

# Retinal nerve fiber layer thinning: a window into rapid eye movement sleep behavior disorders in Parkinson's disease

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## Abstract

**Purpose** Retinal nerve fiber layer (RNFL) thinning occurs in Parkinson's disease (PD) and other neurodegenerative diseases. Idiopathic RBD (iRBD) is a well-established prodromal hallmark of synucleinopathies and occurs secondary to many neurodegenerative diseases, including PD. The aim of this study is to determine whether or not retinal structures are altered with the onset of rapid eye movement (REM) sleep behavior disorders (RBD).

**Methods** In all, a total of 63 patients with PD, 14 patients with idiopathic RBD, and 26 sex- and age-matched healthy controls were enrolled and underwent optical coherence tomography measurements (HD-OCT (Zeiss)) for the average and every quadrant of RNFL thickness. The REM Sleep Behavior Disorder Screening Questionnaire (RBDSQ) was used to classify PD patients with clinically probable RBD (PD + pRBD) or without probable RBD (PD – pRBD). Patients with iRBD were identified by polysomnography.

**Results** For patients with RBD (idiopathic or secondary to PD), we found a significant decrease in RNFL thickness compared with groups without RBD (PD – pRBD and healthy controls) (all  $p < 0.05$ ). Average RNFL thickness in patients with iRBD is significantly thinner than in healthy controls ( $p < 0.05$ ). In PD, the average RNFL thickness was dramatically thinner in the PD + pRBD group than the PD – pRBD group ( $p < 0.005$ ). Compared with healthy controls, RNFL thickness was slightly thinner in the drug-naive PD group but not the PD group with drug treatment. Multiple linear regression analysis showed that RBDSQ score was negatively associated with average and inferior RNFL variation in PD (all  $p < 0.005$ ).

**Conclusions** The findings show that RNFL was slightly but significantly thinner in idiopathic RBD. In PD, RNFL thickness may vary depending on the presence of RBD.

**Keywords** Idiopathic rapid eye movement sleep behavior disorders · Rapid eye movement sleep behavior disorders · Parkinson's disease · Retinal nerve fiber layer thickness · Optical coherence tomography measurement

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## Abbreviations

PD + pRBD	PD patients with clinical probable RBD
PD – pRBD	PD patients without probable RBD
RNFL	Retinal nerve fiber layer
PDND	newly diagnosed PD patients with drug-naive
PDED	PD patients exposure to drug treatment

## Introduction

Rapid eye movement (REM) sleep behavior disorders (RBD) are characterized by a loss of typical muscle atonia during

REM sleep and prominent motor activity associated with dreaming. RBD is a well-established prodromal hallmark of synucleinopathies and occurs secondary to neurodegenerative diseases [1, 2]. The prevalence of RBD is approximately 0.38 % in the general population [3], but a much higher frequency is found in patients with neurodegenerative disorders, especially synucleinopathies [1]. Idiopathic RBD may precede onset of parkinsonism or dementia with a risk of 81 % after RBD diagnosis within 10 years [4]. Parkinson's disease (PD) is a progressive neurodegenerative disorder with loss of dopaminergic neurons primarily in the substantia nigra. The classical characteristic of PD is accumulation of the aggregation-prone protein alpha-synuclein in Lewy bodies [5]. Increased clinical awareness of the impact of RBD in subtypes of PD has been recognized in recent years. In patients with PD, RBD is associated with specific clinical features such as older age, longer disease duration, non-tremor motor subtype and more severe parkinsonism [6, 7]. Accurate clinical diagnosis and treatment of PD is still challenging owing to atypical parkinsonism [8]. Finding objective disease- and stage-specific biomarkers to track disease progression and distinguish between subgroups is an important area of research for individualizing treatments for patients with PD. Though it is still controversial, growing evidence suggests that characteristics of the retina could be used as a new biomarker to identify early PD and to predict disease severity and clinical characteristics [9–12].

In the eye, dopamine functions as an essential neurotransmitter or modulator in the retina and is produced by the A18 subtype of amacrine cells in the inner plexiform layer of the retina [13]. In 1990, decreases in dopamine in retinal tissues of patients with PD were first reported [14]. Interestingly, a recent study reported that in retinal wholemounts of nine subjects with Parkinson's disease, and three subjects with dementia with Lewy bodies (DLB), which were immunohistochemically stained with an antibody against  $\alpha$ -synuclein phosphorylated at serine 129, phosphorylated synuclein-immunoreactive (p-syn IR) nerve fibers in the retinas were present in 7/9 PD subjects and in 1/3 DLB subjects. As the antibody is a specific molecular marker of synucleinopathy, the presence of p-syn IR nerve fibers in the retina in these PD and DLB subjects is consistent with retinal synucleinopathy [15].

