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ORIGINAL ARTICLE

Correlations among multifocal electroretinography and optical coherence tomography findings in patients with Parkinson's disease

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Abstract

To assess the correlation between functional and anatomical evaluations with multifocal electroretinography (mfERG) and spectral-domain optical coherence tomography (SD-OCT) in patients with Parkinson's disease (PD). This cross-sectional study involved 116 eyes of 58 patients with PD and 30 age- and sex-matched control subjects. All study participants underwent a comprehensive neuro-ophthalmic examination, retinal single-layer thicknesses and volumes, and peripapillary retinal nerve fiber layer (pRNFL) measurements with SD-OCT, and the patients' mfERG recordings were evaluated. The macular retinal nerve fiber layer (mRNFL), ganglion cell layer (GCL), inner plexiform layer (IPL), outer nuclear layer (ONL), retinal pigment epithelium (RPE), and photoreceptor layer (PR) thicknesses, and mRNFL, RPE, and PR volumes were found lower in PD compared to those of controls, while outer plexiform layer (OPL) volumes were increased ($p < 0.05$). We found delayed implicit times and decreased amplitudes in the mfERG of PD patients versus those in control subjects ($p < 0.05$). We found significant correlations between outer macular volumes, PR thicknesses, and N1 amplitudes of rings 2 and 3and P1 amplitudes of rings 3, 4, and 5. Our study revealed thinning of both inner and outer retinal single layers, increased OPL volume, and delayed implicit times and decreased amplitudes in the mfERG of PD patients versus control subjects and correlation between structural and functional parameters. Our findings point out that SD-OCT and mfERG could both serve as non-invasive tools for evaluating ophthalmic manifestations of Parkinson's disease.

Keywords Parkinson's disease · Optical coherence tomography · Retinal nerve fiber layer · Retinal single layers · Multifocal electroretinography

Introduction

Parkinson's disease (PD) is a common neurodegenerative condition which is represented by the selective destruction of dopaminergic neurons at the central nervous system, including regions for instance the dopaminergic amacrine cells and the retinal ganglion cells [1]. Clinical symptoms include movement disorders likewise non-motor symptoms, including dementia, depression, and autonomic disability. Reduction in the foveal vision, contrast sensitivity, and color perception, reduced corneal thickness and blink rate, tear dysfunction, slowed visual evoked potentials (VEP), and pattern electroretinogram (PERG) abnormalities have been outlined in PD patients [2–4].

Optical coherence tomography (OCT) with retinal segmentation test is a useful device in determining ganglion cell damage and neurodegeneration in multiple sclerosis and PD by in vivo imaging and measure of the retinal segments [5, 6]. The multifocal ERG (mfERG) was established to contribute a topographical assessment of retinal electrophysiological response [7]. The principal scientific use of the mfERG is to recognize spatial variations in mfERG activities that pinpoint retinal damage to distinct zones of the retina: the macula, paramacula, or distinct peripheral regions [7].

Numerous studies were performed using OCT on PD patients, but only few attempted to assess the correlation between functional and structural changes in the peripapillary retinal nerve fiber layer (pRNFL) and macular thickness [6, 8]. To the best of our knowledge, there are no reports of relationship between topographic measurement of retinal electrophysiological activity and mfERG that could localize the defect in the retina, and retinal layer segmentation findings by

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OCT. Furthermore, earlier reports have suggested that the correlation of retinal changes to the first affected body side could be crucial in PD [9]. To evaluate this hypothesis, in this study, we also compared the findings of unilateral and bilateral patients with PD.

The primary objective of this study is to measure the structural parameters (OCT segmentation data) and functional parameters (mfERG responses) among patients with bilateral and unilateral Parkinson's disease. The secondary objective was to evaluate the correlation between these parameters to find the usability of these parameters as disease progression markers.

Methods

This cross-sectional, non-randomized, comparative study involved 116 eyes of 58 patients with Parkinson's disease according to the UK Brain Bank Diagnosis Criteria [10], (bradykinesia, rigidity, resting tremor, postural instability) and 30 age- and sex-matched healthy participants without systemic or ophthalmic disease.

The study protocol adhered to the tenets of the Declaration of Helsinki. The study protocol and informed consent forms were approved by the Institutional Review Board of the University Hospital.

In the PD group, disease severity was evaluated with the Hoehn and Yahr scale, and disease duration was registered. The Hoehn and Yahr scale is frequently used for evaluating the PD severity [11]. Stages range from 0 (no manifestations) to 5 (needing a wheelchair). We have divided the Parkinson subjects in this study based on clinical presentation, i.e., bilateral Parkinson or unilateral Parkinson subgroups. Medication for PD was recorded.

Exclusion criteria included a history of previous eye surgery, history of retinal pathology (macular edema, epiretinal membrane, diabetic retinopathy, age-related macular degeneration), and media opacity. Patients with refraction higher than 4 diopters (D) of spherical equivalent or 4 D of astigmatism were also excluded from the investigation.

