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ORIGINAL RESEARCH ARTICLE

Retinal dysfunction in Parkinson's disease—results of the extended protocol for photopic negative response (PHNR) full-field electroretinogram (ERG)

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Abstract

Background We investigated whether the photopic negative response (PhNR) in the electroretinogram (ERG) was affected in Parkinson's disease (PD) patients and whether it was associated with retinal changes on optical coherence tomography (OCT).

Methods Thirty-two patients with PD and 31 age and sex-matched healthy controls from a single tertiary centre were included in the study. Hoehn and Yahr scale scores and the presence of REM sleep behaviour were recorded. PhNR, a-wave and b-wave responses in photopic ERG (red on blue background) and retinal layer thicknesses in OCT were obtained.

Results The mean age was 61 ± 10.4 in the PD group (female/male: 18/14) and 60.9 ± 7 in the control group (female/male: 18/13). The amplitudes of the PhNR, a- and b-waves in the ERG were significantly decreased in the PD group, but the implicit times were not significantly different. BCVA was significantly correlated with Hoehn and Yahr scores ($p < 0.001$, $r = -0.596$). There was a significant correlation between BCVA and a-wave amplitude ($p = 0.047$, $r = -0.251$). On OCT analysis, the thickness of the nasal INL was increased, and the temporal and inferior OPL and temporal peripapillary RNFL were decreased in the PD group compared to healthy controls ($p = 0.032$, $p = 0.002$, $p = 0.016$ and $p = 0.012$, respectively).

Conclusion This study demonstrated reduced a-wave, b-wave and PhNR-wave amplitudes on ERG measurements in PD patients. These findings suggest that the whole ERG response, not just the PhNR, is attenuated in patient with PD, suggesting a possible involvement of the visual system in the disease.

Keywords Photopic negative response · Electroretinography · Optical coherence tomography · Parkinson's disease · ERG

Introduction

Parkinson's disease (PD) is a neurodegenerative disease characterised by loss of dopaminergic neurons in the substantia nigra and associated motor dysfunction. Functional visual impairment and structural retinal changes, particularly in the inner retinal layers, have been reported in PD [1–4]. Degeneration of dopaminergic cells and the deposition of phosphorylated α-synuclein in the retina, similar to Lewy bodies in the brain, have been shown histologically in patients with PD [5–7]. Deterioration of retinal ganglion cells (RGCs) and the retinal nerve fibre layer (RNFL), which is composed of RGC axons, has been shown

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in PD using optical coherence tomography in previous studies [8–10]. In addition, it has been observed that there is a decrease in PERG responses caused by dopaminergic deficiency in the retina [11, 12].

The photopic negative response (PhNR) is a slow negative component of the photopic full-field electroretinogram (ERG) that originates predominantly from the inner retina and mainly from RGCs [13]. To obtain larger responses, the PhNR is recorded with red flashes on a rod-suppressing blue background [14]. The PhNR has been shown to be reduced in glaucoma, optic atrophy, anterior ischaemic optic neuropathy, compressive optic neuropathy, optic neuritis and preclinical Alzheimer's disease [15–18]. Degeneration of melanopsin-expressing, human, intrinsically-photosensitive retinal ganglion cells has been proposed to cause sleep and circadian rhythm disturbances in PD [19]. Rapid eye movement (REM) sleep behaviour disorders are common in PD. In a meta-analysis, the prevalence of REM sleep disorder in PD was estimated to be 42% (95%CI: 37–47%) [20, 21]. In a large series comparing PD patients with and without REM sleep disorder, the Hoehn Yahr score was found to be significantly higher in PD with REM sleep disorder [22]. REM sleep disorder is considered a possible marker of more widespread brainstem pathology [23]. Therefore, it remains to be investigated whether RGC function, as measured by PhNR, is additionally affected in PD patients with REM sleep disorders.

This study aimed to investigate whether PhNR was affected in patients with PD and whether it was associated with retinal changes on optical coherence tomography (OCT). The secondary aim was to compare PhNR and OCT findings between PD patients with and without REM sleep behaviour disorder.