Within the past decade, a considerable body of research has demonstrated that retinal nerve fibers, as detected by optical coherence tomography (OCT), are altered in PD, dementia, multiple system atrophy (MSA), and other neurodegenerative diseases [10, 16, 17]. However, less attention has been given to retinal alterations in RBD. Therefore, our study set out to evaluate the correlation between the presence of RBD and RNFL thinning in patients with PD and idiopathic RBD. As RBD may occur in early PD, we performed a cross-sectional observational

survey to assess alterations in RNFL thickness using multivariate analysis to clarify the contribution of potential factors.

## Methods

### Study subjects

A cross-sectional study was conducted between March 2014 and March 2015 at the Department of Neurology and Sleep Center in the Second Affiliated Hospital of Soochow University. This study was approved by the ethics committee of our hospital. Patients and healthy controls signed written consent to agree with participation in our research. A total of 63 patients with PD, 14 patients with idiopathic RBD, and 26 sex- and age-matched controls were screened for OCT measurements and received ophthalmologic examination (by ophthalmologist W.J.) to exclude ocular related disease. The subjects all met the inclusion criteria and agreed to participate in this study. Among them, all the probable idiopathic clinical RBD patients completed an overnight video polysomnography (PSG) study to further clarify diagnosis. Thirty patients with PD volunteered to complete the overnight PSG evaluation, which confirmed objective sleep structure (PSG data in Sup. 1). The inclusion criteria for patients were: (1) meeting the UK brain bank criteria for the diagnosis of idiopathic PD, (2) being free of ocular disease (other than visually non-significant mild cataract), (3) having no systemic disorders potentially affecting vision, such as diabetes, (4) having best-corrected visual acuity equal to or better than 6/10, (5) having intraocular pressure lower than 21 mmHg, (6) having the ability to follow the study protocol, and (7) having repeatability in the OCT examination. All patients were asked for medication history, were evaluated using the Unified PD Rating Scale (UPDRS) and the Hoehn and Yahr (H&Y) scale, and underwent a fundamental ophthalmologic examination including visual acuity, Goldmann applanation intraocular pressure measurement, slit lamp biomicroscopy examination of the fundus, and OCT. From all patients, we obtained information regarding: gender, age, PD or RBD duration, and medication treatment history. PD patients with exposure to drug treatment were classified as PDED, and newly diagnosed PD patients with drug-naïve were classified as PDND. We used the motor UPDRS score in the “off” medication state to acquire the “maximum” level of disease severity.

### OCT measurements

The retinal nerve fiber layer (RNFL) measurement was performed by a single experienced examiner using HD-OCT (Carl Zeiss Meditec, Inc., Dublin, CA). Pupils were dilated

for the test. The optic nerve head cube  $200 \times 200$  scan protocol was used respectively in each eye. This protocol generates a  $6 \times 6$  mm cube of data after a series of 200 B-scans with 200 A-scans per B-scan (40,000 points) in approximately 1.5 s (27,000 A-scans/s). The instrument uses the intrinsic algorithms to delineate the boundaries of the RNFL automatically and to calculate the RNFL thickness in the average and quadrant on a 3.46-mm-diameter circle provided by the system's software (Version 5.1.1.6). Only images with quality above 7 were included. We used the Cirrus HD-OCT optic disk protocol as previously described [18]. All patients with PD underwent the ophthalmologic examination and OCT measurements in the “drug-on” state to better coordinate the examination.

### REM Sleep Behavior Disorder Screening Questionnaire and polysomnography

The REM Sleep Behavior Disorder Screening Questionnaire (RBDSQ), a well-established self-rating test, have been used to screen preliminarily for RBD cohorts in patients with PD and idiopathic RBD in the general population [19, 20]. Scores of more than 6 points are considered suggestive of clinical RBD subjects [19]. We classified patients as having PD with probable clinical RBD (RBDSQ score  $> 6$ ; PD + pRBD) or PD without probable RBD (RBDSQ score  $< 6$ ; PD – pRBD). All the probable idiopathic clinical RBD patients (RBDSQ score  $> 6$  as well) completed an overnight video-PSG study to further clarify diagnosis according to the criteria of the International Classification of Sleep Disorders—2nd Edition (ICSD-2) [21].