All participants underwent detailed neurologic and ophthalmologic examinations, including best-corrected visual acuity, color vision assessment with Ishihara color plates, intraocular pressure measurement with Goldmann applanation tonometry, slit-lamp biomicroscopy, and fundus examination. Retinal single-layer thicknesses and volumes, pRNFL measurements with SD-OCT, and patients' mfERG recordings were evaluated in the study.

OCT imaging

Imaging was performed after standard pupillary dilation using tropicamide 0.5% drops with the Spectralis (Heidelberg Engineering, Heidelberg, Germany) with a ~840-nm wavelength. We analyzed the images whose signal-to-noise rate was greater than 25 dB, and scans with misalignment, decentration of the measurement, and poor brightness were excluded from the study.

All scans were carried out with support of the eye tracking system. Retinal layers segmentation was performed for calibrating the thicknesses of the macular retinal nerve fiber layer (mRNFL), ganglion cell layer (GCL), inner plexiform layer (IPL), inner nuclear layer (INL), outer plexiform layer (OPL), outer nuclear layer (ONL), photoreceptor layer (PR), and retinal pigment epithelium (RPE). To evaluate the peripapillary RNFL (pRNFL), a circular scan with a 3.4-mm diameter was performed after manually placing the center on the optic disc. The pRNFL Spectralis protocol creates a map that shows the average thickness and maps with six sector thicknesses (superotemporal, temporal, superonasal, nasal, inferonasal, and inferotemporal) [12].

Macular volumes were calibrated using the software of the company established in the ETDRS protocol. Three retinal volumes were focused on the foveola with radii of 1, 3, and 6 mm. Macular volumes were divided into two regions as inner and outer. Inner macular volume was defined as the average of five measurements at the foveal center and 3 mm away from the nasal, temporal, superior, and inferior directions of the foveal center. Outer macular volume was defined as the average of four measurements between 3- and 6-mm ETDRS ring.

Multifocal electroretinography

Multifocal ERG (Vision Monitor, Monpack 3, Metrovision, France) was recorded according to the ISCEV guidelines [7]. Patients were light adapted for at least 15 min in room light, with fully dilated pupils. A liquid crystal display screen was used to produce 61 scaled hexagonal stimulus patterns (30° horizontal and 24° vertical field) with central fixation point. Luminance of bright and dark hexagons was kept at 100 and < 1 cd/m^2, respectively. The recording was performed monocularly using contact lens electrodes after anesthetizing the cornea with topical 1% proparacaine drops, with refractive correction prescribed for near vision. The right eye was tested first, followed by the left eye, each with fresh disposable corneal electrodes. The stimulus frequency was set at 17 Hz, and overall duration of pseudo-random stimulation was 5 min.

Analysis of mfERG

The first-order mfERG responses were analyzed using color maps of amplitudes given as density and implicit times of N1, P1, and N2 wave peaks. The typical waveform of the mfERG response is a biphasic wave with an initial negative deflection followed by a positive peak. There is usually a second negative deflection after the positive peak. These three peaks are

called N1, P1, and N2, respectively. The average responses were over a group of up to five rings from 0° to 25° of eccentricity relative to fixation. The analysis develops a histogram for each of the extended zones indicating the average amplitude of the N1, P1, and N2 peaks (Fig. 1).

Statistical analysis

Data were analyzed using SPSS software (SPSS 18.0, SPSS Inc., Chicago, IL). Descriptive statistics were performed for all parameters. Data were tested for normal distribution using the Kolmogorov-Smirnov test. Spearman's correlation was used to evaluate the correlations between bilateral Parkinson and unilateral Parkinson groups with mean Hoehn and Yahr scores, disease duration, retinal single-layer thicknesses and volumes, pRNFL values, and mfERG parameters. P values < 0.05 were considered significant for statistical test.

Results

A total of 58 PD (116 eyes) patients were compared to 30 healthy (60 eyes) controls. Demographic and clinical characteristics of the PD patients and healthy controls are shown in Table 1. "Drugs which increase dopamine levels" was the most frequent treatment (72.5% of patients), and combination therapy with levodopa, carbidopa, and entacapone was the most common therapy (30.8%). Twenty-eight (48%) of the PD patients had unilateral PD (UPD), while 30 (52%) had bilateral PD (BPD). There were no differences between participants in the UPD, BPD, and control groups with respect to age or gender. Color vision scores were significantly poorer in BPD compared to those of controls (10 ± 3 vs 13 ± 1 out of 14 Ishihara plates) ($p = 0.01$). Subjects with BPD had a longer mean disease duration compared to UPD subjects (10.80 ± 6.15 vs. 3.23 ± 2.21 years; $p < 0.001$). The Hoehn and Yahr score was significantly higher in BPD 2.90 ± 0.39 compared to that in UPD 1.21 ± 0.31 ($p < 0.001$).

There was significant thinning in macular RNFL (mRNFL), GCL, IPL, ONL, RPE, and PR in both UPD and BPD compared to healthy subjects ($p < 0.05$) (Table 2). The mRNFL was significantly thinner in BPD compared to that in UPD patients ($p = 0.006$), moreover, there was a decreasing trend towards the retinal layers except mRNFL being thinner in BPD than UPD patients ($p > 0.05$).