Methods

All procedures performed in human participants were in accordance with the ethical standards of the Erciyes University Local Ethics Committee and with the 1964 Helsinki declaration and its subsequent amendments or comparable ethical standards. The study protocol was approved by Erciyes University Local Ethics Committee (No: 2021/566). Written informed consent was obtained from all individual participants included in the study.

Participants

Thirty-two PD patients and 31 age and sex-matched healthy controls were included in the study. One eye of each participant was randomly selected for statistical analysis. The PD patients were followed up at the Neurology Department of Erciyes University. The disease severity scores of the PD patients were recorded according to the Hoehn and Yahr scale [24]. The presence of REM sleep behaviour disorder was also recorded by interviewing both the patient and the spouse. The Turkish version of REM sleep behaviour disorder screening questionnaire was used for evaluation [25]. Five points and above on the questionnaire was accepted as positive. All patients were taking medication for PD. Systemic and neurological exclusion criteria for the PD group were: diabetes mellitus, history of a cerebrovascular incident, alcoholism or any other drug abuse, history of severe head trauma, deep brain stimulation, history of malignancy, history of demyelinating disease, severely uncooperative patients, severe head tremor preventing reliable imaging, and use of sedatives. The exclusion criteria for the control group were any systemic disease or medication. Ocular exclusion criteria for both groups were: best-corrected visual acuity (BCVA) less than 0.3 decimal (Snellen), cataract surgery within 6 months, any vitreoretinal surgery, retinal and macular pathology, congenital or acquired optic neuropathy, severe media opacities preventing retinal examination and imaging, history of ocular trauma, and refractive error greater than 6 diopters of spherical equivalent.

Ophthalmologic examination and imaging

All participants underwent a complete ophthalmologic examination including slit-lamp examination, intraocular pressure (IOP) measurement, refraction, BCVA, fundus examination and OCT. OCT imaging of the macula was performed using a Spectralis OCT (Heidelberg Engineering, Germany). Automatic retinal layer segmentation was performed with the Spectralis software (version 6.3.3.0). The retinal layers included the retinal nerve fibre layer (RNFL), ganglion cell layer (GCL), inner plexiform layer (IPL), inner nuclear layer (INL), outer plexiform layer

(OPL), outer nuclear layer (ONL) and retinal pigment epithelium (RPE). The retinal layers were analysed according to the ETDRS subfields, which were central 1 mm, superior, temporal, inferior and nasal subfields between 1 and 3 mm circles. Peripapillary retinal nerve fibre layer (RNFL) thicknesses (global, nasal, temporal, inferonasal, inferotemporal, superonasal and superotemporal) were also measured automatically with the OCT software. Macular and peripapillary retinal layer analysis is shown in Fig. 1.

Electroretinography and photopic negative response

In the present study, protocol for the PhNR (Metrovision Monpack 3, Metrovision, France) was performed according to the approved extended protocol of the International Society for Clinical Electrophysiology of Vision (ISCEV) [14]. Pupils were maximally dilated (7 to 9 mm in diameter) with tropicamide (1%) and phenylephrine hydrochloride (2.5%). After 10 min of adaptation to photopic conditions, a topical anaesthetic (0.5% proparacaine hydrochloride) was applied to the eyes before placement of a single-use unipolar gold-based contact lens active electrode (ERG Jet, Metrovision, Perenchies, France). A reference electrode was placed near each orbital rim, with the skin temporal to the outer canthus used as the reference electrode for the corresponding eye. The stimulus duration was less than 5 ms red (630 nm) flashes (1.7 cd.s/m^2) on a rod-suppressing blue (465 nm) background (8 cd.s/m^2). The inter-flash

