, Department of Ophthalmology, Seoul National University-Seoul Metropolitan Government Boramae Medical Center and College of Medicine, Seoul National University, Seoul, Republic of Korea; twkim93@medimail.co.kr; or Dr. Jee-Young Lee, Department of Neurology, Seoul National University-Seoul Metropolitan Government Boramae Medical Center and College of Medicine, Seoul National University, Seoul, Republic of Korea; wieber04@snu.ac.kr

Relevant conflicts of interest/financial disclosures: Nothing to report. Full financial disclosures and author roles may be found in the online version of this article.

Funding agencies: This study was supported by a clinical research grant from Seoul National University-Seoul Metropolitan Government (03-2011-13).

Received: 9 November 2012; **Revised:** 29 April 2013; **Accepted:** 6 May 2013

Published online 17 June 2013 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.25543

problems were reportedly another significant risk factor for VHs.[8]

The retina has dopaminergic A18 amacrine cells located in the inner nuclear layer (INL) at the border of the inner plexiform layer (IPL).[9,10] There is evidence of dopaminergic cell loss in the retina both in patients with PD and in 2-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated animal models.[11,12] Several studies have investigated retinal thinning in PD by means of optical coherence tomography (OCT) scans, which enables in vivo histopathological imaging of the retina.[13–21] However, the exact clinical consequence of retinal thinning and its relation to VHs in PD is still under investigated.

We hypothesized that retinal thinning may contribute to the appearance of VHs, especially in patients who have persistent VHs despite the absence of dementia. We measured total macular thickness and the thicknesses of each retinal layer in patients with PD and in a group of healthy controls using spectral-domain OCT scans, and we conducted a comparative analysis with regard to the presence of VHs and dementia.

Patients and Methods

Participants

This study protocol was approved by the Institutional Review Board of Seoul National University Boramae Medical Center, and informed consent was obtained from all participants. This study adhered to the tenets of the Declaration of Helsinki.

Study participants consisted of a group patients who were diagnosed with PD according to United Kingdom PD Brain Bank Society criteria[22] and had been followed in the Boramae Medical Center Movement Disorders Clinic between September 2010 and September 2011, and a group of healthy controls who received the ophthalmological examinations for routine check-up and were in the same age ranges as the patients with PD. Individuals with the following comorbid ophthalmic pathologies were excluded: retinal diseases capable of affecting retinal thickness, such as age-related macular degeneration, diabetic retinopathy, retinal vein or artery occlusion, epiretinal membrane, macular hole, or glaucomatous optic neuropathies, defined as either cup-disc asymmetry between fellow eyes $\geq$0.2, rim thinning, notching, excavation, or defect of the retinal nerve fiber layer. Individuals who had media opacity capable of inducing poor-quality OCT images, such as severe cornea opacity or advanced cataract, or the inability to cooperate with the OCT procedure because of severe cognitive impairment or parkinsonian motor disability were also excluded.

The patients with PD were classified into 3 subgroups: PD control with no VH and no dementia (PC), PD with VH and no dementia (PH), and PD with both VH and dementia (PHD).The presence of dementia was defined according to the criteria for probable dementia associated with PD suggested by the Movement Disorders Society (MDS) Task Force,[23] and the presence of VH was identified using a semi-structured interview[24] with patients and their care-givers during a follow-up visit. In the PH subgroup, only VHs with persistence $\geq$6 months were considered. In the PHD subgroup, we excluded patients who had developed dementia before or within 1 year after the onset of motor symptoms and those who had excessive daytime sleepiness or orthostatic hypotension. Those who developed VHs before or within 1 year after the onset of motor symptom also were excluded in both the PH and PHD subgroups. Demographic and clinical information, such as age at the study evaluations, sex, Mini-Mental Status Examination (MMSE) score, MDS revised Unified PD Rating Scale (UPDRS) score,[25] Hoehn and Yahr (H&Y) stage, dosages of anti-parkinsonian drugs, and age at PD onset, were collected.