There was significant decrease in volumes of mRNFL, RPE, and PR in both UPD and BPD compared to healthy subjects ($p < 0.05$) (Table 2). The OPL volumes in both UPD and BPD were significantly thicker compared to those in healthy controls ($p = 0.01$).

The temporal and superotemporal pRNFL in BPD was thinner than that in UPD ($p = 0.003$, $p = 0.04$; respectively) and healthy controls ($p = 0.001$, $p = 0.04$; respectively). None of the other pRNFL values for the average, nasal, superonasal, inferonasal, and inferotemporal retinal regions disclosed any significant differences between the three groups (Table 3).

When eyes were separated according to the ipsilateral and contralateral body side in UPD patients, no significant differences in retinal layer thickness, retinal volumes, and pRNFL parameters between the groups were seen.

The mean mfERG N1, P1, and N2 amplitudes are presented in Table 4. There was significant difference in the N1, P1, and N2 amplitudes for all rings in both UPD and BPD versus control subjects ($p < 0.001$) (Fig. 2). There was also significant difference in the mean N1, P1, and N2 implicit times for four of five rings in both UPD and BPD compared to healthy controls ($p < 0.05$). There was no difference in the mean N1, P1, and N2 implicit times for ring 1 (< 2°) between the three groups. The mean mfERG N1, P1, and N2 amplitudes and implicit times for all rings were the same for eyes on the ipsilateral side and the contralateral side in UPD patients.

Spearman correlation analyses was performed to evaluate the association between disease severity (using Hoehn and Yahr scale), disease duration, and OCT and mfERG parameters (Fig. 3). The Hoehn and Yahr score was negatively correlated with various retinal single-layer thicknesses (mRNFL, ONL thicknesses ($r = -0.733$; $p = 0.04$, $r = -0.779$; $p = 0.01$; respectively)) and mRNFL volume ($r = -0.633$; $p = 0.04$), as well as positive correlation with OPL volume ($r = 0.546$; $p = 0.02$). We found moderate correlations between the Hoehn and Yahr score and mfERG N1 implicit times of rings 4 and 5 ($r = 0.733$; $p = 0.007$ and $r = 0.561$; $p = 0.03$, respectively), P1 implicit times of rings 3 and 4 ($r = 0.654$; $p = 0.006$ and $r = 0.571$; $p = 0.002$, respectively), and N2 implicit times of ring 5 ($r = 0.551$; $p = 0.002$). No significant correlations between disease duration and pRNFL parameters and mfERG recordings were found.

In addition, we found moderate-to-strong correlations between outer macular volumes and N1 amplitudes of rings 2 and 3; P1 amplitudes of rings 3, 4, and 5; N2 amplitudes of rings 3, 4, and 5; and N1 implicit times of rings 4 and 5. Furthermore, there was a significant negative correlation between PR thicknesses and N1 amplitudes of rings 2 and 3 and positive correlation between PR thickness and P1 amplitudes of rings 3, 4, and 5.

Discussion

Our study revealed thinning of both inner and outer retinal single layers, increased OPL volume, and delayed implicit times and decreased amplitudes in the mfERG of PD patients compared with healthy subjects. To the best of our knowledge, this is the first study assessing the correlation between retinal layer segmentation findings and mfERG recordings.

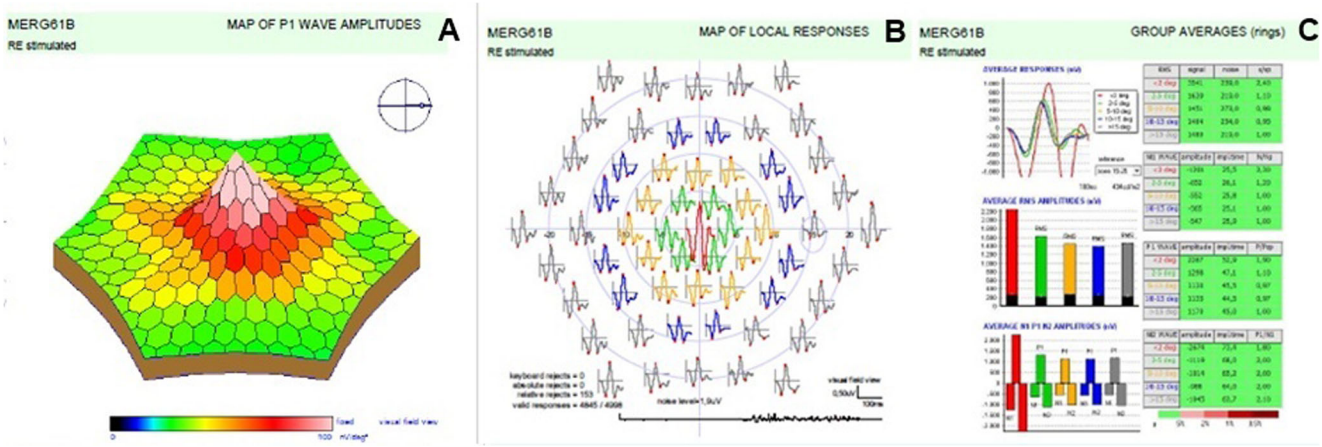

Fig. 1 Example of mfERG recordings of a normal subject. **a** Response density three-dimensional plot at the central macula. **b** First-order trace array. **c** Average amplitudes and implicit times of rings