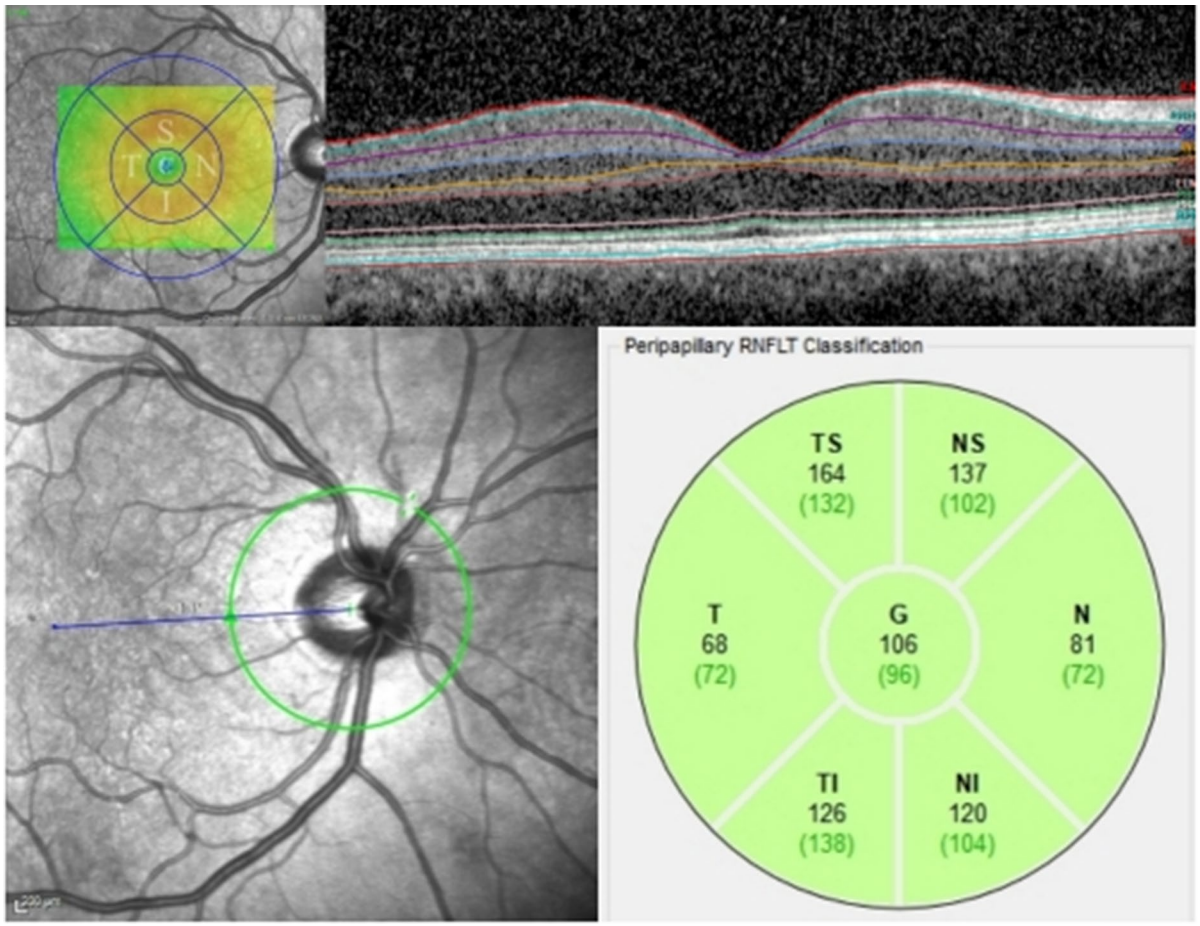

Fig. 1 Segmentation of retinal layers in horizontal scans of the fovea was performed automatically. Mean retinal layer thicknesses were analysed in 5 sectors (temporal, inferior, nasal, superior and central). Mean peripapillary RNFL thickness was analysed in 6 sectors (superonasal, nasal, inferonasal, inferotemporal, temporal and superotemporal)

interval was 500 ms. Electrical signals were amplified 1000 times and digitised. The signal cut-off frequency was between 0.3 Hz and 300 Hz and an average of 100 responses was used. Previous studies have confirmed that this colour combination is a good stimulus for eliciting the PhNR [13, 26]. The amplitudes and implicit times of a-wave, b-wave and PhNR were recorded. The fellow eye was covered during the recording of the corresponding eye.