Ophthalmologic Evaluations

To screen for ophthalmic diseases, general ophthalmologic examinations, consisting of best-corrected visual acuity, intraocular pressure, slit lamp biomicroscopy, indirect ophthalmoscopy, and axial length (IOLMaster, Carl Zeiss Meditec, Jena, Germany)[26] were conducted by an ophthalmologist (T.W.K.) who was blinded to the clinical diagnosis. High-resolution spectral domain-OCT (SD-OCT) scans (Opko OTI Spectral SLO/OCT; Ophthalmic Technologies, Inc., Toronto, Ontario, Canada) were performed on the dominant eye. The axial and transverse resolution of the SD-OCT is 5 μm and 20 μm, respectively, and it is capable of measuring the retinal layer thickness with an error of 5 μm. A horizontal scan image traversing the fovea was manually segmented by 2 independent ophthalmologists (J.A. and J.M.K.) who were blinded to patients' diagnoses to confirm segmentation reproducibility[27] using the caliper tool within the Spectral OCT/SLO at 5 regions: the fovea center (FC); temporally 1 mm, 2 mm, and 3 mm from the FC (T1, T2, and T3, respectively); and nasally 1 mm from the FC (N1). Segmentation consisted of 6 layers: the retinal nerve fiber layer (RNFL), the inner plexiform layer and ganglion cell layer (IPL + GCL), the inner nuclear layer (INL), the outer plexiform layer (OPL), the outer nuclear layer and photoreceptor inner segments (ONL + PIS), and the photoreceptor outer segments and retinal pigment epithelium (POS + RPE) (Fig. 1A). Retinal topographic maps were acquired by 256 serial parallel B-scans covering a 9 $\times$ 9 mm area in the macula. Mean macular thickness was automatically measured in the 9 macular Early Treatment Diabetic Retinopathy Study

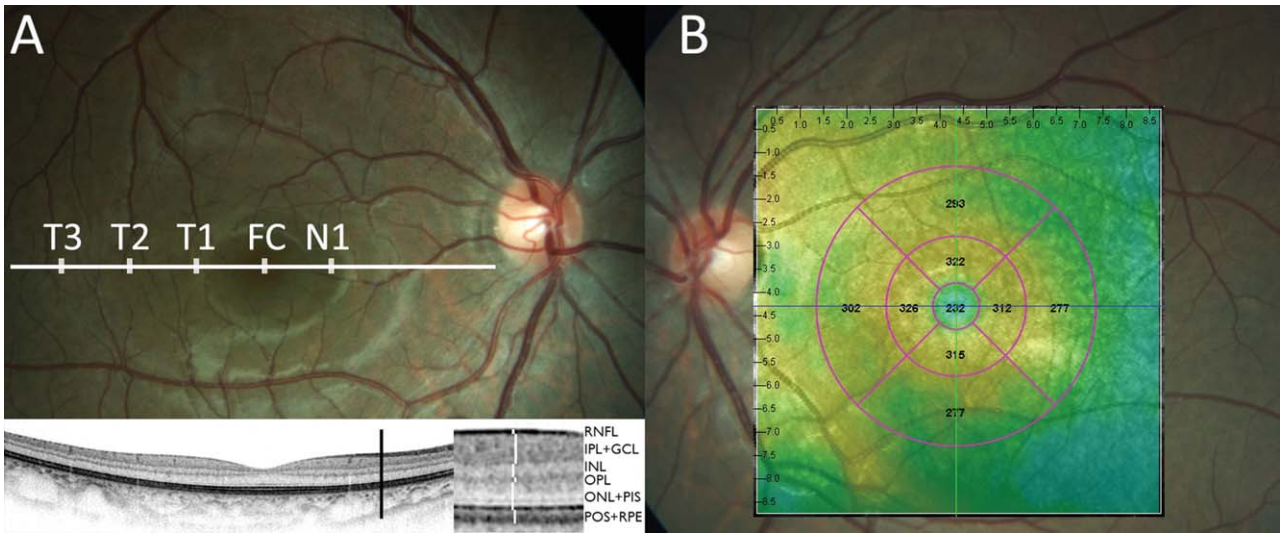

FIG. 1. (**A**) The measurement of retinal layer thickness and (**B**) a retinal topographic map on high-resolution spectral domain optical coherence tomography are shown. (**A**) A horizontal scan traversing the fovea was manually segmented into 6 layers. Retinal thickness was measured at 6 locations, the fovea center (FC), nasally 1 mm from the FC (N1), temporally 1 mm, 2 mm, and 3 mm from the FC (T1, T2, and T3, respectively). RNFL indicates retinal nerve fiber layer; IPL, inner plexiform layer; GCL, ganglion cell layer; INL, inner nuclear layer; OPL, outer plexiform layer; ONL, outer nuclear layer; PIS, photoreceptor inner segment; POS, photoreceptor outer segment; RPE, retinal pigment epithelium. (**B**) Mean macular thickness was measured in the 9 Early Treatment Diabetic Retinopathy Study areas.