Furthermore, we have found significant temporal and superotemporal pRNFL thinning in BPD compared to UPD subjects. This indicates that neurodegeneration characterized by axonal and ganglion cell damage is profound in subjects with more advanced phases of PD associated with the disease duration and severity.

Parkinson's disease (PD) is a neurodegenerative condition that causes the selective destruction of dopaminergic neurons. Numerous mechanisms have been proposed for the axonal damage and retinal ganglion cell loss in PD [13]. The loss of retinal ganglion cells causes a corresponding decrease in retinal single-layer and pRNFL thicknesses that can be disclosed in PD subjects using OCT [9]. However, there are various OCT studies in PD with conflicting findings in the literature. Decreased pRNFL thickness and inner and outer retinal volume changes have been stated [9, 13–16]. Albrecht et al. assessed retinal single-layer thickness in Parkinsonian syndromes, and increased inner nuclear layer in PD patients compared to healthy subjects was found [17]. In accordance with this, other studies failed to show differences in pRNFL and macular volume between PD patients and healthy controls [18, 19]. Schneider et al. did not find any significant changes in retinal single layers in PD patients [20], while other studies stated decreased inner nuclear layer thickness [21] and relationship between neuroaxonal retinal damage and disease severity and duration [13, 22]. Furthermore, Roth et al. reported decreased photoreceptor and outer nuclear layer thicknesses in patients with PD versus healthy subjects, but no differences in the pRNFL, total macular volume, or other retinal layers were noted [23]. Another recent OCT study of decreased thickness of the ONL (including the photoreceptor segments) in PD patients was found [24].

In our study, we found that although the central foveal thickness measurement was not different from controls, both inner (mRNFL, GCL, IPL) and outer (ONL, RPE, PR) retinal single layers were thinner in PD, particularly. We also studied volumes and found that although total macular volume was not different from that of controls, various single-layer retinal

Table 1 Clinical characteristics and demographics of study subject

Parameters	Unilateral Parkinson group (*n* 28)	Bilateral Parkinson group (*n* 30)	Control group (*n* 30)	*P* value (UPD vs BPD)	*P* value (UPD vs control)	*P* value (BPD vs control)
Age (years, mean ± SD)	60.53 ± 9.97	59.06 ± 9.41	60.22 ± 13.41	0.2	0.1	0.3
Gender (male/female)	16/14	15/13	15/15	0.7	0.6	0.6
BCVA (LogMAR)	0.07 ± 0.05	0.08 ± 0.06	0.07 ± 0.04	0.4	0.1	0.2
Color vision	12 ± 3	10 ± 2	13 ± 1	0.1	0.4	0.01*
Intraocular pressure (mmHg)	16.4 ± 2.6	17.1 ± 2.4	16.8 ± 2.1	0.4	0.5	0.4
Refractive error (diopters mean ± SD)	0.00 ± 1.9	0.00 ± 1.8	0.00 ± 2.1	0.3	0.2	0.1
Disease duration (year)	3.23 ± 2.21 (1–10)	10.80 ± 6.15 (2–30)	–	< 0.001*	–	–
Hoehn and Yahr scale	1.21 ± 0.31 (1–2)	2.90 ± 0.39 (2.5–4)	–	< 0.001*	–	–

SD standard deviation, *BCVA* best-corrected visual acuity

**P* value < 0.05 was considered statistically significant

Table 2 Comparison of retinal layer thickness and volumes between Parkinson and control subjects