The first negative wave is referred to as the a-wave and the first positive wave after the a-wave is referred to as the b-wave. The amplitude of the a-wave was measured from the baseline to the negative trough, and the amplitude of the b-wave was measured from the trough of the a-wave to the following peak. After the i-wave, which is the Off-pathway derived positive deviation in the descending arm of the b-wave, the negative wave occurring in the 65–75 ms interval was evaluated as the PhNR. The PhNR amplitude was measured from the baseline to the minimum point in the trough. The implicit times were defined as the time from light onset to wave peak. Figure 2 shows the ERG waveform and its components.

Statistical analysis

Statistical analysis was performed using SPSS software (IBM, version 18). The normality of the data was tested using the Shapiro–Wilk test. The chi-squared test was used for comparisons of nominal-ordinal variables. The Mann–Whitney U test was used for comparisons between independent variables that were not normally distributed. Independent sample t-test was used for normally distributed data. Correlations between parameters were tested using Pearson's test for normally distributed data and Spearman's test for non-normally distributed data. Receiver operating characteristic (ROC) analysis was performed with MedCalc (version 20). ROC was performed for the diagnostic value of a-wave, b-wave and PhNR amplitudes in PD and the Area under the curve (AUC) value was obtained. A p-value of less than 0.05 was accepted as the statistical level of significance.

Results

Thirty-two patients (18 female) with PD and 31 age- and sex-matched healthy controls (18 female) were included in the study. Demographic data, intraocular

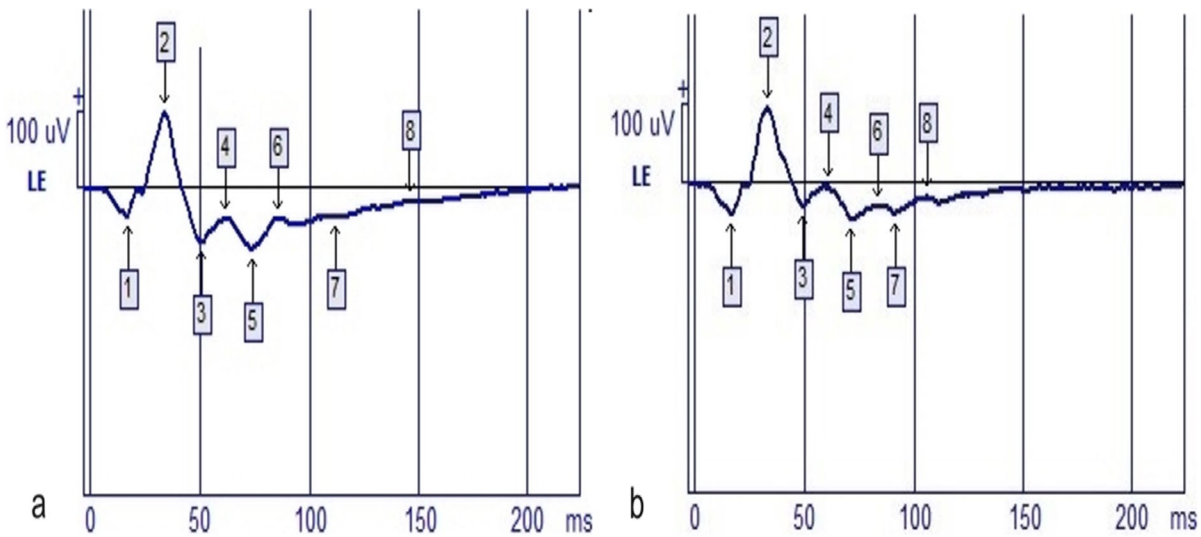

Fig. 2 Red-on-blue ERG presentation in a control subject (**a**) and a PD subject (**b**). The amplitude of the a-wave was measured from the baseline to the negative trough, and the amplitude of the b-wave was measured from the trough of the a-wave to the following peak. The PhNR amplitude was measured from baseline to the minimum point in the trough. The implicit time was defined as the time from light onset to wave peak. In these examples, the negative wave 1 is the a-wave, the positive wave 2 is the b-wave and the negative wave 5 is the PhNR