(ETDRS) areas, including a central 1-mm disc and inner and outer rings of 3 mm and 6 mm, respectively (Fig. 1B).[28]

Statistical Analysis

Continuous and categorical variables were analyzed using the *t* test and the χ^2 test to compare the group PD and the healthy control group and using the Kruskal-Wallis test and the χ^2 test among the PD subgroups. The Mann-Whitney *U* test was used for comparisons between the PD subgroups. Correlations between retinal layer thickness and clinical variables were analyzed using Pearson's correlation analysis. The intraclass correlation coefficient (ICC) was analyzed to determine the inter-rater reliability of retinal layer thickness measurement. Because it is known that retinal thinning correlates with increasing age and axial length, but not with sex or laterality,[29] we made adjustments for age and axial length using the regression method if it was different between the groups. Statistical analyses were conducted using SPSS software (version 19.0; SPSS Inc., Chicago IL, USA) with the limit of significance set at 0.05 (2-tailed) in comparisons between the PD and the healthy control groups and among the PD subgroups, and significance was set at 0.0175 (2-tailed) for analyses within the PD subgroups in reference to the Bonferroni correction for multiple comparisons.

Results

In total, 61 patients with PD (24 men; mean age ± standard deviation, 69.6 ± 7.1 years) and 30 healthy controls (14 men; age, 64.8 ± 7.4 years) were enrolled in this study. Clinical and ophthalmologic characteristics of the participants are summarized in Table 1. There were no significant differences in mean axial length between healthy controls and patients with PD that could affect retinal thickness (23.24 ± 0.98 mm vs 23.58 ± 1.48 mm; $P = 0.352$). Age was adjusted for when comparing retinal thickness measures between the PD and healthy control groups. Comparisons of the characteristics among the 3 PD subgroups are provided in Table 1. The total daily levodopa (L-dopa) equivalent dose (LED)[30] was not significantly different among the PD subgroups; however the L-dopa dose was highest and the daily agonist dose (agonist LED)[30] was lowest in PHD subgroup.

There was a distinction in the pattern of VHs between the PH and PHD subgroups. Minor VHs, such as sensations of passage (25%) or presence (20%); simple illusions of shape or size (5%); amorphous objects or bits of thread (5%); metamorphosis (5%); and small figures resembling those of ticks, ants, and worms (15%)—none of which were accompanied by complex, formed VHs—were reported quite frequently in the PH subgroup. Conversely, 85% of the PHD subgroup had complex, formed VHs.

General Ophthalmologic Findings in Patients with PD and Healthy Controls

Axial length measurement, best-corrected visual acuity, frequency of cataract, and intraocular pressure did not differ significantly between the PD group and healthy controls (Table 1). There also were no significant differences among the PD subgroups, and there

TABLE 1. Clinical and ophthalmologic characteristics of the participants enrolled in this study

Characteristic	Mean ± SD		Median (range)			P^a	P^b
	PD, total	HC	PC	PH	PHD		
No. of individuals	61	30	25	20	16		
Sex: M/F	24/37	14/16	9/16	9/11	7/9	0.506	0.702
Age, y	69.6 ± 7.1	64.8 ± 7.4	70.0 (51–83)	70.5 (56–78)	73.0 (58–82)	0.005	0.389
Age at onset, y	63.6 ± 8.2		64.0 (44–79)	65.0 (43–75)	64.5 (49–76)		0.861
Hoehn & Yahr stage	2.2 ± 0.8[c]		2.0 (1–3)	2.0 (1.5–4)[d]	3.0 (2–5)[e]		0.001
UPDRS score[c]							
Total	52.2 ± 24.6		39.5 (12.5–71)	44.0 (22–89.5)[d]	65.0 (31–124)[e]		<0.001
Part I	12.4 ± 7.8		7.0 (3–24)	12.0 (5–22)[d,f]	18.3 (5–36)[e]		<0.001
Part II	13.2 ± 8.6		9.5 (1–21)	12.0 (0–23)[d]	17.5 (7–41)[e]		0.007
Part III	26.4 ± 13.5		20.0 (4.5–47)	22.0 (12.5–58.5)[d]	30.5 (17–60)[e]		0.007
MMSE score	24.1 ± 4.5		26.0 (14–30)	26.0 (19–29)[d]	19.5 (12–25)[e]		<0.001
LED, mg/day	679.7 ± 342.1		535.0 (80–1237)	675.0 (150–1510)	715.0 (400–1340)		0.188
Levodopa, mg/d	566.7 ± 339.9		445.0 (0–962)	530.0 (0–1510)	685.0 (400–1340)[e]		0.028
Agonist LED, mg/d	112.5 ± 121.5		112.5 (0–575)	75.0 (0–625.5)	0.0 (0–300)[e]		0.062
Axial length, mm	23.6 ± 1.5	23.2 ± 1.0	23.5 (22.6–26.0)	22.9 (21.5–25.2)	23.4 (22.5–31.2)	0.352	0.346
BCVA, logMAR	0.16 ± 0.31	0.14 ± 0.31	0.05 (0–0.52)	0.10 (0–2.2)	0.15 (0–2.00)	0.242	0.081
Cataract: No. [%]	35 [83.3]	22 [81.5]	13 [76.5]	11 [84.6]	11 [91.7]	1.000	0.551
IOP, mm Hg	12.8 ± 3.3	14.7 ± 3.9	12.0 (7–22)	12.5 (6–18)	12.0 (7–20)	0.039	0.859