Retinal OCT parameters	Unilateral Parkinson (*n* 28)	Bilateral Parkinson (*n* 30)	Control group (*n* 30)	*P* value (UPD vs BPD)	*P* value (UPD vs control)	*P* value (BPD vs control)
Retinal layer thickness (τm)						
Central fovea	265.80 ± 28.40	263.27 ± 19.12	268.48 ± 15.44	0.2	0.5	0.1
mRNFL	30.99 ± 3.26	29.90 ± 3.06	31.53 ± 2.55	0.006*	0.01*	0.001*
GCL	43.88 ± 3.80	43.06 ± 4.07	45.54 ± 2.82	0.1	0.004*	0.002*
IPL	35.52 ± 2.84	34.75 ± 2.75	37.02 ± 2.14	0.1	0.01*	0.0001*
INL	36.78 ± 2.91	36.47 ± 2.88	36.89 ± 3.87	0.9	0.2	0.2
OPL	30.39 ± 3.25	31.06 ± 2.73	29.28 ± 2.71	0.09	0.3	0.02
ONL	61.21 ± 9.91	58.16 ± 6.28	68.80 ± 15.36	0.1	0.01*	0.001*
RPE	13.81 ± 1.08	13.58 ± 1.53	15.14 ± 2.09	0.8	0.0001*	0.0001*
PR	77.34 ± 1.79	77.21 ± 2.60	80.62 ± 5.01	0.8	0.006*	0.003*
Retinal layer volumes (mm^3)						
mRNFL	0.93 ± 0.14	0.92 ± 0.11	0.99 ± 0.07	0.2	0.03*	0.01*
GCL	1.10 ± 0.09	1.09 ± 0.10	1.13 ± 0.07	0.5	0.1	0.6
IPL	0.90 ± 0.07	0.86 ± 0.06	0.93 ± 0.04	0.15	0.3	0.01*
INL	0.96 ± 0.07	0.96 ± 0.07	0.96 ± 0.04	0.6	0.6	0.3
OPL	0.83 ± 0.06	0.84 ± 0.06	0.81 ± 0.07	0.8	0.02*	0.01*
ONL	1.62 ± 0.17	1.59 ± 0.17	1.64 ± 0.13	0.1	0.9	0.1
RPE	0.38 ± 0.04	0.37 ± 0.02	0.40 ± 0.03	0.9	0.002*	0.001*
PR	2.18 ± 0.05	2.18 ± 0.06	2.20 ± 0.08	0.9	0.02*	0.02*
Inner macula	0.96 ± 0.07	0.96 ± 0.07	0.96 ± 0.04	0.7	0.6	0.7
Outer macula	6.25 ± 0.25	6.24 ± 0.24	6.32 ± .0.17	0.8	0.03*	0.01*

mRNFL macular retinal nerve fiber layer, *GCL* ganglion cell layer, *IPL* inner plexiform layer, *INL* inner nuclear layer, *ONL* outer nuclear layer, *OPL* outer plexiform layer, *RPE* retinal pigment epithelium layer, *PR* photoreceptor layer

*P value < 0.05 was considered statistically significant

(RNFL, RPE, and PR) volumes were significantly reduced; on the contrary, the OPL was thicker in PD. These findings of our study shows the importance of retinal segmentation analyses rather than evaluating simply the foveal thickness or total macular volume as a whole, while trying to outline the retinal pathologies in neurodegenerative diseases. In addition, we found moderate-to-strong correlations between outer macular volumes and N1 amplitudes of rings 2 and 3; P1 amplitudes of rings 3, 4, and 5; N2 amplitudes of rings 3, 4, and 5; and N1 implicit times of rings 4 and 5. Our study showed decreased inner retinal layers' thicknesses in PD consistent with the loss of retinal dopaminergic amacrine cells. Recently, photoreceptor thinning in the inner and outer segments was found in the ONL with retinal layer segmentation [25]. Chorostecki et al. [26] found reduced GCL, IPL, INL, and ONL volumes and increased OPL volume in PD. They stated that increased OPL

Table 3 Comparison of pRNFL parameters between Parkinson and control subjects

pRNFL parameters	Unilateral Parkinson (*n* 28)	Bilateral Parkinson (*n* 30)	Control group (*n* 30)	*p* value (UPD vs BPD)	*p* value (UPD vs control)	*p* value (BPD vs control)
Average	98.38 ± 9.58	96.72 ± 7.59	100.08 ± 10.17	0.2	0.6	0.5
Nasal	73.26 ± 13.87	71.74 ± 14.09	77.17 ± 15.10	0.5	0.2	0.15
Inferonasal	106.61 ± 21.07	105.2 ± 21.08	107.68 ± 23.71	0.5	0.5	0.3
Inferotemporal	144.75 ± 21.53	139.98 ± 19.29	145.77 ± 20.79	0.1	0.2	0.4
Temporal	76.25 ± 11.95	70.38 ± 12.99	78.31 ± 11.56	0.003*	0.4	0.001*
Superotemporal	134.48 ± 17.23	128.52 ± 20.36	138.68 ± 15.91	0.04*	0.1	0.04*
Superonasal	104.75 ± 20.35	100.54 ± 18.62	105.31 ± 12.57	0.2	0.8	0.2