pressure, BCVA, disease duration and Hoehn and Yahr scale scores of the participants are summarised in Table 1. There was no significant difference between groups for sex, age and IOP ($p=0.88$, $p=0.99$ and $p=0.17$, respectively). The mean age was 61 ± 10.4 in the PD group and 60.9 ± 7 in the control group. BCVA was significantly decreased in the PD group ($p=0.002$, Table 1). The disease duration of PD was 5.1 ± 3.6 years. Hoehn and Yahr scores were significantly higher and REM sleep behaviour frequency was significantly higher in the PD group compared to the control group ($p<0.001$ and $p<0.001$, respectively, Table 1).

For flash photopic ERGs, the amplitudes of a-, b- and PhNR-waves were significantly reduced in the PD group compared to the control group, but the peak time were not significantly different between groups (Table 2). The median PhNR/b wave ratio was -0.43 ± 0.13 in the PD group and -0.39 ± 0.24 in the control group and there was no significant difference between the groups ($p=0.514$). There was no significant inverse correlation between the wave amplitudes (a, b and PhNR) and the PD duration. There was no significant correlation between Hoehn and Yahr scores and wave amplitudes (a, b and PhNR) in the ERG. BCVA was significantly correlated with Hoehn and Yahr scores in this study indicating worse visual acuity with more severe PD ($p<0.001$, $r=-0.596$). There was a significant correlation between BCVA and a-wave amplitude ($p=0.047$, $r=-0.251$). However, there was no significant correlation between BCVA and b and PhNR amplitude.

In OCT analysis, there were significant differences between the control and PD groups, which were greater thickness in the nasal 1–3 mm INL in PD, and lesser thickness in the temporal and inferior 1–3 mm OPL, and in temporal peripapillary RNFL in PD ($p=0.032$, $p=0.002$, $p=0.016$ and $p=0.012$, respectively), but the remaining retinal layers and sectors were not significantly different (Supplementary file 1, $p>0.05$). The correlations between ERG amplitudes and sectors of retinal layers in OCT were also analysed and statistically the significant results are summarised in Table 3. The other layers and sectors were not significantly different (p<0.01) and are not shown in the table due to the large amount of the data. Correlation plots of a-wave and PhNR are presented in Fig. 3.

ROC analysis was performed to evaluate the diagnostic value of PhNR amplitude in PD and the AUC

Table 1 Demographic data and clinical findings of participants

Variables	Control	PD	*p*
Gender (F/M)	18/14	18/13	0.88
Age (years, mean ± SD)	60.9 ± 7	61 ± 10.4	0.99
IOP (mmHg, mean ± SD)	14.6 ± 2.2	13.6 ± 3.3	0.17
BCVA logMAR (median, min–max)	0 (0–0.2)	0.07 (0–0.5)	**0.002**
Parkinson's Disease Duration (years, mean ± SD)	–	5.1 ± 3.6	–
Hoehn and Yahr Scale (median, mix-max)	0 (0–0)	2 (1–3)	**< 0.001**
REM sleep behaviour disorder	0/31	13/32	**< 0.001**

PD—Parkinson's disease, *F*—female, *M*—male, *SD*—standard deviation, *IOP*—intraocular pressure, *BCVA*—best corrected visual acuity, *REM*—rapid eye movement

Table 2 Amplitudes and implicit times of a, b, and PhNR waves in ERG

Variables	CG *N* = 31	PD *N* = 32	*p*
a wave amplitude (μV, median and 25–75%)	− 32.4 (− 38.5/− 27.2)	− 24.1 (− 30.3/− 20.0)	**< 0.001**
a wave implicit time (ms, Mean ± SD)	15.9 ± 1.3	16.1 ± 1.7	0.614
b wave amplitude (μV, median and 25–75%)	110.5 (91.0/147.4)	92.4 (75.5/114.6)	**0.011**
b wave implicit time (ms, Mean ± SD)	32.5 ± 1.4	32.1 ± 1.8	0.364
PhNR wave amplitude (μV, median and 25–75%)	− 48.6 (− 62.6/− 39.7)	− 40.2 (− 45.1/− 25.8)	**0.001**
PhNR wave implicit time (ms, median and 25–75%)	72.3 (70.5/73.1)	70.5 (68.0/73.1)	0.050
PhNR/b wave ratio (Mean ± SD)	− 0.43 ± 0.13	− 0.39 ± 0.24	0.514