[a]These *P* values are for comparisons between the PD total group and the HC group.
[b]These *P* values are for comparisons among the 3 PD subgroups.
[c]Scores are according to the Movement Disorders Society-sponsored revised version of the UPDRS published in 2008.
[d]Significance was $P < 0.0175$ for a comparison between the PH and PHD subgroups.
[e]Significance was $P < 0.0175$ for a comparison between the PC and PHD subgroups.
[f]Significance was of $P < 0.0175$ for a comparison between the PC and PH subgroups.
SD, standard deviation; PD, Parkinson's disease; HC, healthy control; PC, PD control; PH, PD with visual hallucination no dementia; PHD, PD with visual hallucination and dementia; M, male; F, female; UPDRS, Unified Parkinson's Disease Rating Scale; MMSE, Mini-mental Status Examination; LED, daily levodopa equivalent dose; BCVA, best-corrected visual acuity; logMAR, logarithm of the minimum angle of resolution; IOP, intraocular pressure.

were no significant associations between ophthalmologic findings and VH in the PD group.

OCT Analyses in Patients with PD and Healthy Controls

Images from a total of 86 participants were included in the OCT analysis. Images from 5 patients (3 in the PH subgroup and 2 in the PHD subgroup) were inadequate for precise thickness measurement because of the insufficient image quality from intolerability to scanning or poor compliance. The average ICC of thickness measures in this study was 0.96 (range, 0.86–0.98).

Comparisons of Total Macular Thicknesses and Retinal Layer Thicknesses between Patients with PD and Healthy Controls

The mean values of macular thicknesses for the entire group of patients with PD and the healthy control group are summarized in Table 2. There was a marginally significant reduction in superior outer macular thickness ($P = 0.036$) in the PD group. Other measures did not differ significantly between patients with PD and healthy controls.

With regard to retinal layer thickness, there was a tendency toward thinning in PD only at the INL (Table 2). It is noteworthy that INL thinning in PD was statistically significant in the T1 area (30.7 ± 6.3 μm in PD vs 35.2 ± 7.5 μm in healthy controls; $P = 0.013$). The thicknesses of the IPL + GCL at the T1, T2, and N1 areas also was low but with no statistical significance (Table 2).

Comparisons of Total Macular Thicknesses and Retinal Layer Thicknesses Among the PD Subgroups

When we compared the thickness of each layer among the 3 PD subgroups, we observed significant differences only in RNFL thickness (at the T1, T2, T3, and N1 areas: $P = 0.204$, $P = 0.025$, $P = 0.025$, and $P = 0.018$, respectively). RNFL thinning was most prominent in the PH subgroup, and this feature was consistently observed at the T1, T2, T3, and N1 areas (Fig. 2). The PH subgroup had significant RNFL thinning at T2, T3 and N1, but not at T1, compared with the PC group ($P = 0.007$, $P = 0.006$, $P = 0.007$, and $P = 0.111$, respectively). Although there were no significant differences between the PH and PHD subgroups in all these areas (at T1, T2, T3, and N1; $P = 1.000$, $P = 0.565$, $P = 0.296$, and $P = 0.469$, respectively), the tendency of RNFL thinning in the PHD subgroup, compared with the PC subgroup, did not have statistical significance (at T1, T2, T3, and N1; $P = 0.167$, $P = 0.111$, $P = 0.197$, and $P = 0.074$,

TABLE 2. Macular thickness and thickness of 6 retinal layers on the horizontal scan in patients with Parkinson's disease and healthy controls