The overnight video-PSG (Compumedics-E series, Australia) evaluation was performed by two sleep specialists who were blinded for the subjects category. PSG recording included standard electroencephalographic (EEG) derivations (C3–A2, C4–A1, O1–A2, O2–A1), electrooculogram (EOG; LE–A2, RE–A1), electrocardiogram (ECG), chin electromyogram (EMG), bilateral leg EMG (anterior tibialis muscles), oronasal airflow by thermocouple and nasal pressure measurements, snoring sound, oxyhemoglobin saturation, and thoracic and abdominal respiratory efforts. All PSG data were recorded with continuous video monitoring PSG and were scored according to the standard criteria of the AASM [22]. All idiopathic RBD patients met International Classification of Sleep Disorders-II criteria for RBD, having REM without atonia, with history or videographic evidence of dream enactment and were free of parkinsonism or dementia [21].

### Data analysis

Statistical package SPSS 17.0 was used to perform the statistical analysis. Distribution of data was examined for normality (Shapiro-Wilk test). Means and standard

deviations (SDs) were calculated. First, two-way analysis of variance (ANOVA) test was used to examine differences in RNFL thickness regarding of both PD group and RBD group. Multiple comparison for post hoc comparison with the each case group (PD – pRBD, PD + pRBD, idiopathic RBD) and healthy controls was made with Dunnett's test. Various ANOVAs were used for each independent variable with post hoc pairwise comparisons using the Scheffé procedure. The statistical analysis was performed at a 95 % confidence level and a *p* value less than 0.05 was considered statistically significant. Moreover, RNFL analysis was reaffirmed for the above subgroup with sex and age included as covariates. PD groups with and without drug treatment were compared. Finally, the contribution of RBDSQ score to RNFL thickness alterations was examined using multiple linear regression analysis for PD patients, adjusting for potential confounders (age, UPDRS motor score, LEDD).

## Results

### Clinical demographic data

By using the RBDSQ score to classify PD patients and the PSG evaluation for idiopathic RBD patients, a total of 37 PD patients with probable RBD, 26 PD patients without RBD, 14 patients with idiopathic RBD and 26 sex-age-matched healthy controls were enrolled in our study. The mean age of patients in the PD groups was 61.2 years, and mean age of the iRBD groups was 62.7 years, that of healthy controls was 61.2 years. Age ( $p = 0.811$ ), sex ( $p = 0.428$ ), and intraocular pressure ( $p = 0.303$ ) did not differ statistically between the three groups. However, the mean age and sex differed slightly in PD subgroups with and without RBD. The mean age of the PD + pRBD group was 63.5 years, whereas that of the PD – pRBD group was 59.5 years ( $p = 0.022$ ). Moreover, male sex was the majority of the subgroup PD + pRBD versus the group PD – pRBD ( $p = 0.006$ ). The patients' disease severity ranged from mild to moderate according to the Hoehn and Yahr (H&Y) staging criteria [23] as early-stage PD (H&Y stage: I–II) and advanced-stage PD (H&Y stage: III). Specifically, in our PD group, 31 patients were stage I, 29 patients were stage II, and 3 patients were stage III. The PD + pRBD group had an H&Y score similar to the PD – pRBD group ( $p = 0.965$ ). There were no significant differences in UPDRS motor score (UPDRS III) between PD patients with and without probable clinical RBD ( $p = 0.256$ ). Moreover, the levodopa dose did not differ between PD subgroups (PD + pRBD,  $382.62 \pm 150.10$ ; PD – pRBD,  $293.57 \pm 171.16$ ;  $p = 0.068$ ). Out of all patients with PD, 15 were newly diagnosed PD patients with no previous drug treatment (Table 1).