pRNFL peripapillary retinal nerve fiber layer

*P value < 0.05 was considered statistically significant

Table 4 Comparison of mfERG parameters between Parkinson and control subjects

mfERG parameters	Unilateral Parkinson (*n* 28)	Bilateral Parkinson (*n* 30)	Control group (*n* 30)	*p* value (UPD vs BPD)	*p* value (UPD vs control)	*p* value (BPD vs control)
	Amplitude N (Nv/deg^2)					
Ring 1 (< 2°)	− 783.87 ± 456.11	− 781.55 ± 356.62	− 1521.74 ± 315.78	0.7	< 0.001*	< 0.001*
Ring 2 (2°–5°)	− 464.22 ± 219.14	− 463.06 ± 163.01	− 801.97 ± 145.97	0.3	< 0.001*	< 0.001*
Ring 3 (5°–10°)	− 468.43 ± 155.87	− 430.45 ± 139.91	− 706.88 ± 103.66	0.1	< 0.001*	< 0.001*
Ring 4 (10°–15°)	− 456.28 ± 127.16	− 439.57 ± 154.61	− 677.42 ± 104.97	0.2	< 0.001*	< 0.001*
Ring 5 (> 15°)	− 492.00 ± 140.93	− 464.45 ± 127.69	− 610.45 ± 529.78	0.8	< 0.001*	< 0.001*
	Amplitude P1 (Nv/deg^2)					
Ring 1 (< 2°)	1291.25 ± 544.50	1292.85 ± 551.26	2516.57 ± 546.64	0.8	< 0.001*	< 0.001*
Ring 2 (2°–5°)	954.11 ± 290.66	918.42 ± 251.28	1542.60 ± 327.30	0.5	< 0.001*	< 0.001*
Ring 3 (5°–10°)	941.71 ± 221.49	888.91 ± 232.24	1448.25 ± 193.67	0.2	< 0.001*	< 0.001*
Ring 4 (10°–15°)	986.57 ± 203.11	925.78 ± 252.95	1436.22 ± 208.51	0.2	< 0.001*	< 0.001*
Ring 5 (> 15°)	1078.44 ± 225.22	1026.01 ± 273.21	1458.68 ± 686.02	0.2	< 0.001*	< 0.001*
	Amplitude N2 (Nv/deg^2)					
Ring 1 (< 2°)	− 1219.94 ± 532.02	− 1175.10 ± 657.30	− 2327.14 ± 575.09	0.5	< 0.001*	< 0.001*
Ring 2 (2°–5°)	− 854.88 ± 242.95	− 786.85 ± 353.60	− 1220.14 ± 674.08	0.4	< 0.001*	< 0.001*
Ring 3 (5°–10°)	− 826.50 ± 219.84	− 807.71 ± 190.60	− 1159.37 ± 482.14	0.3	< 0.001*	< 0.001*
Ring 4 (10°–15°)	− 888.86 ± 225.73	− 815.85 ± 278.10	− 1303.61 ± 228.08	0.2	< 0.001*	< 0.001*
Ring 5 (> 15°)	− 936.90 ± 382.77	− 918.75 ± 244.00	− 1444.51 ± 258.29	0.4	< 0.001*	< 0.001*
	Implicit time N1 (ms)					
Ring 1 (< 2°)	27.43 ± 5.65	27.85 ± 4.58	26.88 ± 1.66	0.3	0.4	0.3
Ring 2 (2°–5°)	26.77 ± 2.33	27.09 ± 1.84	26.28 ± 1.30	0.4	0.02*	0.007*
Ring 3 (5°–10°)	26.70 ± 7.07	27.74 ± 1.51	25.41 ± 1.57	0.6	< 0.001*	< 0.001*
Ring 4 (10°–15°)	26.48 ± 1.86	27.00 ± 1.44	25.31 ± 1.19	0.1	< 0.001*	< 0.001*
Ring 5 (> 15°)	26.57 ± 1.68	26.84 ± 1.74	25.90 ± 3.87	0.9	< 0.001*	< 0.001*
	Implicit time P1 (ms)					
Ring 1 (< 2°)	49.60 ± 3.55	49.65 ± 4.82	49.50 ± 2.61	0.5	0.5	0.9
Ring 2 (2°–5°)	46.46 ± 1.95	46.65 ± 1.83	45.56 ± 1.46	0.5	0.03*	0.01*
Ring 3 (5°–10°)	44.79 ± 1.86	45.28 ± 1.63	43.83 ± 1.37	0.1	0.003*	< 0.001*
Ring 4 (10°–15°)	44.31 ± 1.99	44.93 ± 1.51	43.22 ± 1.31	0.1	< 0.001*	< 0.001*
Ring 5 (> 15°)	44.81 ± 1.88	44.90 ± 3.17	43.86 ± 4.02	0.5	< 0.001*	< 0.001*
	Implicit time N2 (ms)					
Ring 1 (< 2°)	70.32 ± 6.84	71.96 ± 6.35	69.89 ± 3.56	0.2	0.5	0.7
Ring 2 (2°–5°)	66.31 ± 3.53	66.49 ± 4.78	64.57 ± 1.98	0.6	0.01*	0.007*
Ring 3 (5°–10°)	63.40 ± 2.64	63.76 ± 3.65	61.92 ± 1.51	0.1	0.01*	0.001*
Ring 4 (10°–15°)	63.15 ± 3.73	63.58 ± 4.69	61.17 ± 1.60	0.3	0.003*	0.001*
Ring 5 (> 15°)	61.99 ± 2.35	62.65 ± 1.69	60.93 ± 1.56	0.2	0.003*	0.001*

mfERG multifocal electroretinography

*P value < 0.05 was considered statistically significant

thickness is a crucial finding which may correspond to the localization of α-synuclein in the OPL of PD patients.