Layer(s)	Macular Thickness: Mean ± SD, μm		
	PD group (n = 56)	HC group (n = 30)	P^a
Macular Thicknesses			
Total	270.08 ± 23.27	275.17 ± 20.30	0.411
FC	186.13 ± 24.57	179.8 ± 30.65	0.255
Center circle	214.00 ± 30.26	205.07 ± 29.56	0.186
IS	285.42 ± 33.79	281.87 ± 26.02	0.589
II	281.42 ± 30.76	279.37 ± 22.19	0.639
IT	271.87 ± 37.88	276.27 ± 22.57	0.677
IN	283.42 ± 27.50	282.97 ± 25.51	0.899
OS	273.91 ± 22.02	285.37 ± 23.02	0.036[b]
OI	264.45 ± 27.22	274.89 ± 25.05	0.164
OT	250.81 ± 33.42	254.78 ± 17.80	0.497
ON	286.77 ± 23.06	292.63 ± 25.88	0.527
FC			
ONL + PIS	132.02 ± 19.16	136.50 ± 13.84	0.644
POS + RPE	36.28 ± 4.83	36.67 ± 4.61	0.724
T1			
RNFL	17.45 ± 4.15	17.33 ± 4.10	0.504
IPL + GCL	70.21 ± 17.63	79.83 ± 15.84	0.087
INL	30.74 ± 6.34	35.17 ± 7.48	0.013[b]
OPL	32.13 ± 7.92	29.67 ± 5.07	0.070
ONL + PIS	125.96 ± 14.62	125.17 ± 11.93	0.731
POS + RPE	35.53 ± 4.69	36.67 ± 4.61	0.443
T2			
RNFL	17.45 ± 4.41	18.00 ± 5.35	0.904
IPL + GCL	83.83 ± 14.07	87.00 ± 12.84	0.529
INL	33.09 ± 7.63	36.33 ± 7.06	0.135
OPL	32.23 ± 5.50	32.17 ± 6.11	0.428
ONL + PIS	105.11 ± 11.82	106.50 ± 10.01	0.695
POS + RPE	35.53 ± 4.69	36.50 ± 4.18	0.572
T3			
RNFL	16.70 ± 3.34	16.50 ± 6.18	0.878
IPL + GCL	69.57 ± 10.52	69.33 ± 11.58	0.803
INL	27.98 ± 7.2	28.83 ± 5.97	0.464
OPL	28.51 ± 5.2	29.00 ± 4.62	0.633
ONL + PIS	92.55 ± 11.37	94.83 ± 7.93	0.525
POS + RPE	35.21 ± 4.89	36.50 ± 3.75	0.320
N1			
RNFL	21.49 ± 4.77	22.33 ± 5.21	0.905
IPL + GCL	75.11 ± 16.83	79.50 ± 15.67	0.601
INL	38.09 ± 7.91	38.67 ± 8.30	0.791
OPL	40.74 ± 12.42	39.83 ± 15.62	0.882
ONL + PIS	114.36 ± 17.99	117.50 ± 16.01	0.426
POS + RPE	35.74 ± 4.66	36.50 ± 3.75	0.672

[a]Comparisons were between the PD group and the HC group; *P* values were adjusted for age.
[b]This *P* value indicates a statistically significant difference.
SD, standard deviation; PD, Parkinson's disease; HC, healthy controls; FC, fovea center; IS, inner superior; II, inner inferior; IT, inner temporal; IN, inner nasal; OS, outer superior; OI, outer inferior; OT, outer temporal; ON, outer nasal; ONL, outer nuclear layer; PIS, photoreceptor inner segment; POS, photoreceptor outer segment; RPE, retinal pigment epithelium; T1, temporal 1 mm; RNFL, retinal nerve fiber layer; IPL, inner plexiform layer; GCL, ganglion cell layer; INL, inner nuclear layer; OPL, outer plexiform layer; T2, temporal 2 mm; T3, temporal 3 mm; N1, nasal 1 mm.

respectively). The thicknesses of all retinal layers examined did not reveal any significant correlations with clinical variables, such as H&Y stage, UPDRS scores, MMSE scores, LED, daily L-dopa doses, agonist LED, or duration of PD.

Discussion

This is the first study investigating the associations between VHs and structural changes in the retinal layers of patients with PD using high-resolution SD-OCT images. Our results suggest that VHs—especially those that occur in nondemented patients with PD—may be associated with RNFL thinning. General ophthalmologic findings were not associated significantly with VHs in PD, in line with previous studies.[1,31] RNFL thinning may be either a primary process or a secondary result from a dying-back phenomenon or a retrograde, trans-synaptic degeneration that reflects primary involvement of the central visual pathway.[32]