**Table 1** Demographic and clinical characteristics of the study population

	HC ( <i>n</i> = 26)	PD ( <i>n</i> = 63)	PD – pRBD ( <i>n</i> = 37)	PD + pRBD ( <i>n</i> = 26)	iRBD ( <i>n</i> = 14)	<i>P</i>
Number of eyes	52	126	74	52	28	NA
Gender (M/F)	13/13	33/30	14/23	19/7	10/4	0.428 <sup>a</sup> , 0.026 <sup>b</sup>
Age (years)	61.23 ± 6.86	61.19 ± 7.43	59.54 ± 8.41	63.53 ± 5.02	62.71 ± 12.76	0.811 <sup>a</sup> , 0.244 <sup>b</sup>
Disease duration (years)	–	2.76 ± 2.28	2.46 ± 2.33	3.29 ± 2.19	–	0.748 <sup>c</sup>
RBD duration (years)	–	–	–	8.09 ± 12.43	9.11 ± 8.11	0.398 <sup>d</sup>
H&Y stage	–	1.71 ± 0.53	1.70 ± 0.52	1.73 ± 0.56	–	0.994 <sup>e</sup>
UPDRS III	–	18.34 ± 8.90	17.43 ± 9.47	19.68 ± 7.99	–	0.256 <sup>c</sup>
LEDD (mg/day)	–	330.67 ± 167.05	293.57 ± 171.16	382.62 ± 150.10	–	0.068 <sup>c</sup>
RBDSQ score	–	4.87 ± 3.60	2.21 ± 1.37	8.65 ± 2.05	9.35 ± 1.44	0.000 <sup>e</sup>
PDND ( <i>n</i> )	–	15	9	6	–	NA
IOP (mmHg)	13.61 ± 2.57	14.14 ± 2.40	13.75 ± 2.49	14.69 ± 2.18	14.92 ± 3.17	0.303 <sup>a</sup> , 0.219 <sup>b</sup>

Values are mean ± standard deviation, or frequencies (percentage)

HC healthy controls; PD patients with Parkinson's disease; PD – pRBD PD patients with no probably RBD; PD + pRBD PD patients with probable RBD; UPDRS III Unified Parkinson's Disease Rating Scale, part III (motor assessment); H&Y Hoehn and Yahr; LEDD L-dopa equivalent daily dose; RBDSQ REM Sleep Behavior Disorder Screening Questionnaire; PDND newly diagnosed PD patients with no previous drug treatment; IOP intraocular pressure; NA not applicable

<sup>a</sup> Between groups HC, PD, iRBD comparison

<sup>b</sup> Between groups HC, PD – pRBD, PD + pRBD, iRBD comparison

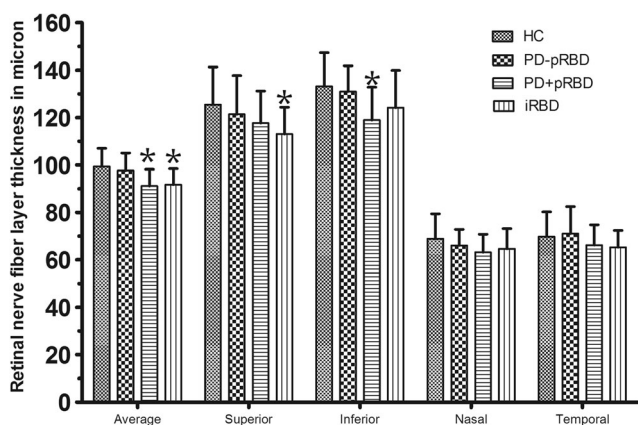
<sup>c</sup> Between groups PD – pRBD, PD + pRBD comparison

<sup>d</sup> Between groups PD + pRBD, iRBD comparison

<sup>e</sup> Between groups PD – pRBD, PD + pRBD, iRBD comparison

## Group comparisons

Retinal nerve fiber layer thickness in average and every quadrant RNFL thickness of different groups are shown in Fig. 1. Two-way ANOVA test showed that RNFL thickness in all patients with RBD (idiopathic or secondary to PD) was significantly thinner than patients without RBD (average:



**Fig. 1** This diagram demonstrates retinal nerve fiber layer (RNFL) thickness in PD patients with and without RBD, idiopathic RBD, and healthy controls. HC healthy controls; PD – pRBD PD patients without probable RBD; PD + pRBD PD patients with clinical probable RBD; iRBD idiopathic RBD. RNFL thicknesses are expressed as mean ± standard. \*Comparison to healthy controls significance at 0.05 level