All patients in our study had normal visual acuity, but color vision scores were significantly poorer in BPD compared to those in controls. Patients with PD frequently suffer from reduced visual function even when they have normal visual acuity levels, which may, in part, be due to decreased contrast sensitivity, color perception abnormalities, and defective spatial processing [3]. Many of these functions are mediated by dopamine. Yet, our results support the previous observation that retinal thinning occurs before involvement of visual signal transmission [27]. This tissue loss is probably associated with dopaminergic amacrine cells and pathologic changes due to synuclein, which is found throughout the retina [28].

Electrophysiologic analyses such as VEP, PERG, and mfERG have also been assessed in PD subjects. Pattern electroretinogram displays retinal ganglion cell activity [7]. Garcia-Martin et al. [6] demonstrated delayed implicit times

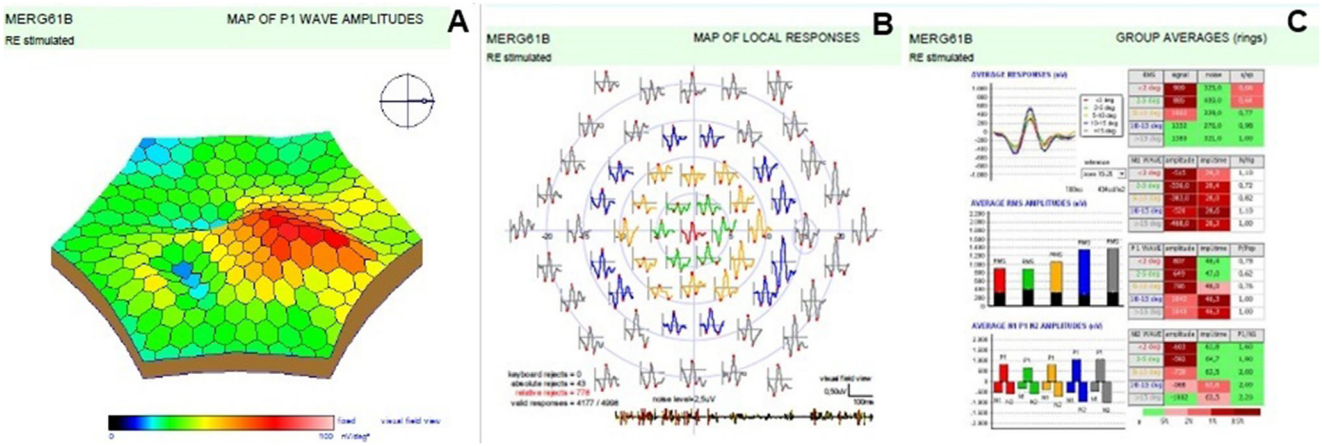

Fig. 2 Example of mfERG recordings of a Parkinson patient. **a** Response density three-dimensional plot at the central macula. **b** First-order trace array. **c** Average reduced amplitudes and increased implicit times of rings

and decreased amplitude responses in the VEP and PERG of PD subjects versus control subjects. They also reported that the implicit time and amplitude of the VEP and the implicit time of PERG worsen prolonged disease duration.