The pathophysiology of VHs in PD is not fully understood, but many have suggested that it is multifactorial.[7,31,33] Dysfunctions in the frontoparietal cortex involved in visual attention and dysfunctions in the visual association cortex, disturbed modulations of cholinergic and serotonergic inputs from subcortical and brainstem structures, deficits in visual afferent (such as retinal changes), and dream overflow from the rapid eye movement sleep pontogeniculo-occipital regulating system[33] all theoretically may induce VHs in PD.[7,31,33] Thus, it is believed that both "top-down" control and "bottom-up" input processing are mutually important.[6,7] If RNFL thinning is a primary process, then our finding can support a role for afferent visual deficit in the development of VH in nondemented PD. Weakening of retina-cortical signals, whether alone or in combination with dysfunctions in

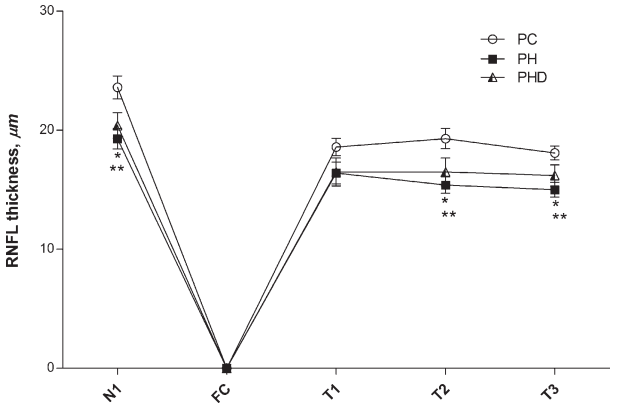

FIG. 2. This chart illustrates retinal nerve fiber layer (RNFL) thickness on the horizontal axis through the fovea in patients with Parkinson's disease (PD). Thickness measures of RNFL at each point from the fovea center (FC) are shown. Because the fovea is populated by cone photoreceptors and Müller cells only, there is no RNFL, and it is only possible to measure thickness of the outer nuclear layer and photoreceptor inner segment (ONL+PIS) and of the photoreceptor outer segment and retinal pigment epithelium (POS+RPE) at the FC. Symbols and error bars indicate the mean thickness and standard error, respectively. N1 indicates nasal 1 mm from the FC; T1, temporal 1 mm from the FC; T2, temporal 2 mm from the FC; T3, temporal 3 mm from the FC; PC, PD with no visual hallucination and no dementia; PH, PD with visual hallucination and no dementia; PHD, PD with visual hallucination and dementia. A single asterisk indicates $P < 0.05$ in a comparison among the PD groups; double asterisks, $P < 0.0175$ in a comparison between the PC and PH groups.

cortical visual information processing, may lead to VH through the loss of signal synchrony at the cortical level,[34] which may result in aberrant release of previously stored internal images, as in Charles Bonnet syndrome.[34,35]

If RNFL thinning is a secondary result, then there would be central visual dysfunctions in nondemented PD. There are only few functional imaging studies suggesting cortical dysfunctions in nondemented PD with VHs. Those studies showed less activation of the visual cortex and greater activation of the frontal or orbitofrontal cortex in response to visual stimuli,[34] gray matter reduction in the superior parietal cortex,[36] and hypometabolism in the ventral and dorsal visual pathways, sparing the occipital pole.[37] However, imaging data are scarce regarding differences between nondemented and demented patients with PD who have VHs.

Through segmental measurement of each retinal layer using SD-OCT, our study revealed that the INL was significantly thinner in the T1 area (where the INL is the thickest) in the entire PD group, regardless of VH, compared with the INL in healthy controls. The total macular volume was thinner in the superior outer region in the patients with PD compared with healthy controls, but the macular volumes were not different in the temporal regions; whereas INL thinning on horizontal image was observed in the temporal region. Changes in the parafoveal INL may be too small to be reflected in total volumes, and automated estimation of macular volume may not be sensitive enough for the detection of small parafoveal changes. Foveal vision is important for various visual functions, such as contrast sensitivity and color vision, which some have suggested are impaired in PD. This issue is beyond the scope of the current study; thus, it would be better to introduce a recent review article on the topic for interested readers.[38]

Retinal thickness in PD using OCT has been reported in several studies.[10,13–21] Many of them analyzed peripapillary thickness and reported RNFL thinning in PD,[12,14,20,21] although some did not support those findings.[16–18] Macular changes in PD were revealed by 6 studies, including ours, although different methods were used.[13,14,17–19] In the report by Aaker et al.,[17] the superior outer macular region was thinner in PD than the published normal values, consistent with our finding. A recent study on the fovea demonstrated that the foveal pit is thinner and broader in PD compared with normal controls, providing evidence of the thinning of the perifoveolar inner retinal layer in PD.[19]

Interocular asymmetry in the parafoveal region reportedly is marked in PD,[10] which may lead to false-negative results. This could be related to asymmetric involvement of the retina in PD, although this has not yet been proven. We compared data from dominant eyes for the purpose of analyzing eyes that more dominantly affected an individual and, thus, tried to reduce the type II errors. However, it may be a limitation of the present work.