$F = 21.62$ ,  $p < 0.0001$ ; superior quadrant:  $F = 6.95$ ,  $p = 0.01$ ; inferior quadrant:  $F = 14.53$ ,  $p < 0.0001$ ; nasal quadrant:  $F = 4.17$ ,  $p = 0.044$ ; temporal quadrant:  $F = 4.89$ ,  $p = 0.029$ ). And the differences among the four groups were the main effect only from RBD but not PD. In further, multiple-pair comparisons with each case group and healthy controls, for the subgroup PD + pRBD, the differences were statistically different from healthy controls in average thickness and inferior quadrants (Fig. 1 all  $p < 0.005$ ). Figure 1 also demonstrates that average and superior RNFL thickness in iRBD was significantly thinner than controls (all  $p < 0.05$ ). Moreover, an obvious decrease in RNFL thickness on average and in the inferior quadrant was observed in the group PD + pRBD compared with the group PD – pRBD (average:  $t = -3.525$ ,  $p = 0.008$ ; inferior quadrant:  $t = -3.575$ ,  $p = 0.001$ ). Taking the statistically minor difference of age and sex of PD subgroup into account, analysis of covariance was performed to reaffirm the subgroup comparisons. Likewise, we obtained similar differences between pairwise comparisons adjusted for sex and age. In particular, another statistical difference was explored between the group PD – pRBD and iRBD (average:  $p = 0.041$ ).

Retinal nerve fiber layer thickness in patients with PD did not differ statistically from the group without PD (including both iRBD and healthy controls). To determine if drug treatment influences the retinal fiber layer thickness alterations, comparisons were performed among the PD patients exposure



to drug treatment (PDED), newly diagnosed PD patients with drug-naive (PDND), iRBD and healthy controls (see Fig. 2). The PDND group had a moderately thinner RNFL in the inferior quadrant compared with the healthy controls. However, we observed no significant difference in RNFL thinning in PDED patients compared with healthy controls.

### Multivariate analyses

In order to explore the association between RBDSQ score (dependent variable) and RNFL thickness (independent variables) for the whole PD cohort, linear regression models controlled for potential confounders—age, disease severity (UPDRS III), and l-dopa treatment dose (see Table 2). There was a negative correlation between RBDSQ score and RNFL thickness in every quadrant. This correlation acquired significance for average thickness and for the inferior quadrant. To be specific, a higher RBDSQ score, indicating increased probability of comorbidity with clinical RBD, correlated with a statistically smaller average RNFL thickness in PD (adjusted model:  $\beta = -0.441$ ;  $p = 0.002$ ). This correlation was evident in the inferior quadrants as well (adjusted model:  $\beta = -0.457$   $p = 0.002$ ). However, for the dependent variable such as age and UPDRS III, there was no correlation with RNFL thickness and statistical differences were explored in every quadrant.

### Polysomnography parameters

The PSG parameters of 30 patients with Parkinson's disease and 14 idiopathic RBD are shown in Sup. Table 1. Sleep polysomnography parameters between the PD group and

iRBD group did not differ significantly except that patients with iRBD had a lower apnea-hypopnea index.

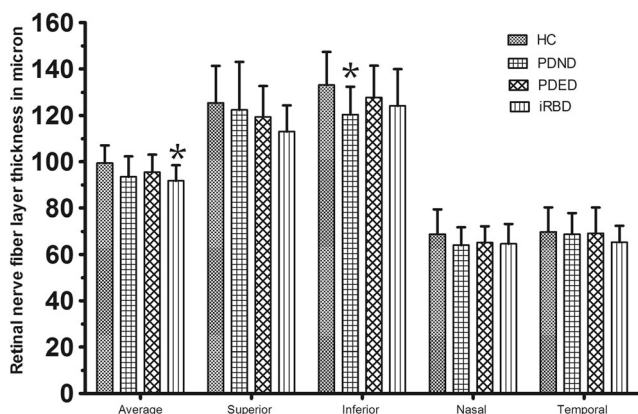
### Discussion

Patients with idiopathic RBD have been considered to be at high risk for the development of neurodegenerative synucleinopathy. Mounting evidence from prospective cohort studies suggests that a large percentage of patients with idiopathic RBD are in prodromal stages of neurodegeneration. Specifically, multicenter research has found that as many as 33.3 % of patients develop synucleinopathies with illnesses such as PD, dementia, or MSA after a follow-up of approximately 3.8 years [4, 24, 25].