CG—control group, *PD*—Parkinson's disease

Table 3 Significant correlations between ERG responses and sectors of retinal layers in OCT in all group

Variables/test	*r*	*P*
a wave amplitude—i-INL	− 0.258	0.041
a wave amplitude—t-OPL	− 0.266	0.035
b wave amplitude—i-INL	0.305	0.015
b wave amplitude—ts-pRNFL	− 0.252	0.046
b wave amplitude—t-pRNFL	− 0.261	0.039
PhNR wave amplitude—n-IPL	− 0.316	0.012

A—amplitude, *IT*—implicit time, *c*—central 1 mm, *s*—superior 1–3 mm, *i*—infeior 1–3 mm, *n*—nasal 1–3 mm, *t*—temporal 1–3 mm in ETDRS grid. *INL*—inner nuclear layer, *ONL*—outer nuclear layer, *OPL*—outer plexiform layer, *pRNFL*—peripapillary retinal nerve fibre layer, *RPE*—retina pigment epitelium

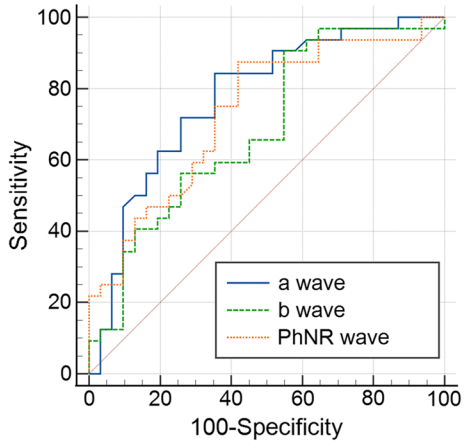

Fig. 4 ROC curve of a-, b- and PhNR-waves amplitude

value was 0.734 (95%CI: 0.608–0.837, $p<0.001$) (Fig. 4). The AUC values for a- and b-wave amplitudes were 0.773 (95%CI: 0.650–0.869, $p<0.001$) and 0.685 (95%CI: 0.556–0.796, $p=0.006$), respectively. The sensitivity, specificity and cut-off values of ERG waves are summarised in Table 4. There was no significant difference in the pairwise comparison of ROC curves (PhNR—a wave p = 0.59; PhNR—b wave $p=0.51$, a-b wave $p=0.06$).

There was no statistical difference in ERG amplitudes orimplicit times between PD patients with and without REM sleep behaviour disorder ($p>0.05$).

Discussion

This study found significantly lower amplitudes of the PhNR, a- and b-waves in the red-on-blue ERG in PD patients compared to healthy controls. Pattern ERGs have been investigated in PD but PhNR in the ffERG has some advantages over the PERG in that it is less affected by refractive status and media opacities [27, 28]. PD has been associated with reduced scotopic and photopic a- and b-wave amplitudes [29, 30]. In Parkinson's disease, dopaminergic amacrine cells and their plexuses are depleted in the human retina, followed by global dysfunction of the dopaminergic system. Dopaminergic amacrine cells are regulators of horizontal cells and rod-cone coupling. They also modulate ganglion cells [5]. The a-wave originates mainly from cone photoreceptors and some bipolar cells. The b-wave is mainly caused by bipolar cells and their interaction with Müller cells. These cells have dopamine receptors and dopamine modulation [5, 31]. Therefore, reduced dopaminergic activity in PD may result in functional changes in the retina and optic nerve that can be detected by electrophysiological testing [32, 33].α-Synuclein accumulation in