This study also has other limitations. First, the sample size was small, especially in the PHD subgroup, because there was difficulty in recruiting demented patients, who required a considerable degree of compliance to perform OCT and ophthalmic examinations. RNFL thinning seemed to be more prominent in our PH subgroup than in our PHD subgroup. However, because of the small number of patients in the PHD subgroup, further studies with larger samples will be necessary to validate this finding.

Second, to our knowledge, there has been no standard OCT protocol to measure retinal thickness in PD. A recent review on the variability of OCT measurements indicated that there was a significant difference in the absolute values of RNFL thickness measured by different OCT devices, although reproducibility and the ICC were good for all types of devices, and the Fourier-domain devices were reliable for detecting axonal atrophy in the RNFL in PD.[20] Third, our method of segmental layer analysis was too limited to reveal the changes in all retinal layers; thus, studies using multiple samplings with improved accuracy of the vertical layer measures are warranted in the future. Fourth, we did not have longitudinal data regarding the temporal relation between the timing of VH onset and thinning of the retina; thus, the result was not sufficient to extend to a causal relation.

To date, it is not known why RNFL thinning takes place in patients with PD who have VHs or precisely how it affects visual information processing in PD. The results from this study support the notion that visual afferent dysfunction can be 1 factor that renders an individual with PD vulnerable to VHs, and RNFL thinning may be a possible biomarker of PD progression. Replication studies and further works to define the functional consequence of RNFL thinning and its temporal correlation with hallucinatory phenomena are needed in the future. ■

References

1. Archibald NK, Clarke MP, Mosimann UP, Burn DJ. Visual symptoms in Parkinson's disease and Parkinson's disease dementia. Mov Disord 2011;26:2387-2395.
2. Khoo TK, Yarnall AJ, Duncan GW, et al. The spectrum of nonmotor symptoms in early Parkinson disease. Neurology 2013;80:276-281.
3. Fenelon G, Mahieux F, Huon R, Ziegler M. Hallucinations in Parkinson's disease: prevalence, phenomenology and risk factors. Brain 2000;123:733-745.
4. Papapetropoulos S, Argyriou AA, Ellul J. Factors associated with drug-induced visual hallucinations in Parkinson's disease. J Neurol 2005;252:1223-1228.
5. Hely MA, Reid WG, Adena MA, et al. The Sydney multicenter study of Parkinson's disease: the inevitability of dementia at 20 years. Mov Disord 2008;23:837-844.
6. Onofrj M, Bonanni L, Albani G, et al. Visual hallucinations in Parkinson's disease: clues to separate origins. J Neurol Sci 2006;248:143-150.