To our knowledge, no published studies have correlated RNFL alterations with the onset and presence of RBD. Our study is the first to show a significant decrease in RNFL thickness in idiopathic RBD patients compared with healthy controls. We also found a statistical difference in RNFL thickness between the PD + pRBD and PD – pRBD groups, even after adjusting for sex and age. Interestingly, a slight thinning is observed in specific inferior quadrant in the group PD + pRBD in contrast to the group PD – pRBD, which suggests that the involvement of RBD may aggravate PD following by a specific pattern starting from the inferior quadrant of the retina. Moreover, we highlight that the RBDSQ score was negatively associated with RNFL thickness in PD, which indicates that an increased risk of RBD may have some correlation with RNFL thinning.

Our results confirm an association between the presence of RBD (idiopathic or secondary to PD) and RNFL thickness, suggesting that the retinal changes become more pronounced as the disease progresses. However, little is known about the time at which RNFL thinning begins, especially in idiopathic RBD. This will require longitudinal studies examining the degree of association between RNFL thinning and RBD, which our group is currently planning.

A significant decrease in RNFL thickness during PD was first reported in 2004 [16]. In the last 10 years, a considerable body of research has confirmed RNFL thinning in PD by OCT [10–12]. This may illustrate that retinal pathology in PD presents as a thinning of neural tissues involved in the processing of visual signals before they reach the optic nerve [26–27]. We did not detect retinal alterations on average or in any specific quadrants in PD patients with drug treatment compared with the control group. It has been reported the disease was more severe in PD patients with drug treatment than in those without drug use, without a significant difference in retinal thickness between the two groups [28]. It was suggested that levodopa may have a protective effect on the retina [28]. This may explain why the retinal nerve fiber layer thickness in PDED group did not differ from the control group but the PDND



**Fig. 2** This diagram represents comparison of retinal nerve fiber layer thickness (RNFL) among PD patients with and without drug treatment, idiopathic RBD and healthy controls. *HC* healthy controls; *iRBD* idiopathic RBD; *PDND* newly diagnosed PD patients with drug-naive, *PDED* PD patients exposure to drug treatment. RNFL thicknesses are expressed as mean  $\pm$  standard. \*Multiple pair comparison, significance at 0.05 level (average: iRBD vs. HC  $p = 0.036$ ; inferior quadrant: PDND vs. HC  $p = 0.049$ )

**Table 2** Multiple linear regression to identify association between RNFL and RBDSQ score in PD patients

Regression models	Unadjusted model		Adjusted model			
	$\beta$	Std. Error	$\beta$	95 % CI	<i>P</i> value	
Average						
		Model	<i>P</i>	= 0.008	$R^2 = 0.270$	
Age	-0.190	0.135		-0.191	(-0.462, 0.081)	0.165
UPDRS III	-0.051	0.111		-0.061	(-0.275, 0.173)	0.650
LEDD	0.004	0.006		0.093	(-0.008, 0.017)	0.493
RBDSQ	-1.002	0.311		-0.441	(-1.628, -0.375)	0.002
Superior quadrant						
		Model	<i>P</i>	= 0.239	$R^2 = 0.118$	
Age	-0.263	0.260		-0.150	(-0.788, 0.261)	0.317
UPDRS III	-0.197	0.215		-0.134	(-0.630, 0.235)	0.363
LEDD	-0.002	0.012		-0.027	(-0.026, 0.022)	0.857
RBDSQ	-0.871	0.601		-0.218	(-2.082, 0.341)	0.154
Inferior quadrant						
		Model	<i>P</i>	= 0.006	$R^2 = 0.280$	
Age	-0.338	0.239		-0.190	(-0.819, 0.143)	0.163
UPDRS III	-0.037	0.197		-0.025	(-0.434, 0.360)	0.851
LEDD	0.005	0.011		0.057	(-0.017, 0.027)	0.672
RBDSQ	-1.849	0.551		-0.457	(-2.960, -0.739)	0.002
Nasal quadrant						
		Model	<i>P</i>	= 0.126	$R^2 = 0.151$	
Age	-0.102	0.135		-0.109	(-0.375, 0.171)	0.457
UPDRS III	-0.151	0.112		-0.194	(-0.376, 0.074)	0.183
LEDD	0.006	0.006		0.151	(-0.006, 0.019)	0.304
RBDSQ	-0.595	0.313		-0.281	(-1.225, 0.036)	0.064
Temporal quadrant						
		Model	<i>P</i>	= 0.768	$R^2 = 0.041$	
Age	0.007	0.224		0.005	(-0.446, 0.460)	0.975
UPDRS III	0.135	0.185		0.111	(-0.238, 0.508)	0.470
LEDD	0.005	0.010		0.081	(-0.015, 0.026)	0.602
RBDSQ	-0.549	0.158		-0.166	(-1.594, 0.496)	0.295