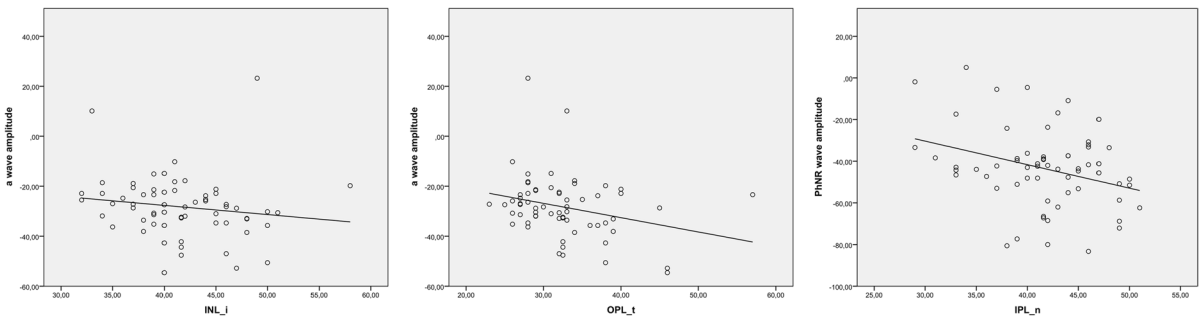

Fig. 3 Scatter plots showing the relationship between OCT thickness parameters and the amplitudes of a-waves and PhNRs

Table 4 ROC analysis results of ERG waves amplitudes

Variables	Cut off	Sensitivity	Specificity	Area under curve	Confidence interval (95%)	*p*
a wave amplitude	− 30.8	0.843	0.645	0.773	0.650–0.869	**< 0.001**
b wave amplitude	127.8	0.906	0.451	0.685	0.556–0.796	**0.006**
PhNR amplitude	− 47.7	0.875	0.580	0.734	0.608–0.837	**< 0.001**

RGCs resembling Lewy bodies in the brain has been demonstrated in PD. RGC α-synuclein accumulation has been suggested to be an in vivo indicator of the severity of brain pathology [6, 7]. We measured PhNR from baseline to trough; the PhNR is mainly derived from RGCs [27]. The decrease in PhNR amplitude in PD patients in our study may be attributed to the loss of RGC cells and function. However, a decrease in the a- and b-wave components will lead to some decrease in the PhNR. A recent study by Mello et al. comparing ffERG scans from PD patients with a control group found a decrease in the amplitudes of the b-wave and the PhNR in PD patients, and the authors suggested that the PhNR might be a potential new biomarker [34]. However, our results did not confirm this. The fact that there was no significant difference in the PhNR/b-wave ratio in our study or in the study by Mello et al.[34], which confirms that PD causes generalised retinal dysfunction.

BCVA was significantly reduced in the PD group compared to the control group. Previous studies have shown alterations in visual acuity, contrast sensitivity, colour discrimination, pupil reactivity, eye movements, motion perception, visual field sensitivity and visual processing speed in PD [28, 35]. Visual dysfunction is attributed to alterations in both the retina and the brain [28]. Retinal electrophysiological studies have supported retinal dysfunction, which may explain the reduced visual function in PD. BCVA was significantly associated with Hoehn and Yahr scores in this study, suggesting that visual acuity is worse with more severe PD. We did not find a significant correlation between BCVA and PhNR amplitude, however, BCVA was negatively correlated with a-wave amplitude.

Previous OCT studies showed structural retinal changes mostly in inner retinal layers in PD, but variable results were reported. Previous meta-analysis studies reported decreased GCL and IPL layer thicknesses is common, but conflicting results exist about other layers of macular RNFL, INL, OPL, ONL and peripapillary RNFL thicknesses [1, 36, 37]. In our study, we found thicker nasal INL, and thinner temporal and inferior OPL in the macula, as in previous reports [38, 39], however, the GCL thickness was not significantly different between PD and control groups. This result might be explained by the patients in the PD group not having high severity scores (Hoehn and Yahr, range 1–3) and ganglion cell loss was not severe enough to cause thinner GCL or subsequent IPL and RNFL. α-synuclein accumulation was also reported in the INL layer [40] and this may explain increased INL thickness. Temporal peripapillary RNFL was significantly reduced in the PD group compared to the control group, which supports previous reports that showed temporal preferential loss patterns in PD patients [8]. Structural parameters with OCT and functional parameters with multifocal ERG have been shown to have some correlation in PD [4]. In this study, significant correlations were found between a, b and PhNR amplitudes and sector OCT layer thickness.