7. Diederich NJ, Goetz CG, Stebbins GT. Repeated visual hallucinations in Parkinson's disease as disturbed external/internal perception: focused review and a new integrative model. Mov Disord 2005;20:130-140.
8. deMaindreville AD, Fenelon G, Mahieux F. Hallucinations in Parkinson's disease: a follow-up study. Mov Disord 2005;20:212-217.
9. Frederick JM, Rayborn ME, Laties AM, et al. Dopaminergic neurons in the human retina. J Comp Neurol 1982;210:65-79.
10. Schrier EM, Adam CR, Spund B, Glazman S, Bodis-Wollner I. Interocular asymmetry of foveal thickness in Parkinson's disease [serial online]. J Ophthalmol 2012;728457.
11. Harnois C, Di Paolo T. Decreased dopamine in the retinas of patients with Parkinson's disease. Invest Ophthalmol Vis Sci 1990;31:2473-2475.
12. Tatton WG, Kwan MM, Verrier MC, et al. MPTP produces reversible disappearance of tyrosine hydroxylase-containing retinal amacrine cells. Brain Res 1990;527:21-31.
13. Altintas O, Iseri P, Ozkan B, Caglar Y. Correlation between retinal morphological and functional findings and clinical severity in Parkinson's disease. Doc Ophthalmol 2008;116:137-146.
14. Hajee ME, March WF, Lazzaro DR, et al. Inner retinal layer thinning in Parkinson's disease. Arch Ophthalmol 2009;127:737-741.
15. Inzelberg R, Ramirez JA, Nisipeanu P, Ophir A. Retinal nerve fiber layer thinning in Parkinson disease. Vis Res 2004;44:2793-2797.
16. Archibald NK, Clarke MP, Mosimann UP, Burn DJ. Retinal thickness in Parkinson's disease. Parkinsonism Relat Disord 2011;17:431-436.
17. Aaker GD, Myung JS, Ehrlich JR, Mohammed M, Henchcliffe C, Kiss S. Detection of retinal changes in Parkinson's disease with spectral-domain optical coherence tomography. Clin Ophthalmol 2010;4:1427-1432.
18. Albrecht P, Muller AK, Sudmeyer M, et al. Optical coherence tomography in parkinsonian syndromes [serial online]. PLoS One 2012;7:e34891.
19. Spund B, Ding Y, Liu T, Selesnick I, Glazman S, Shrier EM, Bodis-Wollner I. Remodeling of the fovea in Parkinson disease. J Neural Transm 2013;120:745-753.
20. Garcia-Martin E, Satue M, et al. Ability and reproducibility of Fourier-domain optical coherence tomography to detect retinal nerve fiber layer atrophy in Parkinson's disease. Ophthalmology 2012;119:2161-2167.
21. Moschos MM, Tagaris G, Markopoulos I, Margetis I, Tsapakis S, Kanakis M, Koutsandrea C. Morphologic changes and functional retinal impairment in patients with Parkinson disease without visual loss. Eur J Ophthalmol 2011;21:24-29.
22. Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. J Neurol Neurosurg Psychiatry 1992:55:181-184.
23. Emre M, Aarsland D, Brown R, et al. Clinical diagnostic criteria for dementia associated with Parkinson's disease. Mov Disord 2007;22:1689-1707.
24. Mosimann UP, Collerton D, Dudley R, et al. A semi-structured interview to assess visual hallucinations in older people. Int J Geriatr Psychiatry 2008;23:712-718.
25. Goetz CG, Tilley BC, Shaftman SR, et al. Movement Disorder Society UPDRS Revision Task Force. Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results. Mov Disord 2008;23:2129-2170.
26. Verhulst E, Vrijghem JC. Accuracy of intraocular lens power calculations using the Zeiss IOL master. A prospective study. Bull Soc Belge Ophtalmol 2001;281:61-65.
27. Bagci AM, Shahidi M, Ansari R, et al. Thickness profiles of retinal layers by optical coherence tomography image segmentation. Am J Ophthalmol 2008;146:679-687.
28. Forte R, Cennamo GL, Finelli ML, de Crecchio G. Comparison of time domain Stratus OCT and spectral domain SLO/OCT for assessment of macular thickness and volume. Eye (Lond) 2009;23:2071-2078.
29. Budenz DL, Anderson DR, Varma R, et al. Determinants of normal retinal nerve fiber layer thickness measured by Stratus OCT. Ophthalmology 2007;114:1046-1052.
30. Lee JY, Lee EK, Lim JY, et al. Association of DRD3 and GRIN2B with impulse control and related behaviors in Parkinson's disease. Mov Disord 2009;24:1803-1810.
31. Gallagher DA, Parkkinen L, O'Sullivan SS, et al. Testing an aetiological model of visual hallucinations in Parkinson's disease. Brain 2011;134:3299-3309.
32. Jindahra P, Petrie A, Plant GT. Retrograde trans-synaptic retinal ganglion cell loss identified by optical coherence tomography. Brain 2009;132:628-634.
33. Onofrj M, Thomas A, Bonanni L. New approaches to understanding hallucinations in Parkinson's disease: phenomenology and possible origins. Expert Rev Neurother 2007;7:1731-1750.
34. Stebbins GT, Goetz CG, Carrillo MC, et al. Altered cortical visual processing in PD with hallucinations: an fMRI study. Neurology 2004;63:1409-1416.
35. Abbott EJ, Connor GB, Artes PH, Abado RV. Visual loss and visual hallucinations in patients with age-related macular degeneration (Charles Bonnet syndrome). Investigative Ophthalmol Vis Sci 2007;48:1416-1423.
36. Ramirez-Ruiz B, Marti MJ, Tolosa E, et al. Cerebral atrophy in Parkinson's disease patients with visual hallucinations. Eur J Neurol 2007;14:750-756.
37. Boecker H, Ceballos-Baumann AO, Volk D, Conrad B, Forstl H, Haussermann P. Metabolic alterations in patients with Parkinson disease and visual hallucinations. Arch Neurol 2007;64:984-988.
38. Bodis-Wollner I. Foveal vision is impaired in Parkinson's disease. Parkinsonism Relat Disord 2013;19:1-14.