Significance at 0.005 level  $\beta$  linear regression coefficient

CI confidence interval

group did differ in the inferior quadrant. Furthermore, RBD may affect clinical characteristics and potential mechanisms of PD such as alpha-synuclein oligomer formation and inflammation [7]. Our results found that the PD with RBD group had a thinner RNFL on average and specifically in the inferior quadrants. These results are in agreement with a series of studies that find RBD to be related with increased severity of clinical motor and non-motor PD symptoms [6].

PD is a neurodegenerative disorder characterized by the loss of dopaminergic neurons. Although the central dopaminergic system implicated in motor function is largely located in the substantia nigra pars compacta, dopaminergic neurons that undergo degeneration are also found in the retina, an important circadian organ [5, 11, 14, 29]. Previous studies have found that dopamine is decreased in the retinal tissue

of patients with PD [14]. Interestingly, a group recently found p-syn IR nerve fibers in the retina of seven patients with PD and one with dementia with Lewy bodies (DLB); this is consistent with retinal synucleinopathy [15]. Retinal alterations in PD likely indicate the presence of dopaminergic amacrine cell distress and may be correlated with a more general neurodegenerative process, possibly linked to alpha-synuclein pathology [15].

It is reported that idiopathic RBD may precede onset of parkinsonism or dementia with a risk of 81 % after RBD diagnosis within 10 years [4]. In our study, retinal nerve fiber layer thickness between idiopathic RBD and drug-naive PD had no statistical difference. Idiopathic RBD coupled with retinal thinning may represent impending Parkinson's disease. Verification of this theory will require a longitudinal follow-

up study of a large population of subjects with iRBD. On the other hand, in dementia, DLB, and Alzheimer's disease [17], RNFL thickness is altered as well. A small population of intrinsically photosensitive retinal ganglion cells (ipRGCs) plays a substantial role in circadian rhythms, human health, and sleep. These ipRGCs may also be decreased in PD [30]. Increased awareness of circadian rhythms in early PD and other neurodegenerative diseases [31] and the retinal alterations observed in idiopathic RBD or RBD secondary to PD in our study suggest that these various illnesses may share a common association: disruption of the clock underlying circadian rhythms. This hypothesis may explain our finding that a higher RBDSQ score indicates a thinner RNFL regardless of whether the PD patient has RBD.

In our study, most patients with PD were in the early stages of the disease. We attempted to reduce the effects of some confounding factors such as age, severity of disease, and previous medication. However, the main weakness of our study is that the number of patients recruited, especially in the idiopathic RBD group, was relatively small. Furthermore, not all patients with PD underwent comprehensive sleep assessment confirmed for objective RBD. Furthermore, it was not possible to include only unmedicated patients in a cross-sectional observational study of this type, since some patients start therapy at the time of diagnosis.

According to the Braak theory, the distribution of Lewy bodies in PD progresses from peripheral to central neurons in a caudocranial direction with increasing stage [32]. Our data support the occurrence of RNFL thinning in idiopathic RBD, which is of high risk in PD and other neurodegenerative diseases. The increased risk of probable RBD in PD found in our study implies that the RNFL is much thinner. Overall, RNFL thinning may be related to the increased probability of comorbid RBD. Further studies are needed to determine the extent to which each layer can predict the onset of RBD in the early stages of PD or idiopathic RBD. We hypothesize that RNFL alterations in idiopathic RBD or secondary RBD may serve as a “window” to explore the potential pathogenesis of the development of neurodegenerative synucleinopathy. OCT measurements are objective and available tools that can be applied in combination with other clinical examinations.

## Conclusions

Our study has demonstrated that RNFL thinning occurred in patients with RBD (idiopathic or secondary to PD). It indicates that, in the prodromal stage of neurodegenerative disease, the retina may have structural alterations that precede the onset of motor symptoms. Furthermore, our study suggests that the presence of RBD may have correlation with the RNFL alterations in PD.

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## Compliance with ethical standards

**Financial disclosures** All funding sources and potential conflicts of interest from each author that relate to the research were covered in the article.

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**Ethical approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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