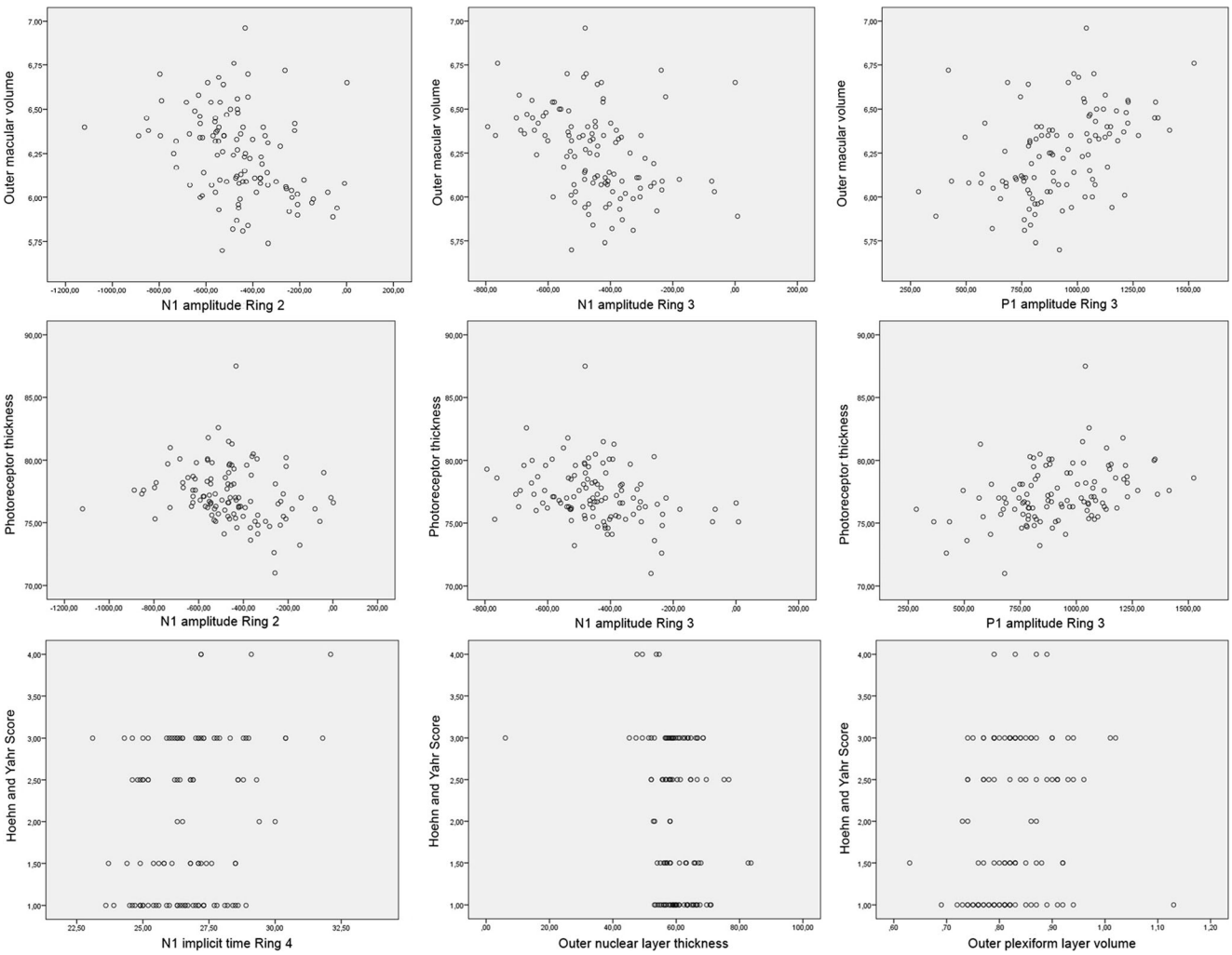

Fig. 3 Scatter plots showing the association between OCT parameters (outer macular volume, PR thickness, ONL thickness, and OPL volume), mfERG findings (N1 amplitude rings 2 and 3, P1 amplitude ring 3, N1 implicit time ring 4), and the Hoehn and Yahr scores

Moschos et al. [29] evaluated pRNFL and mfERG changes in patients with PD without visual loss, and they found a decrease in the P1-response amplitude of ring 1 which represents electrical activity of the fovea, an increase of the mean P1-response latency of ring 2 which represents the parafovea, as well as a decrease in the thickness of the pRNFL. Furthermore, Palmowski-Wolfe et al. [30] stated that lack of dopamine in patients with mild-to-moderate signs of PD seems to have little impact on mfERG. The mfERG is a tool which reflects regional electrophysiologic activities from distinct areas of the retina. Clinical application of mfERG findings allows clinicians to determine destruction to the retina up to the inner nuclear layer [7]. In patients with MS, studies have shown that outer retinal involvement is established by disclosure of mfERG abnormalities [31, 32]. We have found latency delay for four of five rings (latency for ring 1 was not significantly delayed) in the mfERG of PD patients compared with healthy controls. Presumably, this may be related to the structure and the organization of visual pathways of the fovea and parafoveal area. We also found significant amplitude reduction for all rings in the mfERG of PD patients compared with healthy subjects.

Previous studies have suggested that the correlation of retinal changes to the first affected body side seems to be crucial in PD [9]. Comparable asymmetry effects were reported in the substantia nigra, with higher neuronal damage found contralaterally to the initially affected body side [33]. In our study, when eyes were separated according to the ipsilateral and contralateral body side in UPD patients, no significant differences in retinal layer thickness, retinal volumes, pRNFL parameters, and mfERG findings between the groups were seen.

Previous studies reported macular thinning in PD subjects versus healthy controls, a negative correlation with Hoehn and Yahr severity [13, 22]. In our study, the Hoehn and Yahr score was negatively correlated with some retinal single-layer thicknesses (mRNFL, ONL) and mRNFL volume as well as positive correlation with OPL volume. In addition, we found moderate correlations between the Hoehn and Yahr score and mfERG N1 implicit times of rings 4 and 5, P1 implicit times of rings 3 and 4, and N2 implicit time of ring 5. No significant correlations between disease duration and pRNFL parameters and mfERG recordings were found. Furthermore, there was a significant negative correlation between PR thicknesses and N1 amplitudes of rings 2 and 3 and positive correlation between PR thickness and P1 amplitudes of rings 3, 4, and 5.

In conclusion, our study revealed thinning of both inner and outer retinal single layers, increased OPL volume, and delayed implicit times and decreased amplitudes in the mfERG of PD patients compared to healthy controls. Our findings point out that SD-OCT and mfERG could both serve as non-invasive tools for evaluating ophthalmic manifestations of Parkinson's disease.

Compliance with ethical standards All the patients enrolled provided informed written consent, and this study was reviewed and approved by the EU institutional review board.

Conflict of interest The authors declare that they have no conflict of interest.

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