Sleep disorders including REM sleep behaviour disorders are common in PD [19, 41]. Degeneration of the retinal melanopsin system including melanopsin-containing RGCs (ipRGC) is blamed for sleep and circadian rhythm disorders in PD [19, 42]. Melanopsin is a vitamin A-derived photopigment [43]; melanopsin-containing RGCs are intrinsically photosensitive retinal cells that have been shown to be decreased in PD [19]. A previous study that analysed immunotoxin-induced ablation of the ipRGCs in rhesus monkeys reported diminished PhNR amplitudes with red on blue flashes after toxin injection compared with contralateral control eyes [44]. Thus, we compared RGC function with ERG, particularly with PhNR, and retinal layer thicknesses between PD patients with or without REM sleep behaviour disorders and there was no significant difference between the two patient

groups. These results suggest that ipRGCs may not make a significant contribution to the PhNR. In the ROC analysis, the AUC value of PhNR was 0.761 and a-wave was 0.773 (Fig. 4). AUC values below 0.5 means poor diagnostic capacity for discriminating subjects with or without disease [45]. A value between 0.7—0.8 is considered acceptable, which means PhNR and a-wave are acceptable tools for discriminating study subjects with PD disease or without [45].

This study had several limitations. First, the PD group consisted of patients with Hoehn and Yahr scores below 3 and there were no patients with severe disease. Second, all the patients were under anti-PD medications, which have been shown to affect ERGs. Since PD medications upregulate dopaminergic activity, it may have a positive effect on ERG amplitudes [12, 46–48]. Nevertheless, our results suggest that patients with PD have generalised retinal dysfunction. Third, other visual functions including colour vision and contrast sensitivity were not evaluated in the study population. The subjective nature of the assessment of REM sleep is a further limitation of this study. The study did not have pupil light reflex data to confirm ipRGC involvement.

In conclusion, the present study provides evidence of reduced a-wave, b-wave and PhNR amplitudes in PD patients. The researchers also performed ROC analysis and found that the a-wave amplitude and PhNR amplitude had acceptable discriminatory ability in distinguishing PD patients from healthy subjects. These findings suggest that the whole ERG response, not just the PhNR, is attenuated in people with PD, suggesting a possible involvement of the visual system in the disease. Further research is needed to better understand the underlying mechanisms and clinical implications of these observations.

Author Contributions Conceptualization was contributed by [OAP, HŞ]; data curation was contributed by [MG, FO]; formal analysis was contributed by [HS]; investigation was contributed by [HS]; methodology was contributed by [HS, HA]; project administration was contributed by [HA]; software was contributed by [HS]; supervision was contributed by [HA]; validation was contributed by [OAP]; visualisation was contributed by [HA]; writing—original draft, was contributed by [OAP, HS]; writing—review and editing was contributed by [MG, FO, HA].

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Data statement The data that support the findings of this study are available from the corresponding author, Osman Ahmet Polat, upon reasonable request.

Declarations

Conflict of interest No potential conflict of interest was reported by the authors.

Ethic approval All procedures performed in human participants were in accordance with the ethical standards of the Erciyes University Local Ethics Committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Study protocol was approved by Erciyes University Local Ethics Committee (No: 2021/566).

Informed consent Written informed consent was obtained from all individual participants included in the study.

Statement on the welfare of animals: No animals were used in this research.

Statement of human rights 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 Declaration of Helsinki and its later amendments or comparable ethical standards.

Statement on the welfare of animals No animals were used in this research.

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